Rhodium (II) catalysed reactions of α-Diazo phosponates

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To Mum and Dad,
with love
Rhodium (II) Catalysed Reactions of α-Diazo Phosphonates

by

Eric-Robert Hian Bing Sie

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of

Doctor of Philosophy
of the
Loughborough University of Technology

September 1992

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Abstract

The syntheses and reactions of some α-diazo phosphonates are reviewed. The work presented is based on the inter- and intra-molecular reactions of the previously proposed, transient rhodium carbenoid species with nucleophiles. In order to shed some light on the mechanism of the rhodium (II) catalysed insertion reactions of diazo compounds with nucleophiles and consequently to verify the presence of the rhodium carbenoid species or not, studies have been carried out to determine what factors affect the rate of insertion. Thus, the intermolecular rhodium (II) catalysed insertion reactions of a series of diazo compounds in the presence of various alcohols have been investigated. Some novel diazo compounds have been prepared and more efficient, more amenable routes to some known diazo compounds have been developed. It was found that rhodium (II) trifluoroacetamide is a significantly more active catalyst than rhodium (II) acetate, under the test conditions.

Two new methods leading to the formation of functionalised cyclic ethers (five-, six- and seven-membered rings) have been developed. Both involve the insertion of an alcohol into an α-diazo phosphonate catalysed by rhodium (II) acetate as the initial step but whereas one method proceeds via an intermolecular Wadsworth-Emmons reaction, the other proceeds via the intramolecular variant of the same reaction. 7/6- and 7/7-Fused bicyclic ethers have been prepared from 3-oxooxepane 2-phosphonates via the Wadsworth-Emmons reaction. The oxepanes themselves were prepared in good yields by an intramolecular rhodium (II) catalysed O-H insertion reaction of a parent diazo alcohol. The same bicyclic systems could also be accessed by two different routes starting with t-butyl-7-hexyl-3-oxooxepane-2-carboxylate.

Various novel synthetic routes leading to the formation of functionalised bicyclic, tricyclic and tetracyclic systems have been investigated. All involve the intramolecular rhodium (II) catalysed O-H insertion reaction of a diazo alcohol as a key cyclisation step.
Acknowledgements

This piece of work would not have been possible but for the help and support of a great number of people. As this will be my only opportunity to thank many of these people in public, I make no effort to excuse the long list of acknowledgements that are about to follow.

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Eric-Robert Sie
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<td>Bn</td>
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<tr>
<td>n-BuLi</td>
<td>n-Butyllithium</td>
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<tr>
<td>t-BuOK</td>
<td>Potassium t-butoxide</td>
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<td>N,N-Dimethylformamide</td>
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<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
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<tr>
<td>Ms</td>
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<td>Trifluoromethanesulphonate (triflate)</td>
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<td>Potassium peroxymonosulphate (Aldrich Chemical Co.)</td>
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<td>TIPS</td>
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CHAPTER ONE

THE CHEMISTRY OF α-DIAZO PHOSPHONATES
1.1 Introduction

Since the preparation of the first $\alpha$-diazo phosphonates by Seyferth in 1967\textsuperscript{1} [dimethyl 1-phenyl diazomethylphosphonate ($1, Z = \text{Ph}, R^1 = R^2 = \text{Me}$) and dimethyl 1-methyl diazomethylphosphonate ($1, Z = \text{Me}, R^1 = R^2 = \text{Me}$)], a huge amount of progress has been made in developing the chemistry of diazo compounds of this type ($1$) as well as the closely related analogues, $\alpha$-diazo phosphinates ($2$) and $\alpha$-diazo phosphine oxides ($3$). The chemistry of diazo compounds in general, is almost entirely dominated by the chemistry of the derived carbene and this is no less the case with $\alpha$-diazo phosphonates. The initial importance of phosphoryl-diazoalkanes stemmed firstly from the discovery that the phosphoryl group could be easily introduced into a compound through the carbene chemistry of the parent diazo compound and secondly that the carbenes themselves often readily underwent hydride, allyl, aryl and acyl shifts leading to useful rearranged phosphorylated alkenes.

More recently, work involving these compounds has concentrated more on their (a) transition metal catalysed decompositions due to the more predictable nature of the resulting carbenoid over the carbene generated under photolytic or thermal conditions (Section 1.4) and (b) on the base induced reactions of dialkyl diazomethylphosphonates (DAMP) with carbonyl compounds, leading to either alkynes or more interestingly, diazoethene and alkylidenecarbene transient intermediates, depending on the substrate choice (Section 1.3).

Professor Manfred Regitz at the University of Kaiserslautern has published a huge amount of work in the area of carbene chemistry and his review in 1975 on the
chemistry of phosphoryl carbenes serves as a good introduction to the chemistry of 
α-diazo phosphonate carbenes and phosphorylated carbenes in general. Information 
on all aspects of diazo chemistry can also be obtained from his book (with G. Maas) 
"Diazocompounds-Properties and Synthesis." The aim of this review is therefore to summarise the main aspects of advances made 
in the chemistry of α-diazo phosphonates since 1975 and hopefully give some feel 
for the synthetic scope of reactions involving these types of compound.

The chapter is split into four sections- the first section (1.2) will cover methods 
for the synthesis of α-diazo phosphonates and discuss some electrophilic substitution 
reactions. The second section (1.3) will deal with the reactions of dialkyl diazo-
methylphosphonate (DAMP) with carbonyl compounds in the presence of base. The 
third section (1.4) will deal with the decomposition of α-diazo phosphonates in the 
presence of transition metal salts and the final fourth section (1.5) will deal with 
the photolysis reactions of some α-diazo phosphonates and closely related 
derivatives.

1.2. Preparative Routes to α-Diazo Phosphonates and Some 
Electrophilic Diazooalkane Substitution Reactions

Scheme 1.
There are five general routes leading to the formation of α-diazo phosphoryl compounds and all of these can be applied to the synthesis of α-diazo phosphonates (Methods A-E) (Scheme 1).

1.2.1 Method A Diazotisation of Amines

This was the method by which Curtius synthesised the first aliphatic diazo compound, ethyl diazoacetate. The method has rather limited scope and only the simplest α-diazo phosphonates are accessible by it; for example, dimethyl diazomethylphosphonate (DAMP) (5) can be prepared in 46% yield from the amine (4) (Scheme 2).

Scheme 2.

1.2.2 Method B The Bamford-Stevens Reaction

This reaction is a very versatile method for converting carbonyl compounds into diazo compounds in general and has very wide scope for the synthesis of α-diazo phosphonates and α-diazo phosphinates. The starting materials for this reaction are α-oxophosphoryl compounds which are accessible by means of the Michaelis-Arbusov reaction between trialkyl phosphites and acyl chlorides (Scheme 3). These are converted into tosyl hydrazones using tosyl hydrazide and then cleaved by bases to yield the respective α-diazo phosphonate (Scheme 3).

Scheme 3.
1.2.3 Method C The Diazo Transfer Reaction

This method has almost supplanted all the other methodologies for forming stable diazo compounds, especially those flanked by two electron withdrawing groups. The method involves the transfer of a N₂ group from a transfer agent (usually an azide) to the carbanion of the precursor, hence the requirement for at least one α-electron withdrawing group. For example, reaction of the phosphonate (6) with tosyl azide using potassium hydride as base, afforded the α-diazo phosphonate (7) in 70% yield⁷ and the phosphonate (8) was converted into its diazo derivative (9) in the presence of tosyl azide and piperidine in 78% yield (Scheme 4).⁸ This last example highlights the fact that mild bases are often sufficient to effect the transformation.

Scheme 4.

\[
\begin{align*}
\text{MeO} & \quad \text{P} \quad \text{O} \quad \text{NMe}_2 \quad \xrightarrow{TosN_3, KH} \quad \text{MeO} & \quad \text{P} \quad \text{O} \quad \text{NMe}_2 \\
(6) & \quad \xrightarrow{\text{THF, 0°C}} & \quad \xrightarrow{\text{TosN}_3, \text{DCM}, \text{piperidine}} & \quad \text{MeO} & \quad \text{P} \quad \text{O} \quad \text{OEt} \quad \xrightarrow{\text{N}_2} \\
(8) & \quad & & \quad \text{MeO} & \quad \text{P} \quad \text{O} \quad \text{OEt} \\
(7) & \quad & \quad \text{MeO} & \quad \text{P} \quad \text{O} \quad \text{OEt} & \quad \xrightarrow{\text{N}_2} \\
(9) & \quad & \\
\end{align*}
\]

The active methylene precursors can generally be prepared by the Michaelis-Arbusov reaction. Numerous reagents have been successfully used as diazo transfer agents, each having certain advantages over the others. These include tosyl azide (TosN₃),⁹ mesyl azide (MsN₃),¹⁰ 2-azido-3-ethylbenzthiazolium tetrafluoroborate,¹¹ polymer bound tosyl azide,¹² 4-carboxybenzene-sulphonyl azide,¹³ 4-acetamidobenzenesulphonyl azide (p-ABSA),¹⁴ N,N-dimethylazidochloromethyleniminium chloride¹⁵ and azidotris(diethylamino)phosphonium bromide.¹⁶

1.2.4 Methods D and E C-Alkylation and Acylation

(a) Non-Metallation Reactions

Methods D and E are substitution methods in which dialkyl diazomethylphosphonate
(DAMP) (alkyl = methyl or ethyl) behaves as a nucleophile and hence the reactions are termed "electrophilic diazoalkane substitution reactions."

In this way, DAMP undergoes reactions with many aliphatic, aromatic, heteroaromatic and α, β-unsaturated aldehydes in ether, 1,2-dimethoxyethane or mixtures of both at 0 to -10°C under basic conditions to give α-diazo-β-hydroxyphosphoryl compounds in aldol-like additions (Scheme 5). As the addition is reversible, a solvent system is chosen such that the products are insoluble. The success of the addition is dependent on both the electrophilicity of the carbonyl group and the nucleophilicity of the carbanion. Therefore, reaction will usually occur with carbonyl compounds flanked by electron withdrawing groups (eg. chloro-, cyano-, and nitro-) but the reaction times and product yields reflect the limiting factors described.

Scheme 5.

Dialkyl diazomethylphosphonates react with carbonyl compounds in the presence of potassium t-butoxide to produce diazoethenes via a Wadsworth-Emmons type decomposition. The chemistry of the resulting diazoethene intermediate is dealt with in Section 1.3.

Additions to di- and tri-carbonyl compounds are relatively facile due the high electrophilicity of the reacting carbonyl groups (Scheme 6). Reactions occur with α-dicarbonyl compounds such as 1,2-indanedione, isatin, N-substituted isatins and coumaranedione with the additions occurring at the benzoyl-like carbonyl group. The reaction is facilitated by steric effects of the 3-substituents in the 1,2-diones
and by amide and ester resonance in the heterosubstituted α-dicarbonyl compounds.

Scheme 6.

\[
\begin{align*}
&\text{Scheme 6.} \\
&\text{Additions can also occur with acyl halides to give acyl substituted α-diazo phosphonates. For example, reaction with benzoyl chloride yielded benzoyl-dimethyl phosphono-diazomethane (10) in 61% yield (Scheme 7).}^{20} \text{ Reaction with terephthaloyl chloride furnished the bis-(α-diazo-β-oxophosphonate) (11) in 52% yield (Scheme 7).}^{21} \\
&\text{Scheme 7.} \\
&\text{Carbamoylation is also possible using benzoyl isocyanate, benzoyl isothiocyanate or chlorosulphonyl isocyanate (12) (Scheme 8).}^{22}
\end{align*}
\]
Dialkyl diazomethylphosphonates will also react with electron-rich olefins, like enamines, to afford alkylation products without 1,3-dipolar cycloadditions or cleavage taking place. The reactions occur without the need for base. It is believed that proton transfer from the diazo phosphonate to the β-carbon of the enamine is facilitated by the formation of hydrogen bond intermediates (Scheme 9).23

(b) Metallation Reactions

(i) Silver and Mercury Derivatives of Dialkyl Diazomethylphosphonates

The acidity of the diazomethyl hydrogen in dialkyl diazomethylphosphonates is such that direct metallation is possible using silver oxide or mercury oxide. The diazo group proves to be remarkably stable to the conditions and the resulting metallated derivatives are themselves very thermostable; the mercury diazomethyl phosphonate derivatives are even isolable. The reactions are of preparative interest since the metal can be easily exchanged for other substituents via reactions with electrophiles such as $S_N 1$ reactive halides, allyl cations and donor stabilised and Hückel aromatic cations. In these reactions the silver diazomethyl phosphonate
derivative has been used more successfully than the mercury derivative. For example, reaction with 1-bromo-2-butene afforded the substituted α-diazo phosphonate (13) in 48% yield. The mercury diazomethylphosphonate derivative reacted with bromo-triphenylmethane to furnish the substituted compound (14) in 28% yield (Scheme 10).

Scheme 10.

\[
\begin{align*}
\text{H}_2\text{P(OMe)}_2\text{N}_2 & \xrightarrow{\text{Ag}_2\text{O}} \text{Me}\text{H}_2\text{P(OMe)}_2\text{N}_2 + \text{Me}\text{H}_2\text{P(OMe)}_2\text{N}_2 \\
\text{H}_2\text{P(OMe)}_2\text{N}_2 & \xrightarrow{\text{Hg}_2\text{O}} \text{Hg}\text{H}_2\text{P(OMe)}_2\text{N}_2 \xrightarrow{\text{Ph}_3\text{CBr}} \text{Ph}_3\text{P(OMe)}_2\text{N}_2
\end{align*}
\]

(13) (14)

The silver dimethyl diazomethylphosphonate derivative has been reacted with a range of Hückel aromatic cations. Electrophilic substitution reactions with the cyclopropenylium bromide (15) at both electrophilic centres led to the formation of the diazomethylcyclopropenes (16) and (17) (Scheme 11). The analogous reaction of dimethyl diazomethylphosphonate with cyclopropenylium bromides (or perchlorates) in the presence of triethylamine furnished the same compounds in high yield as well.

Scheme 11.

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{Ag}} \text{Ph} \xrightarrow{\text{Ph}_3\text{CBr}} \text{Ph}_3\text{P(O)}\text{OMe}_2 \\
\text{Ph} & \xrightarrow{\text{t-Bu}} \text{Ph} \xrightarrow{\text{Bu-t}} \text{Bu-t}
\end{align*}
\]

(15) (16) (17)

Reaction of the silver diazomethyl phosphonate derivative with the tropylium
bromide (18) led to the formation of the diazomethylcycloheptatriene (19) (Scheme 12).\textsuperscript{25} There appeared to be no sign of the theoretical equilibrium product, norcaradiene (20), by \textsuperscript{1}H NMR, even at -90°C. Surprisingly, however, on reaction with the triazolinedione (21), the cycloadduct formed (22), was that exclusively derived from the norcaradiene rather the heptatriene (Scheme 12).\textsuperscript{25}

Scheme 12.

\[
\begin{align*}
\text{DCM, O°C} & \quad \text{[4+2]} \\
\text{75%} & \quad (22) \\
\text{92%} & \quad (19)
\end{align*}
\]

Reaction with the 7-bromotropylium bromide (23) afforded the 5-diazobenzocycloheptatriene (24) in high yield (81%) (Scheme 13).\textsuperscript{26} However, in this case, reaction with the triazolinedione (21) afforded the tetracycle (26) (64%). A mechanism was proposed involving the formation of the substituted cyclopropane (25) as an intermediate (Scheme 13).\textsuperscript{27}

The 5-diazobenzocycloheptene (27) substituted in the 7-position with a sulphide moiety could be formed in the same way as the bromo-derivative (24) (40%). This reacted rather differently, however, with the triazolinedione (21). In this case a cycloadduct (28) was formed in which the \(\alpha\)-diazo phosphonate function remained unchanged (65%) (Scheme 14).\textsuperscript{27}
Scheme 13.

\[ (23) \xrightarrow{DCM, 0^\circ C, AgCN_2PO(OMe)_2} (24) \]

\[ (23) \xrightarrow{-N_2} (25) \xrightarrow{[1,5]-ring closure} (26) \]

\[ R = PO(OMe)_2 \]
Reaction of the dichlorobenzocycloheptatriene (29) with the silver derivative of DAMP afforded the diazo-benzocycloheptatriene (30) as the major product in 75% yield. Thermolysis of this diazo-triene in the presence of copper (II) acetylacetonate led to ring expansion and the formation of benzocyclooctatriene (31), also in 75% yield (Scheme 15).28

Similarly, reaction of the benzocycloheptenylium perchlorate (32) with DAMP in the presence of triethylamine yielded the expected 5-substituted diazobenzocycloheptene (33) (35-60%). This product was found to undergo spontaneous intramolecular [4+3]-cycloaddition of the diazo diople to the 1,3-butadiene moiety of the seven membered ring to give the azo-isomers (34) in quantitative yield. On refluxing in xylene for 10-15 min, nitrogen was eliminated leading to the formation of the benzosemibullvalene (35) (100%) (Scheme 16).29
Scheme 15.

Scheme 16.
The electrophilic diazoalkane substitution reaction of the silver derivative of DAMP with 5-chloro-dibenzo-cycloheptene (36) furnished the diazo-dibenzo-cycloheptene (37) (64%). Copper (II) acetylacetonate catalysed decomposition resulted in the formation of the dibenzo-semibullvalene (38) and the dibenzo-cyclooctene (39) in yields of 71 and 9% respectively (Scheme 17).30

Scheme 17.

(ii) Lithium Derivatives of Dialkyl Diazomethylphosphonates

In the same way that dialkyl diazomethylphosphonates can be metallated with silver and mercury, they can also be metallated with lithium. This can be achieved using n-butyllithium in ether (or THF / ether) at -110°C. The resulting lithium diazomethyl phosphonate derivative (40) can be acylated, silylated (although in very poor yield) and transformed into aldol-like products on reaction with aldehydes. For
example, reaction with benzaldehyde, benzoyl bromide and chlorotriphenylsilane afforded the α-diazo phosphonates (41), (42) and (43) in yields of 45, 33 and 6%, respectively.21

Scheme 18.

![Reaction Scheme](image)

Reagents: i. n-BuLi, THF, -110°C; ii. PhCHO; H+; iii. PhCOBr; iv. Ph3SiCl

Pyrylium salts are readily attacked by nucleophiles and it was found that pyrylium tetrafluoroborates and perchlorates reacted with lithiated DAMP exclusively at the 4-position. For example, reaction with the pyrylium tetrafluoroborate (44) led to the formation of the pyran (45) (73%) (Scheme 19).31,32 These pyrans could be decomposed in the presence of a catalytic amount of allyl palladium chloride to give high yields of oxepines (46) (97%) through a ring expansion step. There was no evidence for the presence of the benzene oxide (47) by 1H NMR and Diels-Alder reactions, in this case, gave the adducts expected for an oxepine (compare Scheme 12).31,32
Scheme 19.

\[
\text{Li} = \text{PO(O\text{Me})}_2 + \text{t-BuBF}_4^- \rightarrow \text{t-BuPO(O\text{Me})}_2 \text{Me} \quad \text{(40)}
\]

\[
\text{THF/ether, -78°C} \rightarrow \text{t-BuPO(O\text{Me})}_2 \text{Me} \quad \text{(44)}
\]

\[
(\text{Allyl PdCl})_2 \text{PhH, 20°C} \rightarrow \text{t-BuPO(O\text{Me})}_2 \text{Me} \quad \text{(45)}
\]

\[
\text{t-BuPO(O\text{Me})}_2 \text{Me} \quad \text{(47)}
\]

\[
\text{t-BuPO(O\text{Me})}_2 \text{Me} \quad \text{(46)}
\]
1.3 Reactions of Dialkyl Diazomethylphosphonates

1.3.1 Reactions with Aldehydes and Ketones

In 1977, Colvin and Hamill reported a single step method for the transformation of certain aryl ketones and aldehydes into homologous alkynes (Scheme 20).\textsuperscript{33,34} The method involved the condensation of the anion of dimethyl (or diethyl) diazomethyl phosphonate (DAMP) with the carbonyl compound at -78°C.

Scheme 20.

Two possible reaction pathways were proposed (Scheme 21), both involving elimination of the dialkyl phosphate anion by analogy with the Wadsworth-Emmons modification of the Wittig reaction. One pathway (route A) involved a semi-pinacol type rearrangement to give the intermediate (48) and the other (route B) involved the formation of a diazoethene (49) followed by a Wolff rearrangement step. Colvin and Hamill themselves, favoured the route leading to the diazoethene.

Scheme 21.
The scope of this potentially useful synthetic method was significantly widened by experimental conditions developed by Gilbert and Weerasooriya. They found that by using potassium t-butoxide as base to deprotonate DAMP, THF as solvent, reaction temperatures of -78°C and longer reaction times, all aryl ketones and aldehydes could be converted into alkynes in high yield. However, even under these reaction conditions, dialkyl ketones still failed to react. Like Colvin and Hamill, Gilbert believed that the mechanism for this reaction proceeded via the formation of a diazoethene. There were two reasons for this; (a) reaction with acetone yielded a product arising from reaction with the solvent and (b) introduction of cyclohexene into the reaction mixture yielded a cyclopropane derivative. This latter observation in particular seemed to suggest the formation of a carbene, an alkylidenecarbene, via the decomposition of the diazoethene. That aldehydes and aryl ketones gave alkynes in good yield whereas dialkyl ketones did not, was explained by comparison with the behaviour of carbenes in general. The 1,2-shift of an alkyl group in the alkylidenecarbene would be expected to be relatively difficult, affording an opportunity for trapping of the carbene by solvent or added alkenes as had been observed. The corresponding shift for hydrogen or aryl would be comparatively facile. Numerous examples of the conversion of aldehydes to alkynes using the potassium t-butoxide / DAMP protocol have now appeared in the literature. For example, in Schreiber's total synthesis of FK506, the aldehyde (50) was converted to the alkyne (51) in 95% yield (Scheme 22). In another report, reaction of the 13-α-carboxaldehyde (52) obtained from forskolin with the DAMP anion furnished 14, 15-dehydroforskolin (53) in 81% yield (Scheme 23).

Scheme 22.
1.3.2 Reactions with Olefins

In a subsequent paper, Gilbert reported that the potassium t-butoxide promoted reaction of DAMP at -78°C in THF with various dialkyl ketones in the presence of an olefin (either cyclohexene or cis-4-methyl-2-pentene) led to the formation of methylenecyclopropanes. Some examples of the reported results are shown in Table 1.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Alkene</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetone</td>
<td></td>
<td>[Image]</td>
<td>58</td>
</tr>
<tr>
<td>acetone</td>
<td>[Image]</td>
<td>[Image]</td>
<td>45</td>
</tr>
<tr>
<td>cyclohexanone</td>
<td>[Image]</td>
<td>[Image]</td>
<td>70</td>
</tr>
</tbody>
</table>

Gilbert presented these results as further evidence for an intermediate diazoethene species although whether this decomposed subsequently to give an alkylidenecarbene or the ylide (54), formed by the interaction of the solvent (THF) with the
diazooethene with loss of nitrogen (Scheme 24), which behaved as the reactive intermediate was uncertain.

Scheme 24.

1.3.3 Reactions with Nucleophiles

Studies designed to elucidate the consequences of producing a diazooethene or the carbene (or carbenoid) in the presence of nucleophiles (namely alcohols and amines) were also reported by Gilbert (Scheme 25).\textsuperscript{39,40} The net transformation that occurred was the conversion of dialkyl and cyclic ketones to aldehydic enol ethers and enamines in moderate to good yields (Table 2). Even sterically hindered ketones successfully underwent the reaction. As expected, the reaction was unsuccessful when either an aldehyde or an aryl ketone was used due to the high migratory aptitudes of hydrogen and aryl relative to alkyl in the carbene species, as described previously.

Scheme 25.

Table 2.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Solvent</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclohexanone</td>
<td>CH\textsubscript{3}OH</td>
<td>\includegraphics[width=0.3\textwidth]{cyclohexanone.png}</td>
<td>58</td>
</tr>
</tbody>
</table>
The analogous potassium t-butoxide promoted reaction of DAMP with aliphatic ketones in the presence of allylic alcohols afforded aldehydic allyl vinyl ethers in moderate to high yields (Scheme 26, Table 3). Only a small percentage (ca. 5%) of the product arising from the theoretically competing cyclopropanation of the carbene was observed.

Scheme 26.

Table 3.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Alcohol</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclohexanone</td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>cyclohexanone</td>
<td></td>
<td></td>
<td>56</td>
</tr>
</tbody>
</table>
Similarly, the reaction with allyl amines (55) afforded allylic enamines (56). These enamines underwent [3,3]-sigmatropic rearrangement upon alkylation and could be converted to iminium salts on heating at 80°C. These iminium salts could then be hydrolysed to aldehydes (57, Scheme 27 and Table 4).

**Scheme 27.**

\[
\begin{align*}
R\text{O} + \text{MeNHCH}_2\text{CH=CH}_2 &\quad \xrightarrow{\text{THF, -78°C}} \quad \text{R}_2\text{C=CHN(Me)}\text{CH}_2\text{CH=CH}_2 \\
(55) &\quad \text{PhH} / \text{Me}_2\text{SO}_4 \quad 80°C \quad 3h \\
&\quad \text{H}_2\text{C=CHCH}_2\text{C(R)}_2\text{CHO} \quad [\text{R}_2\text{C=CHN}^+(\text{Me})_2\text{CH}_2\text{CH=CH}_2]
\end{align*}
\]

**Table 4.**

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Amine</th>
<th>Allyl Enamine (%)</th>
<th>Aldehyde (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Cyclopentanone</td>
<td>(55)</td>
<td>63</td>
<td>78</td>
</tr>
<tr>
<td>b Cyclohexanone</td>
<td>(55)</td>
<td>66</td>
<td>77</td>
</tr>
<tr>
<td>c 4-t-Bu-cyclohexanone</td>
<td>(55)</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td>d 5-Nonanone</td>
<td>(55)</td>
<td>70</td>
<td>84</td>
</tr>
<tr>
<td>e Cyclooctanone</td>
<td>(55)</td>
<td>82</td>
<td>76</td>
</tr>
</tbody>
</table>
1.3.4 Intramolecular C-H Insertion Reactions

All the reactions of the diazoethenes derived from aliphatic ketones discussed so far have been intermolecular in type. Gilbert and co-workers have also investigated the intramolecular 1,5-insertion reactions of the diazoethene into carbon-hydrogen bonds.\(^{43,44}\)

Treatment of a mixture of potassium t-butoxide and DAMP at \(-78^\circ C\) with the ketones (58) yielded the cyclopentenes (59) in modest yields (Scheme 28).

Scheme 28.

\[
\begin{align*}
\text{R}_1^1\text{H} & \quad \text{i} \quad \begin{array}{c}
\text{R}_1^1\text{H} \\
\text{CN}_2 \\
\text{R}_2^2 \\
\text{R}_3^3
\end{array} \\
\rightarrow \\
\text{R}_1^1\text{H} \\
\text{C} \\
\text{C} \\
\text{R}_2^2 \\
\text{R}_3^3
\end{align*}
\]

(a) \(R_1^1 = \text{Me}, R_2^2 = \text{H}, R_3^3 = \text{n-Bu} (33\%)\)

(b) \(R_1^1 = \text{Et}, R_2^2 = \text{H}, R_3^3 = \text{n-pentyl} (36\%)\)

*Reagents*: i. DAMP, potassium t-butoxide, \(-78^\circ C\), THF.

The selectivity of the insertion into various types of C-H bond was measured by analysing the cyclopentene formed by treatment of unsymmetrical substituted dialkylketones (60a-c) under potassium t-butoxide / DAMP conditions (Scheme 29, Table 5).

Scheme 29.

\[
\begin{align*}
\text{R}_1^1 \quad \text{R}_2^2 \quad \text{H} \quad \text{R}_3^3 & \quad \text{DAMP} \\
\rightarrow \\
\text{R}_1^1 \quad \text{R}_2^2 \quad \text{H} \quad \text{R}_3^3 & \quad \text{t-BuO}^-\text{K}^+\text{, -78^\circ C}
\end{align*}
\]

(a) \(R_1^1 = \text{Me}, R_2^2 = R_3^3 = \text{H}\); (b) \(R_1^1 = R_2^2 = R_3^3 = \text{Me}\); (c) \(R_1^1 = \text{Ph}, R_2^2 = \text{H}, R_3^3 = \text{Me}\)
Table 5.

<table>
<thead>
<tr>
<th>Competition</th>
<th>Substrate</th>
<th>Ratio (61:62)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° vs 2°</td>
<td>(60a)</td>
<td>1:0</td>
<td>22</td>
</tr>
<tr>
<td>2° vs 3°</td>
<td>(60b)</td>
<td>9.3:1</td>
<td>85</td>
</tr>
<tr>
<td>2° (benzylic) vs 2°</td>
<td>(60c)</td>
<td>7.5:1</td>
<td>95</td>
</tr>
</tbody>
</table>

Thus, the relative order of reactivity for C-H insertion increased in the order:

primary << secondary < secondary (benzylic) < tertiary

The observed selectivity can be ascribed to the differences in bond dissociation energies of the various C-H bonds.

ΔΔG^v values obtained in these experiments provided further evidence for the formation of an alkylidenecarbene from the decomposition of the intermediate diazoethene species.

The formation of nitrogen heterocycles via the same route was also possible. A 1,5-C-H insertion of the alkylidenecarbene derived from the pyruvamides (63), afforded the 3-pyrrol-2-ones (64) and (65) in good yields. Another product, identified as a 2-butynamide (66) originating from a 1,2-shift of the carbene, was also consistently formed (Scheme 30).44,45 Some of the results are summarised in Table 6.

Scheme 30.
Table 6.

<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>Yield (%)</th>
<th>(64):(65)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>50</td>
<td>/</td>
<td>23</td>
</tr>
<tr>
<td>H</td>
<td>n-Pr</td>
<td>H</td>
<td>43</td>
<td>70:30</td>
<td>20</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>56</td>
<td>80:20</td>
<td>16</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>67</td>
<td>/</td>
<td>31</td>
</tr>
</tbody>
</table>

In contrast to the carbocycle formation reaction where no insertion into primary C-H bonds was observed, it was found that insertion occurred readily into primary C-H bonds. The results even seemed to suggest that primary C-H bonds were the most reactive. Additionally, it was found that intramolecular C-H insertion occurred to the exclusion of intermolecular O-H insertion. This again was in stark contrast to the carbocycle formation reaction. These two results clearly pointed to the important role played by the nitrogen atom in the formation of the pyrrolones; that is, the heteroatom activates \( \alpha \)-carbon-hydrogen bonds. The activating effect of a heteroatom on the lability of an \( \alpha \)-C-H bond towards carbone insertion is further demonstrated in the following two examples.

The formation of 5-membered ring oxygen heterocycles have also been reported using the potassium t-butoxide / DAMP protocol. In 1982, Hauske\textsuperscript{46} reported the formation of the erythromycin A derivative (70) in 84\% yield from the ketone (69) (Scheme 32) and more recently workers in Norway have reported the formation of furans (68) from \( \alpha, \alpha \)-dimethoxy ketones (67) (Scheme 31).\textsuperscript{47}

Scheme 31.

\[
\begin{align*}
R^1 &\quad \quad R^2 &\quad \quad R^3
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 = &\quad \text{MeO} &\quad \text{O}\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 &\quad \text{= -(CH}_2\text{)}_4\text{= (72\%);} &\quad \text{R}^1 &\quad \text{= -(CH}_2\text{)}_3\text{= (70\%);} &\quad \text{R}^1 &\quad \text{= Bu , R}^1 &\quad \text{= H (67\%);} &\quad \text{R}^1 &\quad \text{= Ph , R}^1 &\quad \text{= H (75\%)}
\end{align*}
\]
Reagents: i. DAMP, potassium t-butoxide, THF, -40°C

Scheme 32.

Reagents: i. DAMP, potassium t-butoxide, THF, -78°C

Gilbert has also reported on a ring expansion reaction of the cyclobutylidene-carbenes. Thus, the base promoted reaction of cyclobutanone (71) and DAMP in 1-butanol at 0°C afforded the butyloxycyclopentene (72) in 43% yield.

Two pathways were proposed to explain the results (Scheme 33). They involved either chemical equivalency of the vinylic carbons in the form of cyclopentyne (route A) or non-equivalency of these atoms at the time of interaction with 1-butanol (route B). ^13C labelling experiments appeared to suggest that the reaction actually proceeds via the formation of cyclopentyne as the precursor to the cyclopentene i.e. via route A.
Reagents: DAMP, potassium t-butoxide, 1-butanol, 0°C

Most recently Gilbert has reported on the formation of cyclohepta[b]pyrrol-2-ones such as (75) (Scheme 34) using the potassium t-butoxide / DAMP protocol. 49, 50 2-Oxopropanamides (73) reacted to yield heterocycles (75) in good yields (63-82%). The heterocycles are believed to arise from the intramolecular cycloaddition reaction of the carbene to the aromatic ring to give norcaradiene type intermediates (74). Subsequent electrocyclic reaction provides the observed product (Scheme 34).

Scheme 34.
Reagents: i. DAMP, potassium t-butoxide, MeCN, 0°C.

In just one example, products arising from a 1,5-C-H insertion into the N-methyl group and a 1,2- Wolff type shift were observed, although in very low yield.

1.3.5 Routes to Vinyl Cyclopropanes

Motherwell and co-workers have successfully applied the potassium t-butoxide / DAMP protocol to the preparation of 3-phenylselenoalk-1-enylidene carbenes (77). These were trapped to give alkylidene-cyclopropane adducts which were subjected to either [1,3]-allylselenide rearrangements or oxidative selenoxide [2,3]-sigmatropic rearrangements to produce 1-heterosubstituted 1-vinylcyclopropanes (79) and (80) (Scheme 35). The cyclohexanone (76) could be converted to the propanol (79) in 58% yield or converted to the vinyl cyclopropane (81) in 53% yield.51,52

Scheme 35.

Reagents: i. DAMP, potassium t-butoxide; ii. cyclohexene; iii. H2O2.

The formation of arylidene cyclopropanes (84, Scheme 36) has also been reported. Compounds of this type cannot not be prepared in the usual way by addition of an
olefin to an substituted vinylidene carbene due to the competing and precluding Wolff rearrangement as discussed previously. The method involves the Wadsworth-Emmons olefination reaction of an intermediate cyclopropyl phosphonate (82) formed by the cyclopropanation reaction of olefins with DAMP (Scheme 36).53

Scheme 36.

\[
\begin{align*}
&\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\n\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\text{R} &\text{R}^1 &\text{R}^1 &\text{PO(OEt)}_2 &\text{R} &\text{R}^1 &\text{PO(OEt)}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{Reagents: i. DAMP, catalyst MLn; ii. base (NaH or n-BuLi), ArR}^2\text{C}=\text{O}
\end{align*}
\]

Cyclopropanation reactions leading to substrates such as (82) had been previously reported by Seyferth54 using copper metal as the catalyst. However, in the reaction, large amounts of carbene dimerisation products (83) were additionally obtained. Motherwell found that the use of rhodium (II) acetate and rhodium (II) pivalate initiated smooth decomposition of DAMP at room temperature. However, rapid deactivation of these catalysts was observed with these catalysts and repeated additions of fresh catalyst were necesssary to drive the reaction to completion. Copper (I) triflate was found, however, to be a particularly effective catalyst for this reaction. The efficiency may be due to the ability of the copper (I) triflate catalyst to not only coordinate with olefins but to also form the the copper carbenoid and hence bring the two reacting species into close proximity on the metal itself.

Various olefins were successfully cyclopropanated using the procedure. Dihydropyran was converted to the cyclopropyl phosphonate in 71% yield whilst the protected olefin (85) was converted in 73% yield (86) (Scheme 37).53 The procedure failed however when using olefins containing an aldehydic function- hence the necessity for the acetal protecting group in (85).
The subsequent Wadsworth-Emmons olefination step (cf. Scheme 36) yielded the strained tri- or tetra-substituted double bond of the arylidene cyclopropane system in good yields. For example, the cyclopropanes (87), (88) and (89) (Scheme 38) were prepared in yields of 63, 81 and 75% respectively from the phosphonates already described (Scheme 37).

Optimal reaction conditions for this reaction were found to be substrate dependent. In some cases reaction of the phosphonates (82) using n-butyllithium as base furnished olefins directly. Sometimes formation of the olefin was best achieved through isolation of the corresponding β-hydroxy-phosphonate and subsequent exchange of the lithium counterion for sodium (see Scheme 39).

Intramolecular palladium (0) catalysed cycloadditions of diphenylmethylenecyclopropanes (90) with olefinic and acetylenic acceptors have also been successfully carried out providing a regiocontrolled route to highly functionalised bicyclo-
[3.3.0]octane derivatives (Scheme 39).\textsuperscript{55} Thus, the enone (90) prepared using the aryldiene cyclopropane formation method just discussed, reacted with bis-(dibenzylideneacetone) palladium in the presence of tris(isopropyl) phosphite to afford the desired bicyclic ketone (91) in 47%.

Scheme 39.

\[
\begin{align*}
&\text{CHO} \\
&\text{i, ii} \quad \rightarrow \\
&\text{MeO} \quad \text{PO(OEt)}_2 \\
&\text{MeO} \quad \text{MeO} \\
&\text{Ph} \quad \text{Ph} \\
&\text{Ph} \quad \text{Ph} \\
&\text{Ph} \quad \text{Ph} \\
&\text{Ph} \\
&\text{Ph} \\
\end{align*}
\]

Reagents: i. \text{MeOH, Amberlyst 15}; ii. DAMP, copper (I) triflate, DCM, 0°C; iii. \text{n-BuLi, THF, -78°C, Ph}_2\text{C}=\text{O, AcOH}; iv. \text{NaH, DMF, 90°C}; v. \text{HCl (aq)}; vi. vinyl magnesium bromide, Et}_2\text{O, 0°C}; vii. PCC, DCM; viii. Pd(0), P(Oi-Pr)_3, Δ.

Cyclisation of the acetylenic ester (92) under similar conditions afforded the two bicyclic esters (93) and (94) as a 1:1 ratio in 38 and 41% respectively (Scheme 40). These results clearly demonstrate the controlled and predictable regioselectivity obtained in these cycloaddition reactions.\textsuperscript{55}

Scheme 40.
1.3.6 Tin (II) Chloride Catalysed Decompositions

Holmquist and Roscamp have reported that α-diazo phosphonates such as diethyl diazomethylphosphonate (DAMP) add to aldehydes in the presence of a catalytic amount of tin (II) chloride to yield β-keto phosphonates (Scheme 41).56 An analogous process occurs with α-diazo ketones, α-diazo sulphones and α-diazo phosphine oxides, furnishing β-keto esters, β-keto sulphones and β-keto phosphine oxides, respectively. Reaction of diethyl diazomethylphosphonate with the aldehydes (95), (96) and (97) afforded the β-keto phosphonates (98), (99) and (100) in yields of 75, 56 and 5%, respectively (Scheme 41). The yields reflect the general observation that reactions with primary aldehydes proceed in higher yields than those of secondary aldehydes whilst reactions with tertiary aldehydes proceed in poor yield.

Scheme 41.

Reagents: i. SnCl₂ (0.2 equiv.), DCM, rt.
1.4 Transition Metal Catalysed Decompositions of α-Diazo Phosphonates

Since the discovery over eighty years ago that copper metal and copper salts promote the decomposition of diazo compounds,\textsuperscript{57} reactions of this type have been the focus of a great deal of attention. This attention has been largely spurred on by the discovery in 1973, by Teyssié and Hubert,\textsuperscript{58} that rhodium (II) acetate is a particularly efficient catalyst for this decomposition. As a result, the procedure has now become a standard technique in organic synthesis, particularly for cyclopropane and cyclopentanone formation\textsuperscript{59} and the recent development of chiral rhodium based catalysts has further increased the scope and potential of these reactions.\textsuperscript{60}

The decomposition is believed to proceed via the formation of a rhodium carbenoid intermediate (carbenoid = metal bound carbene)\textsuperscript{61} rather than via the formation of the free carbene itself. The carbenoid retains all the properties of the free carbene. However, due to its lower inherent energy and hence reactivity, it reacts in a much milder, more selective and more predictable way. In addition, the generation of the carbenoid is comparatively much milder - thermally and photochemically generated carbenes on the other hand often give products arising from rearrangements and dimerisation. Even so, the highly transient nature of the carbenoid species has so far made it impossible to characterise its structure although stable tungsten, chromium and molybdenum analogues provide some evidence that this picture is correct (for further discussion, see Chapter 2).

The reactions of these rhodium carbenoids are essentially those of the free carbene so reactions of α-diazo ketones can result in four possible types of reaction.

a. Reactions with nucleophiles (insertions into a R-Nu bonds)
b. Insertion into C-H bonds
c. Cyclopropanation (1,2-cycloaddition) and
d. Rearrangements (for example, the 1,2-H shift and the Wolff rearrangement).

In contrast to the vast body of work on α-diazo carbonyl compounds, the rhodium
acetate catalysed decompositions of α-diazo phosphonates have been much less widely studied. This was surprising due to the obvious opportunity for further synthetic elaboration of products afforded by the presence of the phosphonate group through the Wadsworth-Emmons olefination reaction.

1.4.1 Insertions into O-H Bonds

(i) Intermolecular O-H Insertions

Paquet and Sinay used the rhodium (II) catalysed O-H insertion reaction of dimethyl phosphono-methoxy carbonyl-diazomethane to functionalise the primary hydroxyl group of a protected glucose derivative (101). The reaction yielded the phosphonate (102) in 80% yield as a mixture of diastereomers (Scheme 42). This phosphonate was then successfully subjected to the Wadsworth-Emmons olefination reaction with a functionalised aldehyde to give the enol ether required by the authors in good yield.

Scheme 42.

Other similar rhodium mediated O-H insertion reactions have been reported. In a paper relating to a total synthesis of (-)-chorismic acid and (-)-shikimic acid, Berchtold described an O-H insertion reaction of the cyclohexenol (103) with dimethyl phosphono-methoxy carbonyl-diazomethane, catalysed by rhodium (II) octanoate. This afforded the alkoxyphosphono ester (104) in 60% yield. This ester was then converted to the monoanion and quenched with gaseous formaldehyde yielding the allyl ether (105) in 41% yield over the two steps from the cyclohexene (Scheme 43).
Ganem reported that diethyl phosphono-ethoxy carbonyl-diazomethane inserted into cyclohexenol in the presence of rhodium (II) acetate to afford the alkoxyphosphonoester (106) in 65% yield (Scheme 44). The reaction of diethyl phosphono-diethyl phosphono-diazomethane, [bis-(diethyl phosphono)-diazomethane], with cyclohexenol, catalysed by rhodium (II) acetate was also investigated (Scheme 44).65,66

Scheme 44.

Reagents: i. MeO₂C(CN₂)PO(OEt)₂, Rh₂(n-C₇H₁₅CO₂)₄, PhH, reflux; ii. LiN(SiMe₃), H₂CO, THF, -78°C.

In refluxing benzene, the reaction was found to be extremely slow and although some of the desired product (107) could be isolated after 14 h (no yield reported), significant amounts of starting material were also recovered. No cyclopropane or other phosphonate containing by-products were detected in the reaction mixture and no catalyst poisoning or decomposition was observed. Similar results were obtained using the more soluble catalyst, rhodium (II) octanoate. These findings contrast with the much more rapid insertion reactions of most ketone or ester stabilised diazoalkanes.

When the rhodium catalyst was omitted in control experiments in the case of the
diazoo bis-phosphonate, only starting materials were recovered and no product whatsoever was detected. Therefore, the catalyst must have been responsible for the observed decomposition. On the basis of these results, the authors inferred that the formation of the rhodium carbenoid species derived from the diazo bis-phosphonate must be occurring only very slowly and as a consequence, the insertion step into the cyclohexenol O-H bond must also be occurring very slowly. Optimal yields were recorded using refluxing toluene conditions (36 h) and rhodium (II) acetate. Under these conditions, the allyl ether was formed in 48% yield (corrected to 72% for recovered starting material). A subsequent Wadsworth-Emmons olefination reaction with gaseous formaldehyde yielded the corresponding enol ether (108) in 78% yield (Scheme 45).66

Scheme 45.

\[
\begin{array}{c}
\text{LDA, THF, 0°C} \\
\text{H}_2\text{CO(g)}
\end{array}
\]

\(107\) \quad \text{PO(OEt)}_2

\(108\) \quad \text{PO(OEt)}_2

\(108\) \quad \text{PO(OEt)}_2

(ii) Intramolecular O-H Insertions

Two examples of an intramolecular rhodium carbenoid O-H insertion reaction with an α-diazo phosphonate have been reported.67,68 The diazo alcohols (109) and (110) (Scheme 46) were prepared by reaction of lithium diethyl methylphosphonate with valerolactone and undecanoic δ-lactone respectively, followed by diazo transfer with mesyl azide. When heated in boiling benzene in the presence of a catalytic amount of rhodium (II) acetate, these diazo alcohols underwent smooth cyclisation to give the 3-oxooxepanes (111) and (112) in good yields (52 and 54% respectively).

The 2-diethyl phosphono 3-oxooxepane (112) was subjected to several Wadsworth-Emmons olefination reactions with a range of aldehydes to give the oxepanones (113) (Scheme 46) in good yields and as largely the Z isomer (>90%).
Scheme 46.

\[
\begin{align*}
R^1 = H & \quad (109) \quad R^1 = n-C_6H_{13} & \quad (110) \\
R^1 = H & \quad (111) \quad R^1 = n-C_6H_{13} & \quad (112)
\end{align*}
\]

1.4.2 Insertions into N-H bonds

In general, insertion reactions into lactam N-H bonds are very facile and the reason for this is believed to lie in the decreased conformational flexibility of the 4-(γ-diazo-β-carbonyl) substituted 2-azetidinone over the alicyclic amide. The lower entropy of the molecule consequently favours cyclisation. In addition, the lactam nitrogen atom has more nucleophilic character than a normal amide nitrogen atom.

Scheme 47.

Treatment of the α-diazo phosphonate (114) (Scheme 47), prepared from reaction of a functionalised azetidinone using lithium methyl dimethyl phosphonate or the dianion of dimethyl 2-oxopropylphosphonate, with a catalytic amount of rhodium (II) acetate in refluxing dichloromethane (or benzene) afforded the 3-phosphonate
carbapenems (115) in yields of 60-90% as a single diastereomer- the phosphono group being in the α-orientation (Scheme 47).69,70

1.4.3 Insertion into S-R Bonds

The intermolecular reactions of sulphides with α-diazo carbonyl compounds catalysed by copper and rhodium salts are well documented although only a single reference relating to the use of α-diazo phosphonates in the analogous reaction could be found.

The common intermediate in all reactions is a sulphonium ylide derived by attack of the sulphur atom on the carbenoid. Subsequent symmetry allowed [2,3]-shifts are facile.

The rhodium (II) acetate mediated decomposition of diethyl phosphono-ethoxy carbonyl-diazomethane with the 4-thioazetidinone (116) yielded the phosphono substituted, chain extended azetidinone (117) in 58% yield (Scheme 48).71

Scheme 48.

\[
\begin{align*}
\text{SPh} & \quad \text{i. EtO}_2\text{C(CN}_2\text{)PO(OEt)}_2, \text{Rh}_2(\text{OAc})_4 \\
& \quad \begin{array}{c}
\text{PhS} \\
\text{CH}_2\text{CO}_2\text{Bu} \\
\text{N} \\
\end{array} \quad \begin{array}{c}
\text{PO(OEt)}_2 \\
\text{Ph} \\
\text{CH}_2\text{CO}_2\text{Bu} \\
\text{N} \\
\end{array} \quad \begin{array}{c}
\text{PhS} \\
\text{CO}_2\text{Et} \\
\text{PO(OEt)}_2 \\
\text{CH}_2\text{CO}_2\text{Bu} \\
\end{array}
\end{align*}
\]

Reagents: i. EtO\textsubscript{2}C(CN\textsubscript{2})PO(OEt)\textsubscript{2}, Rh\textsubscript{2}(OAc)\textsubscript{4}

Takano has reported the formation of 2-(acylmethylene)-tetrahydofuran derivatives (119) in good yields via the rhodium (II) acetate catalysed reaction of various diazo compounds with (R)-5-(benzyloxymethyl)-tetrahydro-2-furanthione (118).72 Refluxing the thiolactone (118) (formed by reaction of the lactone with Lawesson reagent) in toluene with a mixture of rhodium (II) acetate and diethyl phosphono-ethoxy carbonyl-diazomethane for 40 min afforded the tetrahydrofuran (119) in 96% yield. The mechanistic pathway suggested by the
authors is as shown (Scheme 49). The thioketone by-product (120) however was not observed.

Scheme 49.

\[
\begin{align*}
(118) & \quad \xrightarrow{i} \quad (119) \\
\text{Reagents: i. } & \text{EtO}_2\text{C(CN}_2\text{)PO(OEt)}_2, \text{Rh}_2(\text{OAc})_4, \text{PhMe, } \Delta
\end{align*}
\]

1.4.4 Insertions into C-H Bonds

The use of rhodium (II) acetate for inter- and intramolecular C-H insertions is well known and the intramolecular reaction leading to cyclisation has proved to be of great value in ring, particularly cyclopentanone, synthesis.

Taber discovered that aliphatic α-diazo-β-ketoesters underwent selective γ-C-H insertion reactions with rhodium (II) acetate, to give cyclopentanones in high yield\(^73,74\). Workers in France and Poland have reported similar results using α-diazo-β-ketophosphonates\(^75,76\).

The α-diazo phosphonates (121) were prepared by reaction of the dianion of diethyl 2-oxopropylphosphonate with various alkyl halides followed by diazo transfer. Treatment with rhodium (II) acetate in refluxing dichloromethane yielded α-
phosphorylated cyclopentanones (122) in yields of 33-70% (Scheme 50).75

Scheme 50.

\[
\begin{array}{c}
\text{PO(OEt)}_2 \\
\text{Rh}_2(\text{OAc})_4 \\
\text{DCM} \\
\end{array}
\]

\[
(121)
\]

(1) \(R^1 = H, R^2 = H\); (2) \(R^1 = H, R^2 = \text{Me}\);
(3) \(R^1 = H, R^2 = \text{n-Bu}\); (4) \(R^1 = /, R^2 = =\text{CH}_2\)

Deviations of yield from the quantitative were ascribed as being due in part to a competing Wolff-like rearrangement reaction (Scheme 51). This rearrangement had not been reported as being observed in the cyclisation of \(\alpha\)-diazo \(\beta\)-keto esters.

Scheme 51.

\[
\begin{array}{c}
\text{Z=PO(OEt)}_2 (67\%) \\
\text{Z=Ph}_2\text{PO} (50\%) \\
\end{array}
\]

\[
(124)
\]

The rearrangement was demonstrated by adding ethanol just before the usual work up during the rhodium (II) catalysed decomposition of the \(\alpha\)-diazo phosphonate (123, \(Z =\text{PO(OEt)}_2\)). The \(\alpha\)-substituted phosphonoacetate (125) was obtained in 30% yield as well as the phosphorylated cyclopentanone (67%) (124). In the case of the \(\alpha\)-diazo phosphine oxide (123, \(Z=\text{Ph}_2\text{PO}\)), the yield of "Wolff rearrangement" product was 45% compared to a 50% yield of the cyclopentanone product (\(Z=\text{Ph}_2\text{PO}\)).
The notable differences in behaviour between α-diazo phosphonates and α-diazo esters in these cyclisation reactions (namely lower yields, reflux versus room temperature reaction conditions and the Wolff-like rearrangement) were rationalised in terms of electronic, steric and kinetic effects. The bulky phosphonate group being less electron withdrawing than its carbonyl counterpart renders the rhodium carbenoid intermediate less electrophilic allowing competition between the Wolff rearrangement and the cyclisation to take place.

A subsequent Wadsworth-Emmons olefination reaction involving the cyclopentanone (126) with paraformaldehyde afforded the cyclopentanone (127) in 53% yield (Scheme 52).75

Scheme 52.

In an analogous fashion, Polish workers successfully prepared the antibiotics methylenomycin B (129) and sarkomycin (131) from the α-diazo-β-keto phosphonates (128) and (130) in overall yields of 24 and 9%, respectively (Scheme 53).76,77

Scheme 53.
Reagents: i. $\text{Rh}_2(\text{OAc})_4$, DCM, reflux; ii. NaH, $\text{H}_2\text{CO(g)}$

1.4.5 Insertions into C=C Bonds

Intramolecular cyclopropanations of olefinic $\alpha$-diazoketones and $\alpha$-diazoesters have been widely used in organic synthesis and the tandem cyclopropanation/opening of the resulting electrophilic cyclopropane has been exploited in natural product synthesis (Scheme 54).\textsuperscript{78}

Scheme 54.

![Scheme 54 diagram]

The rate of step (2) is enhanced when an electron withdrawing substituent (Z) is present. An ester group had almost invariably been the substituent of choice. Vandewalle has reported intramolecular cyclopropanation reactions of various $\alpha$-diazo phosphonates catalysed by copper powder.\textsuperscript{79} Addition of the $\alpha$-diazo phosphonate (132) to a suspension of copper powder in refluxing cyclohexane afforded the cyclopropane (133) in 63% yield (Scheme 55). Surprisingly, rhodium (II) acetate was ineffective in catalysing the transformation, as was copper (II) acetylacetonate.

Scheme 55.

![Scheme 55 diagram]

The cyclopropane ring of the cyclopentanone (134) could easily be opened with dimethyl lithiocuprate yielding the substituted cyclopentanone (135) in 90% yield.

50
(Scheme 56).

Scheme 56.

\[
\begin{align*}
\text{Reagents: i. } & \text{Cu powder, cyclohexane, reflux; ii. } \text{Me}_2\text{CuLi, Et}_2\text{O} \\
\end{align*}
\]
1.5 Some Photochemical Reactions of α-Diazo Phosphonates

Most of the work in the literature relating to the reactions of diazo compounds, in general, is concerned with their photochemical reactions. Irradiation with light at 250-500 nm leads to three different pathways depending on the structure and the substitution pattern of the respective diazo compound. These pathways are:

a. reversible rearrangement leading to the cyclic valence isomer: a diazirine
b. nitrogen elimination leading to a carbene
c. rearrangement with loss of nitrogen leading to ketenes or pseudo-ketene reactive intermediates.

By far the main preparative interest is the generation of carbenes (pathway b) and their subsequent reactions. Much of the work involving the photochemistry of α-diazo phosphonates is covered by the Regitz review of 1975 and the work discussed here post-dates that review.2

In 1979, Japanese workers reported that the reactions of phosphorylcarbenes, photolytically generated in alcohols, appeared to be strongly temperature dependent.80 One of the model reactions they studied was the photolysis of dimethyl α-diazobenzyl phosphonate (136) in various alcohols (Scheme 57).

Scheme 57.

\[
\begin{align*}
\text{Ph} & \quad \text{N}_2 \quad \text{P} \quad \text{O} \quad \text{OMe} \\
& \quad \text{hv, ROH} \\
\text{OMe} & \quad \text{O} \quad \text{OMe} \\
\text{Ph} & \quad \text{P} \quad \text{O} \quad \text{OMe} \\
\text{MeOH} & \quad \text{EtOH} \text{ or } \text{i-PrOH} \\
\end{align*}
\]

Photolysis in methanol at room temperature yielded the insertion product (137) in 70% yield with a small amount of the reduced product (<3%) (138). Photolysis at -196°C in a matrix of methanol, however, afforded a 70% yield of the alcohol (139) arising from insertion of the phosphorylcarbene into the C-H bond of methanol plus a 22% yield of the reduction and insertion products (137) and (138). Similar large increases in the yield of C-H insertion product at the expense
of the O-H insertion product were observed on photolysis of the α-diazo phosphonate (136) in frozen ethanol and isopropanol matrices.

Additional photolysis experiments showed that as the temperature decreased the yield of the O-H insertion product gradually decreased (particularly with ethanol and isopropanol) whilst the yield of reduction product increased. Dramatic increases in yield of the C-H insertion product were only observed when the reaction phase was changed from liquid to solid i.e. the photolysis was carried out in a frozen matrix at -196°C.

It had been previously proposed that the O-H insertion reaction of carbenes is the characteristic reaction of singlet arylcarbenes\textsuperscript{81,82} so it was suggested that the ether (137) was derived from the singlet phosphorylcarbene of dimethyl α-diazobenzyl phosphonate (136) on photolysis. Triplet arylcarbenes on the other hand, are expected to abstract hydrogen from the C-H bond of alcohols to give radical pairs which in turn undergo three competing reactions (a) recombination to the insertion product (b) abstraction of a second hydrogen to give the reduction product and (c) dimerisation to a radical dimeric product (Scheme 58).\textsuperscript{81,82}

Scheme 58.

\[
\begin{align*}
\text{Ar}_2\text{CN}_2 & \xrightarrow{\text{hv}} \left[\text{Ar}_2\text{C}^+\right] \quad \text{MeOH} \rightarrow \text{Ar}_2\text{CHOME} \\
\left[\text{Ar}_2\text{C}^+\right] & \quad \text{MeOH} \rightarrow \left[\text{Ar}_2\text{C}^+ + \text{CH}_2\text{OH}\right] \\
\left[\text{Ar}_2\text{C}^+\right] & \rightarrow \left[\text{Ar}_2\text{CH}^+ + \text{CH}_2\text{OH}\right] \\
(a) & \rightarrow \text{Ar}_2\text{CHCH}_2\text{OH} \\
(b) & \rightarrow \text{Ar}_2\text{CH}_2 \\
(c) & \rightarrow \text{Ar}_2\text{CH-CHAr}_2
\end{align*}
\]

The authors therefore concluded that the key intermediate leading to C-H insertion products in the solid phase experiments was also a triplet phosphorylcarbene. Support for this theory was provided by photolysis experiments carried out with the α-diazo phosphonate (136) and a sensitiser at room temperature in ethanol; conditions conducive to the formation of the triplet carbene. Substantial increases in the yields of reduction and C-H insertion products were observed. The mechanism for the formation of the C-H insertion products consequently appears to involve a
hydrogen abstraction step from the solvent followed by efficient radical recombination within the matrix rather than direct insertion. The authors were uncertain why frozen matrices favour triplet carbenes but they suggested that O-H insertion reactions of singlet carbenes might involve ionic species which might be greatly stabilised by solvation. Such solvation would be less important in the solid phase and so O-H insertion would become less important compared to other radical processes of triplet carbene. Additionally the acidity of the alcohols might also be temperature dependent.

The use of α-diazophosphonic acids as potential photoaffinity labelling analogues of phosphate derivatives has been investigated by Bartlett.\textsuperscript{83,84} The novel α-diazo phosphonates; the α-diazo sulphonamide (140), the diazo bis-phosphonate (141) and the diazo amide (142) were prepared in the course of the study.

\[
\begin{align*}
\text{Et}_2\text{NSO}_2 & \begin{array}{cc}
\text{O} & \begin{array}{c}

X
\end{array}
\end{array}
\begin{array}{c}
\text{N}_2
\end{array} \\
\begin{array}{c}

X = \text{OMe (140)}
\end{array}
\begin{array}{c}

X = \text{O}^- (143)
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{iPrO}_2 & \begin{array}{cc}
\text{O} & \begin{array}{c}

X
\end{array}
\end{array}
\begin{array}{c}
\text{N}_2
\end{array} \\
\begin{array}{c}

X = \text{OMe (141)}
\end{array}
\begin{array}{c}

X = \text{O}^- (144)
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{Me}_2\text{N} & \begin{array}{cc}
\text{O} & \begin{array}{c}

X
\end{array}
\end{array}
\begin{array}{c}
\text{N}_2
\end{array} \\
\begin{array}{c}

X = \text{OMe (142)}
\end{array}
\begin{array}{c}

X = \text{O}^- (145)
\end{array}
\end{align*}
\]

Conversion into their α-diazophosphonic acid derivatives (143), (144) and (145) was achieved by transesterification of the esters with bromo-trimethylsilane affording the bis-trimethylsilyl esters which were then hydrolysed under mild conditions to form the respective α-diazo phosphonic acids.

To be of use as a photoaffinity label, the α-diazophosphonic acid derived carbene must react preferentially by intermolecular insertion or addition rather than by intramolecular processes such as a Wolff type rearrangement. Photochemistry experiments of the dimethyl ester derivatives (140) and (141) in methanol and ethanol yielded the expected O-H insertion and reduction products (Scheme 59).
Scheme 59.

\[
\text{hv, ROH} \rightarrow Z\text{PO(OMe)}_2 \rightarrow Z\text{PO(OMe)}_2 + Z\text{PO(OMe)}_2
\]

\[Z = \text{Et}_2\text{NSO}_2 (140) \quad R = \text{Me}(17\%), \text{Et}(24\%) \quad R = \text{Me}(31\%), \text{Et}(33\%)
\]

\[Z = (\text{i-PrO})_2\text{OP} (141) \quad R = \text{Me}(41\%), \text{Et}(95\%) \quad R = \text{Me}(44\%), \text{Et}(0\%)
\]

In contrast to the diesters, the photolysis products arising from irradiation of the \(\alpha\)-diazo phosphonic dianions (143) and (144) in methanol, could not be fully characterised. However, the formation of the \(\alpha\)-hydroxy monomethyl ester (148) was clearly evident and was the major reaction pathway. Although the migration of the oxygen substituent from phosphorous is a Wolff-like rearrangement, Bartlett proposed a mechanism involving an oxophosphirane anion intermediate (146) resulting from intramolecular trapping of the carbenes by phosphonate anion, followed by subsequent protonation (147) and reaction with the alcohol (Scheme 60).

Scheme 60.

\[
Z\text{PO(OH)}_2 ^{\text{Na}^+} \quad \text{hv} \quad \text{ZPO(OH)}_2 ^{\text{Na}^+} \rightarrow Z\text{PO(OH)}_2 ^{\text{Na}^+} \rightarrow Z\text{PO(OH)}_2 ^{\text{Na}^+}
\]

\[Z = \text{Et}_2\text{NSO}_2 (143) \text{ or } (\text{i-PrO})_2\text{PO} (144) \rightarrow \text{H}^+ \quad (146)
\]

\[
\text{ZPO(OH)}_2 ^{\text{Na}^+} \quad \text{MeOH} \quad \text{ZPO(OH)}_2 ^{\text{Na}^+} \quad \text{MeOH}
\]

\[\text{(148)} \quad \text{(147)}
\]

This intramolecular quenching therefore severely reduced the potential for these \(\alpha\)-diazo phosphonic acids (143, 144, 145) to act as photoaffinity labels.
In a later paper, Bartlett reported on the synthesis and stability of the monoester (149) of the α-diazo sulphonamide (140). Photolysis of this compound in methanol yielded the sulphonamide (151) as the major product (20-30%). There was no evidence for formation of reduction or O-H insertion products by analogy with the diester (140, \(X = \text{OMe}\)), nor a hydroxy monoester by analogy with the dianion (143, \(X = 0^-\)). A mechanism involving the formation of the oxophosphirane (150) followed by phosphorus-carbon bond cleavage was proposed, leading to the observed product, although other mechanisms could also be envisaged (Scheme 62).

Scheme 62.

Workers in Japan have also investigated the photochemistry of the monoanions of α-diazo phosphonates. They noticed that the electrophilicity of phosphoryl carbenes was dramatically reduced as the carbene substituents were changed from the phosphoryl diester to its monoanion. Irradiation of dimethyl α-diazobenzylphosphonate (152, \(X = \text{OMe}\)) in a 1:3.8 mixture of methanol and 2-methyl-but-2-ene afforded the insertion product (153) and cyclopropane (154) (mixture of syn- and anti-isomers) in 18 and 81% yields respectively. When the monosodium salt of the α-diazo phosphonate (152, \(X = 0^-\)) was irradiated under the same conditions, followed by neutralisation and esterification with diazomethane, the formation of the cyclopropanes (154) was found to be greatly reduced (16%) and the insertion product (153) became the major product (73%) (Scheme 63).
Simple alkenes such as but-2-ene are effective trapping agents for many electrophilic carbenes but not always for nucleophilic carbenes. Methanol, however, has been shown to be equally reactive to both electrophilic carbenes (by attack of the lone pair of electrons on oxygen) and nucleophilic carbenes (by protonation). Therefore, the phosphonate carbene (152, \( X = \text{O}^- \)) shows enhanced reactivity...
towards alcohols relative to the alkenes.

These workers were unable to detect products like (150) and (151) in analogy to Bartlett's work with their particular diazo compound (152, X = O\textsuperscript{-}). They explained this as being a result of the different carbene substituents. The oxophosphirane anion intermediate (155) would be greatly stabilised by the adjacent strongly electron withdrawing groups present in Bartlett's diazo compounds (143-145 and 149) and therefore would show more anionic than 'carbeneic' character.

Phenylphosphonyl carbenes (as 152) are stabilised by the interaction of their vacant p-orbital with the aromatic \( \pi \)-orbital and therefore would be less likely to accept a negative charge developing at the benzyl carbon atom in the transition state for the formation of an oxaphosphirane intermediate. Thus, these carbenes will behave more like a carbene than an anion. Evidence to support this theory came from the observation that phenylphosphonyl carbenes reacted with alkenes to form cyclopropanes whereas the \( \alpha \)-diazo amide (145) furnished no trace of cyclopropane when generated in the presence of olefins.

The effects of carbenic substituents on the mode of participation by the neighbouring phosphonate anion have been examined in much more detail.\textsuperscript{87} Irradiation of dimethyl \( \alpha \)-diazophenacylphosphonate (156, \( R = \text{Ph}, X = \text{OMe} \) (Scheme 165) in methanol, afforded the Wolff-like rearrangement product (157) (41\%) and reduction product (158) (33\%). However, the monosodium salt (156, \( R = \text{Ph}, X = \text{O}^- \) of the phosphonate yielded only the phosphonate arising from rearrangement (157) (46\%) as the sole isolable product after neutralisation and esterification with diazomethane. A similar effect was observed on photolysis of the diazo derivatives of acetonylphosphonate (156, \( R = \text{Me}, X = \text{OMe and O}^- \) (Scheme 65).

Accepting that the Wolff rearrangement takes place in the singlet state of the carbene whilst the double abstraction product is a reaction of the corresponding triplet carbene, the result suggested to these workers that the neighbouring phosphonate anion completely suppressed the reaction of the triplet state of the carbene. The singlet state is stabilised by the neighbouring phosphonate group as a result of the intramolecular interaction with the vacant p-orbital thus preventing intersystem
crossing to the triplet state.

Scheme 65.

\[
\begin{align*}
\text{hv, MeOH} & \rightarrow \left[ \begin{array}{c} \\
\end{array} \right] \\
\end{align*}
\]

\[
\begin{align*}
(156) & \quad (157) \\
(158) & \\
X = \text{OMe or } \text{O}^{-} \\
R = \text{Ph or Me} \\
\end{align*}
\]

Evidence to support this idea was obtained when the effect of phosphonate groups on the reaction patterns of the carbene were studied by systematically changing the carbenic substituents (Scheme 66) and (Table 7).

Scheme 66.

\[
\begin{align*}
\text{hv, MeOH} & \rightarrow \left[ \begin{array}{c} \\
\end{array} \right] \\
\end{align*}
\]

\[
\begin{align*}
(159) & \quad (160) \\
(161) (162) (163) (164) \\
R = \text{Ph or Me} \\
\end{align*}
\]

The results clearly show that the neighbouring phosphonate groups exert enormous effects not only on product distribution but also on the reaction products. The formation of apparently migrated products (162) and (163) strongly suggests that the phosphonate anion becomes fully bonded or partially bonded to the carbenic centre during the progress of reaction. The workers believed that the results were best explained by assuming that the extent of interaction between the carbenic centre
and oxygen anion is sensitively changed as the carbenic substituents are changed.

Table 7.

Photolysis of diazophosphinates in methanol

<table>
<thead>
<tr>
<th>R</th>
<th>R¹</th>
<th>X</th>
<th>(161)</th>
<th>(162)</th>
<th>(163)</th>
<th>(164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>OMe</td>
<td>OMe</td>
<td>&gt;99</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>O⁻</td>
<td>&gt;99</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>Ph</td>
<td>OMe</td>
<td>48.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>O⁻</td>
<td>5.4</td>
<td>52.9</td>
<td>0</td>
</tr>
<tr>
<td>c</td>
<td>MeO₂C</td>
<td>OMe</td>
<td>OMe</td>
<td>&gt;99</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>O⁻</td>
<td>0</td>
<td>0</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

Thus, (160a, X = O⁻) is stabilised by interaction of its vacant p-orbital with the aromatic π-orbital and therefore less susceptible to accept a negative charge developing at the benzyl carbon for the formation of oxaphosphirane intermediate i.e. it would have behave more like a true carbene. This would react with methanol via protonation to give (161a, X = O⁻). However, the phosphinyl carbene (160b, X = O⁻) would be strongly electrophilic and would be quenched by the neighbouring phosphonate oxygen anion leading to the oxaphosphirane anion which would be immediately protonated by the solvent to give the oxaphosphirane intermediate. Nucleophilic attack of the solvent on phosphorous followed by P-C bond breaking would give the observed product (162b). Absence of the P-O bond fission product (163b) in the reaction mixture is not clear although base catalysed rearrangements of these compounds are well known. The carbene (160c, X = O⁻) would also be expected to be highly electrophilic and would be trapped by the intramolecular phosphonate oxygen leading to the oxaphosphirane anion. The anion would be stabilised by the adjacent carbonyl group as well as the phosphonate group and would be expected to undergo Wolff-type rearrangements of the oxygen anion giving rise to the metaphosphinate which undergoes addition of the alcohol to produce (163c).

Vandewalle has reported a novel entry into substituted phosphonoacetates via
irradiation of α-diazo-β-keto phosphonates in the presence of an alcohol. Thus, the α-diazo phosphonates (165) and (167) were converted into phosphonoacetates (166) and (168) in good yields (Scheme 67). The reaction represents the net insertion of dimethoxyphosphorylcarbene into a C-COOR bond.

Scheme 67.

The phosphonoacetates could then be subjected to the Wadsworth-Emmons reaction to afford the olefins. For example, the ester (169) was converted to the α-substituted acrylic ester (170) in good yield (Scheme 68).

Scheme 68.

Reagents: (i) (a) (MeO)2OPCH2^-Li^+ ; (b) TosN3 , NaH; (c) hv , EtOH; (ii) LDA , THF, CH2O

Japanese workers have investigated the reaction of diketene with various dimethyl (α-diazoalkyl)phosphonates under photolytic conditions. These reactions lead to

61
the formation of E- and Z-mixtures of bicyclic compounds. For example, the reaction of dimethyl diazomethylphosphonate (DAMP) with diketene (171) afforded the bicyles (172) in a combined yield of 87% (Scheme 69).

Scheme 69.

These bi-cycles underwent a range of ring opening reactions. For example, heating in the presence of concentrated sulphuric acid yielded the phosphonate (173) in 65% yield. Similarly, reaction with p-toluidine furnished the phosphonate (174) in 80% yield (Scheme 70).

Scheme 70.
CHAPTER TWO

RHODIUM (II) CATALYSED O-H INSERTION REACTIONS:
MECHANISTIC INVESTIGATIONS
2.1 Introduction

As discussed very briefly in Section 1.4, the transition metal catalysed decomposition of diazo compounds has been known for over eighty years and has now become a standard procedure in organic synthesis.\textsuperscript{59} Rhodium (II) carboxylates which were first introduced in the early 1970's,\textsuperscript{58} are amongst the most efficient catalysts for the decomposition of diazo compounds and the recent development of chiral rhodium based catalysts has further increased the scope and potential of these reactions.\textsuperscript{60}

Our own interest in rhodium (II) catalysed reactions has been concerned with the X-H insertion reaction (X = nitrogen, sulphur or oxygen), particularly in its intramolecular mode.\textsuperscript{67,90,91} For example, the intramolecular rhodium (II) catalysed O-H insertion reaction of a diazo alcohol can yield an oxepane (Scheme 71).\textsuperscript{67}

![Scheme 71](image)

The decomposition is believed to proceed via the formation of a rhodium carbenoid intermediate (carbenoid = metal bound carbene)\textsuperscript{61} rather than via the formation of the free carbene itself. The carbenoid retains all the properties associated with the free carbene. However, due to its lower inherent energy and hence reactivity, it reacts in a much milder, more selective and more predictable way. In addition, the generation of the carbenoid is comparatively much milder; thermally and photochemically generated carbenes on the other hand often give products arising from rearrangements and dimerisation.

The highly transient nature of the rhodium carbenoid species has so far made it impossible to characterise its structure, hence the mechanistic uncertainty, but the most compelling evidence for the imagined scenario comes from a comparison
between the cyclopropanation reactions of olefins with phenyl diazomethane (or alternatively, ethyl diazoacetate) in the presence of the stable electrophilic tungsten carbenoid complex \((\text{CO})_5\text{W}=-\text{CHPh}\), and rhodium (II) acetate, respectively.\(^9\)\(^2\) For the same set of mono-substituted alkenes, a linear log-log relationship between the relative reactivities for the stoichiometric reaction with \((\text{CO})_5\text{W}=-\text{CHPh}\) and the catalytic reaction with rhodium (II) acetate was found. The tungsten system was found to be much faster than the rhodium (II) acetate system \((10^{-3}-10^4\) times) but in each case, \(\text{cis}\)-cyclopropanes were formed preferentially with phenyl diazomethane whereas \(\text{trans}\)-cyclopropanes were formed preferentially with ethyl diazoacetate. Taking together the results of the reactivity and stereoselectivity comparisons, it appears likely that the mechanisms for the formation of the cyclopropanes in each case are quite similar and therefore, in the case of the rhodium (II) catalysed reaction, involves the formation of a metallocarbenoid.

In 1986, Taber suggested a mechanism involving a rhodium carbenoid species to explain the formation of cyclopentanones via a rhodium (II) acetate mediated intramolecular C-H insertion process.\(^9\)\(^3\) This proposed reaction pathway is generally believed to be a fairly good representation of the true mechanism and so we have adapted it to explain the observed formation of oxygen containing heterocycles (Scheme 72).

Rhodium (II) acetate itself is a binuclear compound with four bridging acetate ligands and has octahedral \(D_{4h}\) symmetry;\(^9\)\(^4\) it has therefore been referred to as having a "lantern" structure. It possesses one vacant axial coordination site per metal atom and the first step of the sequence (Scheme 72, step 1) is believed to involve the interaction of the diazo compound with one of these empty coordination sites. Cleavage of the rhodium-rhodium bond (step 2) leads to the expulsion of dinitrogen and the subsequent formation of the rhodium carbenoid species (A).

The electron withdrawing group \(Z\), the carbonyl group and the electron withdrawing acetate ligands in this species cause the metal bond to polarise resulting in a powerfully electrophilic species which is rapidly quenched by a nucleophile (in this case, the pendant hydroxy group) leading to the formation of the heterocycle (step 3). The final steps of the sequence involve the regeneration of rhodium (II) acetate.
and rearrangement of the resulting ylide to the heterocycle (steps 4 and 5). The order of these final steps is unknown but there is good evidence to suggest that the loss of the metal precedes the rearrangement of the heterocycle.95

Scheme 72.

Previous communications from these laboratories have reported the highly successful use of rhodium (II) mediated cyclisations as a route to functionalised medium ring ethers, in particular, seven membered ring cyclic ethers (Table 8, Z = various electron withdrawing groups).67
Table 8.67

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>Z</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>CO$_2$Bu$^t$</td>
<td>48-56</td>
</tr>
<tr>
<td>b</td>
<td>n-C$<em>6$H$</em>{13}$</td>
<td>CO$_2$Bu$^t$</td>
<td>64</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>Ac</td>
<td>62</td>
</tr>
<tr>
<td>d</td>
<td>n-C$<em>6$H$</em>{13}$</td>
<td>Me$_3$Si(H)</td>
<td>56</td>
</tr>
<tr>
<td>e</td>
<td>n-C$<em>6$H$</em>{13}$</td>
<td>SO$_2$Ph</td>
<td>73</td>
</tr>
<tr>
<td>f</td>
<td>n-C$<em>6$H$</em>{13}$</td>
<td>PO(OEt)$_2$</td>
<td>54</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>PO(OEt)$_2$</td>
<td>52</td>
</tr>
</tbody>
</table>

Reaction Conditions: 1 mol% Rh$_2$(OAc)$_4$ in refluxing benzene.

It had been noted that the nature of the electron withdrawing group Z appeared to markedly affect the rate of the cyclisation as monitored by TLC. We wanted to answer three questions which we hoped would explain these observations and simultaneously throw more light on the mechanism of reaction in the absence of an isolable rhodium carbenoid species B (Figure 1; a simplified schematic of the previously postulated rhodium carbenoid species A).

Figure 1.

B

$Z = \text{electron withdrawing group}$

$L = \text{ligand on catalyst}$
(1) What effect would a change in the electron withdrawing group Z and / or the ligands L on the catalyst have on the electrophilicity of the metallocarbenoid? For example, if Z and L were powerful electron withdrawing groups would there be a noticeable increase in the rate of reaction?

(2) How nucleophilic does X (where X = nitrogen, sulphur or oxygen) need to be in order for cyclisation to occur? Or perhaps, how is the rate influenced by the reactivity of the heteroatom; i.e. would primary react faster than secondary than tertiary?

(3) What effect might there be on changing the metal? Perhaps another metal could fulfil the role played by rhodium more efficiently than rhodium itself.

2.2 Diazo Compound Stability towards Rhodium (II) Acetate: Reactions with 2-Propanol

In order to study the effect of the nature of the electron withdrawing group Z on the kinetics of the insertion reaction, the rhodium (II) acetate catalysed decomposition of various diazo compounds in the presence of 2-propanol was investigated. The intention from the start was not to rigorously evaluate reaction kinetics but rather provide a comparison of rate under a set of standard reaction conditions.

Of the diazo compounds (175-186), ethyl diazoacetate (175) is commercially available. Ethyl diazocyanooacetate (176),3,96 benzenesulphonyl-ethoxy carbonyl-diazomethane (177),3,97 diethyl diazomalonate (178),3,98 diphenyl phosphinyl-ethoxy carbonyl-diazomethane (179),3,99 diethyl phosphono-ethoxy carbonyl-diazomethane (180)3,99 and ethyl diazoacetoacetate (181)3,98 are known compounds prepared by diazo transfer to the corresponding methylene compounds. Ethyl 2-diazo-3-phenyl-propanoate (182)3,100 is also a literature compound and was prepared by benzylaion of the organosilver species derived from ethyl diazoacetate. Dimethyl diazomalonate (183)3,98, acetyl-diethyl phosphono-diazomethane (184)3,99 diethyl phosphono-diethyl phosphono-diazomethane (186)3,99 and the novel diazo sulphone (185)178 were also prepared by means of the diazo transfer reaction (Tables 9 and 10).
Although the preparations of ethyl diazocyanocetate (176), diethyl phosphonoethoxy carbonyl-diazomethane (180) and diethyl phosphono-diethyl phosphono-diazomethane (186) are present in the literature, preparative routes were developed which gave these compounds in both better yield and under more amenable conditions. These routes have been illustrated in Tables 9 and 10.

Table 9.

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Diazo Compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N≡C(\text{CO}_2\text{Et})</td>
<td>N≡C(\text{CO}_2\text{Et})</td>
<td>(176) 80</td>
</tr>
<tr>
<td>PhSO_2(\text{CO}_2\text{Et})</td>
<td>PhSO_2(\text{CO}_2\text{Et})</td>
<td>(177) 70</td>
</tr>
<tr>
<td>EtO(\text{CO}_2\text{Et})</td>
<td>EtO(\text{CO}_2\text{Et})</td>
<td>(178) 95</td>
</tr>
<tr>
<td>Ph(\text{PO}(\text{Et})_2\text{OEt})</td>
<td>Ph(\text{PO}(\text{Et})_2\text{OEt})</td>
<td>(179) 50</td>
</tr>
<tr>
<td>EtO(\text{PO}(\text{Et})_2\text{OEt})</td>
<td>EtO(\text{PO}(\text{Et})_2\text{OEt})</td>
<td>(180) 63</td>
</tr>
<tr>
<td>Me(\text{C}O\text{Et})</td>
<td>Me(\text{C}O\text{Et})</td>
<td>(181) 80</td>
</tr>
</tbody>
</table>
These diazo compounds (175-186) (1.0 mmol) were dissolved in 2-propanol (120 mmol) and treated with a catalytic amount of rhodium (II) acetate (1 mol%) at room temperature. The reaction was monitored by TLC and the time for complete decomposition of the diazo compounds was noted (Tables 11 and 12). In the cases where decomposition was very slow at room temperature, the reaction mixture was heated to reflux.

The results demonstrate quite clearly that there is marked difference in reactivity between diazo compounds and it appears that the stability of the diazo compounds (175-186) towards rhodium (II) acetate catalysed decomposition in the presence of 2-propanol decreases in the order:
\[ Z = (\text{EtO})_2\text{OP} > \text{Ph}_2\text{OP} >> \text{CO}_2\text{Et} > \text{PhSO}_2 > \text{CN} > \text{MeCO} > \text{PhCH}_2 > \text{H} \]

Table 11.

<table>
<thead>
<tr>
<th>Diazo Compound</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(175) ( \text{H} = \text{OEt} )</td>
<td>0.5</td>
<td>( \text{H} = \text{OEt} )</td>
<td>64</td>
</tr>
<tr>
<td>(176) ( \text{N} = \text{C} = \text{O} )</td>
<td>3.0</td>
<td>( \text{N} = \text{C} = \text{O} )</td>
<td>86</td>
</tr>
<tr>
<td>(177) ( \text{PhSO}_2 \text{=} \text{OEt} )</td>
<td>18.0</td>
<td>( \text{PhSO}_2 \text{=} \text{OEt} )</td>
<td>64</td>
</tr>
<tr>
<td>(178) ( \text{EtO} \text{=} \text{OEt} )</td>
<td>120-130</td>
<td>( \text{EtO} \text{=} \text{OEt} )</td>
<td>66</td>
</tr>
<tr>
<td>(179) ( \text{Ph} = \text{P} = \text{OEt} )</td>
<td>1.0 reflux</td>
<td>( \text{Ph} = \text{P} = \text{OEt} )</td>
<td>74</td>
</tr>
<tr>
<td>(180) ( \text{EtO} = \text{P} = \text{OEt} )</td>
<td>10.0 reflux</td>
<td>( \text{EtO} = \text{P} = \text{OEt} )</td>
<td>83</td>
</tr>
</tbody>
</table>
For the diazo compounds (175), (176), (177), (178), (180), (182), (183) and (184), the products isolated from the reaction mixture were those arising from O-H insertion- the insertion product being easily identified by the methine proton in
the isopropyl group occurring as a heptet between 3.50 and 4.00 ppm in the $^1$H NMR. In the case of diphenylphosphinyl-ethoxy carbonyl-diazomethane (179) the yield of the O-H insertion product was very low due to competing hydrogen abstraction leading to a "reduced" product, the diazo precursor (191) (74%), whilst the $\alpha$-diazo phosphonates (185) and (186) showed no sign of decomposition under these conditions. Although the diazo compound ethyl 2-diazo-3-oxobutanoate (181) decomposed rapidly under the reaction conditions, no O-H insertion product could be isolated. Surprisingly, in comparison with the other decompositions, a mixture of products was obtained which could not be easily separated. The only product that could be isolated and characterised was a 30% yield of the reduced product. This result was particularly surprising as it was known from previous work in these laboratories that $\alpha$-diazo carbonyl compounds undergo intramolecular rhodium (II) catalysed O-H insertion reactions to give oxepanes in good yield (as seen in Table 8).

In 1970, Regitz compared the thermal stabilities of several substituted diazomethanes and noted the increased stability of $\alpha$-diazo phosphonates over $\alpha$-diazo carbonyl compounds. $^{101}$ This was explained by considering the two mesomers (A) and (B) of $\alpha$-diazo carbonyl compounds (Scheme 73).

Scheme 73.

\[ \text{\textbullet~Scheme~73.} \]

$\alpha$-Diazo carbonyls are able to mesomerise easily between keto and enolate forms. In the latter, delocalisation of the negative charge away from the the diazo group leaves it isolated. $\alpha$-Diazo phosphonates, because of the nature of the P=O bond, do not mesomerise in a similar manner and therefore there is much greater interaction of positive and negative charges around the diazo group resulting in less isolated diazo character and hence increased stability. Applying this model to rhodium (II) acetate
catalysed decompositions, greater stabilisation of charges in the \( \alpha \)-diazo phosphonate means that the diazo carbon is less nucleophilic for the initial interaction with the vacant coordination site on rhodium, the first step in the formation of the metallo-carbenoid.

Although this simple picture explains the high stability of \( \alpha \)-diazo phosphonates (179), (180), (184), (185) and (186) relative to \( \alpha \)-diazo carbonyls, it does not explain the general observed rate order \textit{per se}.

Considering the reactions which do furnish \( O-H \) insertion products, the observed rates do to some extent fit the expected pattern; that is, rate increases with increasing electron withdrawing strength of the group \( Z \). However there are three notable exceptions and these occur when \( Z = H, Z = CH_2Ph \) and \( Z = C\equiv N \). These apparent anomalies demonstrate that the rates observed cannot be explained by simple electron withdrawing arguments alone and that there must be consequently other factors at play.

For example, are diazo compounds like ethyl diazoacetate with one stabilising group \( Z \) (or a second weakly stabilising group) inherently less "stable" than those with two electron withdrawing groups? Does this "instability" result in a more rapid interaction with the catalyst (Scheme 72, step 1) than the equivalent step with "stabilised diazo" compounds? \textit{i.e.} those with two flanking electron withdrawing groups. Is there a point at which the rate of nucleophilic attack on the metallo-carbenoid becomes more important in determining the rate of reaction as the "stability" of the diazo compound increases such that electron withdrawing arguments begin to apply and become more dominant? Would a combination of such factors explain the observed rates?

In addition, the questions why reduction is sometimes preferred over \( O-H \) insertion and why in certain cases a clean reaction, be it reduction or \( O-H \) insertion, is not observed are still to be addressed.

As has already been suggested, the nature of the flanking \( \alpha \)-electron withdrawing group \( Z \) would be expected to have two possible effects (i) influence the "nucleophilicity" of the diazo carbon (Scheme 74) thus affecting the rate of interaction of the diazo compound with the catalyst (step 1, Scheme 72) and (ii)
influence the rate of nucleophilic attack (step 3, Scheme 72) by determining the
electrophilicity of the metallocarbenoid species. However, there appears to be no
clear correlation between the observed order of reactivity and the α-substituent Z in
terms of physical characteristics of the diazo compounds in our series.

Scheme 74.

\[
\begin{array}{c}
\text{Z-} \quad \text{N+} \\
\text{N} & \quad \text{N-} \\
\end{array}
\]

The physical properties measured (Table 13) were (i) the stretch of the diazo group
in the infra-red (ii) the \(^1\text{H}\) chemical shift of the protons attached to the "diazo
carbon" in the diazo precursor ZCH\(_2\)COY (iii) the \(^{13}\text{C}\) chemical shift of the "diazo
carbon" in the diazo precursor ZCH\(_2\)COY and (iv) the \(^{13}\text{C}\) chemical shift of the
carbonyl group in the diazo compound ZCN\(_2\)COY. The \(^{13}\text{C}\) chemical shift of the diazo
carbon itself could not be generally determined as it has such a long relaxation time
that it often fails to appear in the spectrum.

Table 13.

<table>
<thead>
<tr>
<th>Diazo</th>
<th>ZCH(_2)N(_2) (cm(^{-1}))</th>
<th>ZCH(_2)Y (\delta_\text{H}) (ppm)</th>
<th>ZCH(_2)Y (\delta_\text{C}) (ppm)</th>
<th>C=O (\delta_\text{C}) (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(175)</td>
<td>2112</td>
<td>2.05</td>
<td>21.04</td>
<td>166.94</td>
</tr>
<tr>
<td>(176)</td>
<td>2138</td>
<td>3.46</td>
<td>24.79</td>
<td>163.07</td>
</tr>
<tr>
<td>(177)</td>
<td>2129</td>
<td>4.12</td>
<td>60.93</td>
<td>162.36</td>
</tr>
<tr>
<td>(178)</td>
<td>2140</td>
<td></td>
<td>161.09</td>
<td></td>
</tr>
<tr>
<td>(179)</td>
<td></td>
<td>3.49</td>
<td></td>
<td>163.93</td>
</tr>
<tr>
<td>(180)</td>
<td>2131</td>
<td>2.96</td>
<td>34.42</td>
<td>163.43</td>
</tr>
<tr>
<td>(181)</td>
<td>2140</td>
<td>3.45</td>
<td>50.16</td>
<td>161.45</td>
</tr>
<tr>
<td>(182)</td>
<td>2084</td>
<td></td>
<td></td>
<td>167.22</td>
</tr>
<tr>
<td>(183)</td>
<td>2139</td>
<td>3.40</td>
<td>41.13</td>
<td>161.49</td>
</tr>
<tr>
<td>(184)</td>
<td>2123</td>
<td>3.09</td>
<td></td>
<td>163.44</td>
</tr>
<tr>
<td>(185)</td>
<td>2116</td>
<td>3.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(186)</td>
<td>2116</td>
<td>2.45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The decomposition of the α-diazo phosphonate (185) was also attempted using some new chiral rhodium (II) catalysts, rhodium (II) N-benzenesulphonyl L-prolinate and rhodium (II) S-chloropropionate, which have been shown to have higher activity in C-H insertion reactions than rhodium (II) acetate.\textsuperscript{102,103} Although decomposition did occur rapidly (less than two hours), the product in each case was exclusively the reduced product rather than the O-H insertion product. (Scheme 75).

Scheme 75.

\[
\begin{align*}
\text{PhSO}_2\text{P}<\text{OEt} & \quad \text{Rh}_2(\text{L})_4 \\
\text{N}_2 & \quad \text{PhH}_2 \text{reflux} \\
\text{PhSO}_2\text{P}<\text{OEt} & \quad \text{PhH}_2
\end{align*}
\]

(185) \( \text{Rh}_2(\text{L})_4 \quad \text{Rh}_2(\text{N-benzenesulphonyl-L-prolinate})_4 \)

\( \text{Rh}_2(\text{S-chloropropionate})_4 \)

In an attempt to get at least some O-H insertion with the α-diazo phosphonate (185), photolytic decompostion in the presence of 2-propanol was attempted. Not surprisingly the major compound isolated was the product arising from H-abstraction (90%) although some insertion product could be identified by \(^1\text{H}\) NMR. However, O-H insertion products (196) and (197) were obtained in reasonable yields when the photolysis was carried out in methanol or t-butanol respectively (Scheme 76).\textsuperscript{179}

As further proof of its structure, the methoxy-phosphonate (196) was subjected to a Wadsworth-Emmons olefination reaction with benzaldehyde affording an α-sulphonyl vinyl ether (198) in 56% yield as a mixture of E/Z isomers (Scheme 77).
Scheme 76.

\[
\begin{align*}
\text{PhSO}_2\text{P(O)(OEt)}\text{N}_2 & \xrightarrow{hv, \text{MeOH}} \text{PhSO}_2\text{P(O)(OEt)} \quad (185) \\
\text{PhSO}_2\text{P(O)(OEt)}\text{N}_2 & \xrightarrow{hv, \text{tBuOH}} \text{PhSO}_2\text{P(O)(OEt)} \quad (185)
\end{align*}
\]

Scheme 77.

\[
\begin{align*}
\text{PhSO}_2\text{P(O)(OEt)} & \xrightarrow{\text{NaH, THF}} \text{PhSO}_2\text{P(O)(OMe)} + \text{PhSO}_2\text{P(O)(OMe)} \quad (196) \quad (198) \quad \text{E}:\text{Z} \quad 95:5
\end{align*}
\]

The \(\alpha\)-diazo phosphonate (185) was eventually decomposed catalytically to give the isopropyloxy ether (199) by simply heating a mixture of the diazo compound, rhodium (II) acetate (1 mol%) and 2-propanol in toluene for 72 h (Scheme 78a). The \(\alpha\)-diazo bis-phosphonate (186) under the same reaction conditions still showed no sign of decomposition despite prolonged heating (3 days) (Scheme 78b). It is quite apparent that these diazo compounds are remarkably stable in comparison to all of the other diazo compounds investigated.

Scheme 78a.

\[
\begin{align*}
\text{PhSO}_2\text{P(O)(OEt)}\text{N}_2 & \xrightarrow{\text{Rh}_2(\text{OAc})_4, \text{tPrOH}} \text{PhMe, reflux} \quad \text{PhSO}_2\text{P(O)(OEt)} \quad (185) \\
\text{PhSO}_2\text{P(O)(OEt)}\text{N}_2 & \xrightarrow{\text{PhMe, reflux}} \text{PhSO}_2\text{P(O)(OEt)} \quad (199) \quad 72 \text{ h}, \quad 67%
\end{align*}
\]
Scheme 78b.

\[
\begin{array}{cccc}
\text{EtO} & \text{O} & \text{O} & \text{Et} \\
\text{EtO} & \text{P} & \text{N} & \text{Et} \\
\text{N}_2 & & & \\
\end{array}
\xrightarrow{\text{Rh}_2(\text{OAc})_4, \text{iPrOH}}
\begin{array}{c}
\text{PhMe, reflux} \\
\text{No Reaction}
\end{array}
\]

(186)

2.3 Catalyst Effects on O-H Insertion Rate

In conjunction with this work, a series of five different catalysts had been prepared in analogy to those used by Doyle in his investigations into the rhodium (II) catalysed cyclopropanation reactions of ethyl diazoacetate with olefins. The aim of the work was to compare the rate of decomposition of several diazo compounds in the presence of 2-propanol with variation in the catalyst. The catalysts under study were:

(A) \( \text{Rh}_2(\text{OCOCH}_3)_4 \)
(B) \( \text{Rh}_2(\text{OCOCF}_3)_4 \)
(C) \( \text{Rh}_2(\text{OCOCF}_3)_4 \)
(D) \( \text{Rh}_2(\text{NHCOCH}_3)_4 \)
(E) \( \text{Rh}_2(\text{NHCOCH}_3)_4 \)

Rhodium (II) acetate (A) is commercially available. Rhodium (II) trifluoroacetate (tfa) (B)\(^{94}\), rhodium (II) perfluorobutyrate (pfb) (C)\(^{104}\), rhodium (II) acetamide (acam) (D)\(^{105}\) and rhodium (II) trifluoroacetamide (E)\(^{106}\) are literature compounds and were prepared from rhodium (II) acetate by ligand exchange.

All of these rhodium (II) salts had been reported to catalyse the cyclopropanation reactions of \( \alpha \)-diazo ketones with olefins to varying extents but with the exception of rhodium (II) acetate, they had not been previously applied to X-H (X = heteroatom) insertions.

Doyle and co-workers found that all of the catalysts promoted the preferential formation of trans (anti)-cyclopropane products with ethyl diazoacetate (175).
(EDA) and the olefins, ethyl vinyl ether, styrene and cyclohexene respectively (Table 14).  

Rhodium (II) acetamide (D) provided the highest and rhodium (II) perfluorobutyrate (C) the lowest trans (anti)-cyclopropanation selectivities. The extra selectivity shown by rhodium (II) acetamide (D) was ascribed as being due to its metallocarbenoid derivative being comparatively the most stable, consequently stabilising the transition state. Stabilisation of the transition state would lead to preferential trans (anti-selectivity). However, apart from a comparison between rhodium (II) acetate and rhodium (II) acetamide, no comment was made regarding the relative rates of reaction involving these catalysts.

Table 14.

![ Chemical reaction diagram ]

<table>
<thead>
<tr>
<th>catalyst</th>
<th>ethyl vinyl ether</th>
<th>styrene</th>
<th>cyclohexene</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A)</td>
<td>62</td>
<td>62</td>
<td>79</td>
</tr>
<tr>
<td>(B)</td>
<td>59</td>
<td>56</td>
<td>67</td>
</tr>
<tr>
<td>(C)</td>
<td>57</td>
<td>52</td>
<td>66</td>
</tr>
<tr>
<td>(D)</td>
<td>72</td>
<td>68</td>
<td>89</td>
</tr>
<tr>
<td>(E)</td>
<td>62</td>
<td>59</td>
<td>74</td>
</tr>
</tbody>
</table>

A comparative study to investigate the rate at which different diazo compounds underwent insertion into the O-H bond of 2-propanol catalysed by these rhodium (II) salts (A-E) was carried out. The conditions used previously for the rhodium (II) acetate rate experiments were followed.

The diazo compounds chosen as benchmarks for the study were benzenesulphonylmethoxy carbonyl-diazomethane (200), dimethyl diazomalonate.
(183) and dimethyl phosphono-methoxy carbonyl-diazomethane (201). These covered a wide spread of reaction times (from the results of Tables 11 and 12). The methyl derivatives were chosen in preference to the previously used ethyl derivatives in order to simplify the $^1$H NMR analysis.

The results of Table 15 are due to G. Cox (Loughborough University) and are included here (with his permission) so that a more complete picture can be presented.

Table 15.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Substrate</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ins$^\text{A}$</td>
<td>Red$^\text{A}$</td>
</tr>
<tr>
<td>(A)</td>
<td>(200)</td>
<td>26.0</td>
<td>77 /</td>
</tr>
<tr>
<td></td>
<td>(183)</td>
<td>96.0</td>
<td>78 /</td>
</tr>
<tr>
<td></td>
<td>(201)</td>
<td>3.5*</td>
<td>20 50</td>
</tr>
<tr>
<td>(B)</td>
<td>(200)</td>
<td>3.0*</td>
<td>/ 80</td>
</tr>
<tr>
<td></td>
<td>(183)</td>
<td>8.5*</td>
<td>90 /</td>
</tr>
<tr>
<td></td>
<td>(201)</td>
<td>16.0*</td>
<td># 75</td>
</tr>
<tr>
<td>(C)</td>
<td>(200)</td>
<td>4.0*</td>
<td>/ 100</td>
</tr>
<tr>
<td></td>
<td>(183)</td>
<td>4.5*</td>
<td>71 /</td>
</tr>
<tr>
<td></td>
<td>(201)</td>
<td>11.0</td>
<td>34 36</td>
</tr>
<tr>
<td>(D)</td>
<td>(200)</td>
<td>0.5*</td>
<td>61 32</td>
</tr>
<tr>
<td></td>
<td>(183)</td>
<td>1.0*</td>
<td>84 /</td>
</tr>
<tr>
<td></td>
<td>(201)</td>
<td>7.0*</td>
<td>28 /</td>
</tr>
<tr>
<td>(E)</td>
<td>(200)</td>
<td>0.25</td>
<td>89 /</td>
</tr>
<tr>
<td></td>
<td>(183)</td>
<td>2.0</td>
<td>72 /</td>
</tr>
<tr>
<td></td>
<td>(201)</td>
<td>17.0</td>
<td>53 /</td>
</tr>
</tbody>
</table>

* reaction mixture heated to reflux/ # trace amount observed by $^1$H NMR.

No definitive conclusions as such can be drawn from the results in Table 15 but certain trends are evident.

(1) Rhodium (II) trifluoroacetamide (E) is an extremely good catalyst for intermolecular O-H insertion reactions. Rhodium (II) trifluoroacetate (B), rhodium (II) perfluorobutyrate (C) and rhodium (II) acetamide (D) offer no
advantage over the commercially available rhodium (II) acetate (A).

(2) Across different families of catalyst, the order of relative rates of decomposition for a given series of diazo compound remains unchanged. That is, dimethyl phosphono-methoxy carbonyl-diazomethane (201) was always the slowest to decompose and benzene sulphonyl-methoxy carbonyl-diazomethane the quickest (200).

(3) Decomposition of the diazo compound relies on the reversible coordination of the alcohol to the electrophilic rhodium centre. If the metal centre is too electrophilic [e.g. \( L = \text{perfluorobutyrate (C)} \)] complexation of the alcohol becomes irreversible and the rate of decomposition decreases i.e. the diazo is unable to interact with the vacant coordination sites on the catalyst as they are already occupied. On the other hand, if the rhodium centre is not electrophilic enough, decomposition is slow due to the poor initial interaction of the diazo compound with the catalyst (Scheme 79, step 1). Increasing the energy of the diazo compound by heating can increase the rate of interaction however.

(4) For a given diazo compound, as the electrophilicity of the rhodium centre increases with change in ligand, so does the rate of diazo decomposition within the constraints discussed in (2). This is observed with the catalysts (D) and (E).

(5) For a given diazo compound, the relative ratio of reduced product to insertion product is governed by the rate of decomposition. This can be seen comparing the entries for the diazo sulphone (200). Decomposition with catalyst (B) affords no insertion product but 80% reduction product. Slightly faster decomposition is observed with catalyst (D) which affords a mixture of reduced (32%) and insertion product (61%). When the rate of decomposition increases further- catalysts (A) and (E)- no reduced product is observed at all.

In summary, it appears that the rate at which a rhodium (II) catalyst catalyses a reaction depends on three factors;

(1) the rate at which the diazo compound interacts with the catalyst to form the metallocarbenoid species (Scheme 79, step 1).
(2) the rate at which 2-propanol interacts with the metallocarbenoid species (Scheme 79, step 3) and
(3) the affinity for 2-propanol to coordinate to the active sites on the catalyst which is a function of the electrophilicity of the adjacent rhodium metal atom and which is dependent on the electron withdrawing strength of the ligands L.

Scheme 79.

Rhodium (II) trifluoroacetamide (E) appears to be an excellent catalyst for the O-H insertion reactions of diazo compounds with 2-propanol (and alcohols in general as will be seen later) because the electron withdrawing strength of the trifluoroacetamide ligands produces a rhodium centre that has an excellent balance between electrophilicity and coordination strength with the alcohol. That is, the rhodium centre is not so electrophilic that the alcohol coordinates irreversibly to it but is
electrophilic enough to provide a highly reactive centre for the diazo compound to interact with (relative to rhodium (II) acetate) and additionally providing a highly reactive metallocarbenoid species (relative to rhodium (II) acetate) which is rapidly attacked by the alcohol. The increased activity cannot be simply assigned to any increased solubility of the catalyst because rhodium (II) trifluoroacetamide actually appears to be very much less soluble in organic solvent than rhodium (II) acetate (in fact it appears to be virtually insoluble in 2-propanol). Such a solubility argument has been used to explain why at least in some cases, rhodium (II) octanoate exhibits faster rates of reaction with improved product yields compared to rhodium (II) acetate. Structurally, rhodium (II) trifluoroacetamide is more complex than rhodium (II) acetate owing to the increased number of possible geometrical isomers. However, in the preparation, one isomer is formed in much larger amounts relative to the other three (94:4:2: >1%). The X-ray structure of the bis(pyridine) adduct of this preferred isomer has been determined and it can be seen that the ligands prefer to lie cis to one another. 106a

Scheme 80.

Figure 1. Stereoscopic view of the molecule showing the atom-labeling scheme. Hydrogens are numbered the same as the atom to which each is attached. The rhodium and HNOCCF₃ ligands are shown as 40% probability ellipsoids, with the others as spheres of arbitrary diameter. The two disordered ligands at both axial sites are shown simultaneously.

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Some further examples of the remarkable rate of catalysis exhibited by rhodium (II) trifluoroacetamide (E) are shown in Table 16. The numbers in brackets indicate the
times for decomposition and the product yields obtained with rhodium (II) acetate (A).

Table 16.

<table>
<thead>
<tr>
<th>Diazo Compound</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(177) PhSO₂N₂OEt</td>
<td>0.25 (18.0)</td>
<td>PhSO₂O⁻PrO⁻H</td>
<td>(189) 85 (64)</td>
</tr>
<tr>
<td>(178) EtO⁻N₂OEt</td>
<td>1.0 (120)</td>
<td>EtO⁻O⁻PrO⁻H</td>
<td>(190) 74 (66)</td>
</tr>
<tr>
<td>(180) EtO⁻P=O⁻N₂OEt</td>
<td>72.0 (10.0 reflux)</td>
<td>EtO⁻O⁻P⁻O⁻Et⁻PrO⁻H</td>
<td>(192) 80 (83)</td>
</tr>
</tbody>
</table>

We had been previously unable to decompose the α-diazo bis-phosphonate (186) using rhodium (II) acetate as the catalyst (refluxing benzene or toluene conditions). However, heating this diazo compound in toluene in the presence of 2-propanol and a catalytic amount of rhodium (II) trifluoroacetamide (E) led to the smooth formation of the isopropyloxy ether (202) in 81% yield. Additionally, the α-diazo phosphonate (185) which had to be subjected to prolonged heating in toluene for insertion to occur with rhodium (II) acetate could, in comparison, be rapidly decomposed to the isopropyloxy ether (199) with rhodium (II) trifluoroacetamide in similar high yield (79%) (Scheme 81).
Experiments were also carried out to investigate whether the activity of rhodium (II) trifluoroacetamide (E) could be exploited such that intramolecular O-H insertion reactions could be carried out at room temperature as opposed to the refluxing benzene conditions necessary when using rhodium (II) acetate (Table 17). The starting diazo substrates (203) and (205) were prepared by reacting the phenyl lithium methyl sulphone and lithium diethyl methyl phosphonate with undecanoic β-lactone followed by diazo transfer. The diazo ester (204) was prepared by ring opening the same lactone with the anion of t-butyl diazoacetate (TBDA).

Although decomposition took place in all cases to give 2-substituted oxepanes, the reaction occurred satisfactorily only for the diazo sulphone (203) and the diazo ester (204). These afforded the oxepanes (206) and (207) in yields of 55 and 57% respectively. The reaction with the α-diazo phosphonate (205) failed to go to completion and the oxepane phosphonate (208) was isolated in only 24% after 72 h at room temperature. The bracketed figures refer to yields obtained with rhodium (II) acetate.
Table 17.

<table>
<thead>
<tr>
<th>Diazo Compound</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(203)</td>
<td>2.0</td>
<td>206</td>
<td>55 (69)</td>
</tr>
<tr>
<td>(204)</td>
<td>4.0</td>
<td>207</td>
<td>57 (64)</td>
</tr>
<tr>
<td>(205)</td>
<td>72.0</td>
<td>208</td>
<td>24 (60)</td>
</tr>
</tbody>
</table>

# Did not go to completion

2.4. Diazo Compound Stability towards Rhodium (II) Acetate: The Effect of Alcohols

As a continuation of our studies, we were interested in seeing whether different nucleophiles would have any noticeable effect on rate. We chose to study a variation on our intermolecular reaction. The two alcohols chosen to compare with 2-propanol were methanol and t-butanol. The catalyst used was rhodium (II) acetate (A) and the two diazo compounds chosen for the study were benzenesulphonyl-ethoxy carbonyl-diazomethane (177) and diethyl phosphono-ethoxy carbonyl-diazomethane (180). The reaction conditions were the same as those used in the study carried out using 2-propanol. In the cases where decomposition was very slow at room temperature, the
reaction mixture was again heated to reflux. The results are shown in Table 18. The results for 2-propanol are included for comparison and the percentages are isolated yields.

Table 18.

<table>
<thead>
<tr>
<th>Diazocompound</th>
<th>Alcohol</th>
<th>Methanol</th>
<th>$^1$PrOH</th>
<th>$^t$BuOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhSO$_2$N$_2$OEt</td>
<td>0.5 h reflux</td>
<td>18.0 h rt</td>
<td>(189, 64%)</td>
<td>(210, 90%)</td>
</tr>
<tr>
<td>(177)</td>
<td>(209, 92%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EtO$_2$P=N$_2$OEt</td>
<td>No Reaction</td>
<td>10.0 h reflux</td>
<td>(192, 83%)</td>
<td>(211, 63%)</td>
</tr>
<tr>
<td>(180)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The results clearly show that methanol reacts slowest of the three alcohols. The reaction with the diazo sulphone (177) requiring reflux conditions whilst with the $\alpha$-diazo phosphonate (180) there was no reaction, even under reflux conditions.

On the basis that one might expect methanol to exhibit the highest affinity for the vacant coordination sites of the catalyst on account of its small size and higher acidity (relative to 2-propanol and t-butanol) then the results of Table 17 do show some correlation with our understanding of the reaction mechanism thus far. This affinity for coordination would make it more unlikely for the diazo compound to interact with the catalyst to form the metallocarbenoid. Indeed, the diazo phosphonate (180) which is less "nucleophilic" than the diazo sulphone (177) (due to the electron withdrawing strength of a benzenesulphonyl group as compared to a diethyl phosphono group) is unable to displace the coordinated methanol molecules even under reflux conditions. The catalyst is effectively poisoned.
The picture with the secondary and tertiary alcohols is not so clear. One might expect 2-propanol to coordinate more efficiently to the active sites on the catalyst than t-butanol and hence show a decreased reactivity as a result in comparison. This is in fact demonstrated in the reactions with the diazo phosphonate (177); the reaction requiring twice as much time. However, the reactions of the secondary and tertiary alcohols with the diazo sulphone (180) show very little difference in rate. Indeed, the reaction appears to be slightly slower for the tertiary alcohol than for the secondary alcohol. In this case, one might infer that steric effects are now starting to play a part although how justifiable this is, is uncertain; nucleophilic attack of the metallocarbenoid bound with a benzenesulphonyl group might be expected to be more difficult for the tertiary alcohol than for the secondary alcohol and this is sufficient to make up for any influence the coordination effect has on the rate. In the case of the metallocarbenoid bound by a diethyl phosphono group, the tertiary alcohol has little difficulty in reacting as a nucleophile and hence the expected rate pattern is observed.

In 1973, Teyssie reported that ethyl diazoacetate (EDA) (175) showed some selectivity when added to equimolecular mixtures of different alcohols in the presence of rhodium (II) acetate.\textsuperscript{110} Ethanol (rel. rate = 2.12) appeared to be twice as reactive as t-butanol (rel. rate = 1.00) towards the rhodium carbenoid whilst 2-propanol (rel. rate = 1.20) and t-butanol (rel. rate = 1.00) showed approximately equal reactivity towards the same species. This reactivity order is the order of decreasing acidity as well as the order of increasing steric hindrance. If the coordination affinities of these alcohols for the catalyst were roughly similar then one might have predicted such an order of reactivity.

2.5 Other Rhodium (II) Catalysed Heteroatom-H Insertion Reactions

Although rhodium (II) catalysed intramolecular N-H and S-H insertion reactions are known in the literature\textsuperscript{90,91}, intermolecular reactions of this type are very rare.\textsuperscript{59b} Addition of an amine (eg. benzylamine) to an emerald green coloured solution of rhodium (II) acetate and ethyl diazoacetate (175) [or triethyl
diazophosphonoacetate (180)) in dichloromethane (or benzene) led to the immediate formation of a mauve coloured solution, suggesting coordination of the amine to the catalyst. No decomposition of the diazo compound could be effected even at reflux temperatures. It appears that under these conditions amine adduct formation is irreversible with the result that the catalyst is effectively poisoned. Attempts to insert into electron deficient N-H bonds were also unsuccessful although the catalyst in these cases showed no signs of being poisoned. It has been reported in the literature that α-diazo ketones will undergo rhodium (II) catalysed S-H insertions with thiophenol.\(^{60b}\) When this reaction was attempted with ethyl diazoacetate, it was observed that although the addition of the thiol to the reaction mixture turned the solution colour from green to red, suggesting adduct formation with the catalyst, the S-H insertion product was actually isolated in good yield. The presence of the catalyst was found to be essential for the reaction to occur. Obviously, there is great potential for research into this area of chemistry.

2.6 Investigations into the Synthesis of α-Diazo Sulphoxides

The rhodium (II) catalysed O-H insertion reaction of an unsymmetrical diazo compound with an alcohol results in the formation of chiral centre at what was formerly the "diazo" carbon. We were interested in seeing whether a chiral substituent α to the diazo function would be effective in inducing a degree of enantioselectivity into the process (Scheme 82). The substituent as well as being chiral had to be a fairly strong electron withdrawing group in order that the diazo compound itself could be prepared via the diazo transfer reaction. The substituent we decided to investigate was the phenylsulphinyl group and the diazo compound we chose to synthesise was phenylsulphinyl-ethoxycarbonyl-diazomethane (214) (Scheme 82).

The diazo transfer precursor (213) could be easily prepared by reaction of the sodium salt of thiophenol with ethyl bromoacetate (80%) followed by oxidation with sodium periodate (81%) (Scheme 82).\(^{111}\) (We were more interested at this stage in seeing whether the α-diazo sulphinyl compound could be prepared and whether it
would undergo insertion reactions and so did not attempt to prepare immediately the chiral derivative. We envisaged being able to prepare the chiral substrate later, by means of the Sharpless protocol. \(^{112}\)

Scheme 82.

\[
\text{ROH} \quad \text{Rh}_2(\text{OAc})_4 \quad \text{OR}^3
\]

Surprisingly, however, all attempts to prepare the diazo compound using the diazo transfer method with tosyl azide failed. Numerous bases were tried ranging from sodium hydride to DBU but in all cases the major reaction product isolated was an extremely unpleasant smelling sulphide or thiol. This result was in complete contrast to the analogous reaction leading to the \(\alpha\)-diazo sulphone (177).

In 1974, Hodson and Holt reported that their own attempts to prepare \(\alpha\)-diazo-\(\beta\)-keto sulphoxides failed. \(^{113}\) The failure of the diazo transfer reaction was ascribed as being due to the instability of the resulting \(\alpha\)-diazo keto sulphoxide (215) (Scheme 83). This instability was believed to be related to the greater nucleophilicity of the sulphoxide oxygen atom allowing it to assist in the elimination of dinitrogen as the

\[
\text{Reagents: i. PhS}^-\text{Na}^+, \text{EtOH; ii. NaIO}_4, \text{EtOH, H}_2\text{O}
\]

\(90\)
oxygen atom transferred from sulphur to carbon. Alternatively, loss of dinitrogen may have led to the formation of a carbene followed by transfer of the sulphone oxygen to the carbenic carbon (Scheme 83). In either case, solvolysis of the resulting thiol ester (216) would then furnish a keto acid or its ethyl ester and a thiol, which would be rapidly oxidised to the corresponding disulphide.

Scheme 83.

There are very few references pertaining to α-diazo sulfoxides in the literature and none of these compounds have a β-carbonyl substituent. Amongst the α-diazo sulfoxides that are known are the diazo analogues of ceph-3-em (S)-1-oxides (217) (Scheme 84).

Scheme 84.

In this case the extra activation is not provided by an ester or a ketone function but by a "vinyllogous" carbonyl group. This provides further evidence that the carbonyl group plays a significant role in destabilising α-diazo-β-keto sulfoxides and α-diazo-β-ester sulfoxides. In order to test this hypothesis, the synthesis of
phenylsulphinyl-vinyl acetate-diazomethane (222) was attempted (Scheme 85).

Scheme 85.

\[
\begin{align*}
\text{(218)} & \xrightarrow{\text{i}} \text{(219)} \\
\text{(220)} & \xrightarrow{\text{iii}} \text{(221)} \\
\text{(222)} & \xrightarrow{\text{v}}
\end{align*}
\]

Reaction of the sodium salt of thiophenol with bromo-diethylacetal yielded phenyl thiodiethylacetal (218, Scheme 85) (70%).

Hydrolysis of the acetal (219) furnished the aldehyde which underwent a Wadsworth-Emmons olefination reaction with triethyl phosphonoacetate to yield the ester (220) (52%). Oxidation as before with sodium periodate gave the sulphinyl derivative (221) in 51% yield which when subjected to the diazo transfer reaction with tosyl azide afforded the desired diazo compound (222) in 60% yield (Scheme 85).

However, although the diazo compound (222) decomposed rapidly on addition to a solution of rhodium (II) acetate in 2-propanol, a number of reaction products were formed none of which appeared to correspond to the expected insertion product. This was also found to be the case on addition of the same diazo compound to a solution of rhodium (II) acetate in methanol. This was very disappointing as we were aware that vinylidiazomethanes of this type (although with other electron withdrawing groups $\alpha$...
to the diazo function) underwent rhodium (II) acetate catalysed decompositions with pyrroles to afford azabicyclooctadienes\textsuperscript{116} and intramolecular [3+4]-cycloadditions with dienes to furnish fused seven membered carbocycles.\textsuperscript{117}

2.7 Conclusions

We have been able to successfully establish that the rate of rhodium (II) catalysed intermolecular O-H insertion reactions of diazo compounds with alcohols is markedly dependent on three factors; (a) the nature of the reacting diazo compound, (b) the nature of the ligands on the catalyst and (c) the nature of the alcohol.

Although these general observations fit in well with what we would have predicted on the basis of our previously imagined (and purely speculative) picture of the reaction mechanism, a number of other observations suggest that there are several other important factors involved in determining the overall rate of reaction. In spite of this, we are able to explain all of the observed results using our proposed reaction mechanism in conjunction with a number of assumptions. However, it would be very difficult to quantify the effect of these assumptions by themselves as a consequence of their very nature. Thus, although we have provided some evidence for our reaction mechanism, we still cannot rule out the possibility that other processes may be in operation.

In the course of this work, preparative methods for the synthesis of several \(\alpha\)-diazo phosphonates have been developed and a significant number of potentially synthetically useful compounds have been prepared. Additionally, rhodium (II) trifluoroacetamide has been shown to be a significantly more active catalyst than the conventionally used rhodium (II) acetate. Using this catalyst, chemistry has been successfully carried out with diazo compounds which were totally unreactive towards rhodium (II) acetate. All of the work in this chapter provides the basis for a huge amount of investigative chemistry and the results of our investigations into some aspects of this chemistry, provides the foundation for the work that will be discussed in Chapter 3.
CHAPTER THREE

α-DIAZO PHOSPHONATES IN CYCLIC ETHER SYNTHESIS
3.1 Introduction

The intermolecular rhodium (II) catalysed decomposition of α-diazo carbonyl compounds with alcohols has been extensively studied by Teyssie, although as far as we are aware only three examples of the analogous reaction with α-diazo phosphonates have been reported in the literature and these have already been discussed in the review (Chapter 1).

We were interested in probing some of the chemistry of the alkoxy-substituted phosphonate compounds [(192), (195), (199) and (202)] arising from O-H insertion reactions of the α-diazo phosphonates [(180), (184), (185) and (186)] with 2-propanol catalysed by rhodium (II) acetate or rhodium (II) trifluoroacetamide (Chapter 2). Theoretically, these compounds had the synthetic potential (in analogy with their respective parent diazo precursors) to undergo the Wadsworth-Emmons olefination reaction. The reaction products arising from the alkoxy-phosphonates [(192), (194), (199) and (202)] would be enol ethers as opposed to the usual olefins derived from a standard phosphonate.

![Chemical Structures](image)

Compounds with the substructure (RO)₂POCH(OR)C=O are known in the literature although there are only several references relating to them. They have been prepared by means of (a) the Arbusov reaction with suitable halides, (b) reaction of halides with sodium dimethylphosphite, (c) reaction of dimethyl phosphite and methyl glyoxalate hydrate under Dean-Stark conditions and (d) photolytic decomposition of diethyl cyanodiazomethylphosphonate (223) in alcohols (Scheme 86). These substrates did undergo subsequent Wadsworth-Emmons olefination reactions with aldehydes and ketones [for example, (224), Scheme 86].

It had been feared that perhaps one or two of our compounds [(192), (195),
(199) and (202)] would produce anions which due to the additional stabilising effect of the ether oxygen in conjunction with the flanking electron withdrawing groups, would be so stable as not to react with a carbonyl compound.

Scheme 86.

However, in all the examined cases with benzaldehyde, Wadsworth-Emmons reactions occurred smoothly in good yields to give isomeric mixtures of substituted styrenes, although the corresponding reaction with less reactive ketones was not examined. Thus, the reaction of triethyl 1-isopropyl-oxyphosphonate (192), diethyl 1-benzenesulphonyl-1-isopropyloxymethyl-phosphonate (199) and tetraethyl 1-isopropyloxymethyl-phosphonate (202) with benzaldehyde furnished the enol ethers (225), (226) and (227) respectively in good yields (64%, 72% and 85%) (Scheme 87).

Scheme 87.
Of particular synthetic interest was the formation of the $\alpha$-sulphonyl ether (226) and the $\alpha$-phosphono ether (227). A Chemical Abstracts search revealed that $\alpha$-sulphonyl ethers are a very rare species whilst the theoretical $\alpha$-keto sulphone is even rarer. Nearly all of the work reported concerning $\alpha$-sulphonyl ethers has been carried out by workers in Germany who prepared their compounds by reaction of the anions of $\alpha$-benzoylated alkylsulphonylmethyl ethers (228) with formaldehyde.\(^\text{124}\)

For example, the 1-alkoxyvinyl alkyl sulphone (229) could be prepared in 70% yield (Scheme 88).

Scheme 88.

\[
\text{(228)} \quad \xrightarrow{i} \quad \text{(229)}
\]

\text{Reagents: } i. \text{NaH, MeCN; H}_2\text{CO(g).}

With the knowledge that the insertion compounds [(192), (199) and (202)] underwent Wadsworth-Emmons reactions (Scheme 87), it was realised that one might be able to prepare cyclic ethers by exploiting the chemistry of these systems. The work that will be discussed in this Chapter thus involves the application of $\alpha$-diazo phosphonate chemistry to cyclic ether synthesis using two routes; (a) intermolecular rhodium carbenoid O-H insertion followed by Wadsworth-Emmons olefination and acid catalysed cyclisation and (b) intermolecular rhodium carbenoid O-H insertion followed by an intramolecular Wadsworth-Emmons reaction.
3.2. Cyclic Ether Synthesis: The Intermolecular Wadsworth-Emmons Reaction Route

An enol ether of type (230, Scheme 89), which could be derived from a Wadsworth-Emmons reaction between an alkoxy-phosphonate such as (192) and a suitable aldehyde, would theoretically be able to cyclise by a number of different routes; the synthesis of such a substrate is detailed below.

Scheme 89.

The enol ether (231) (Scheme 90) was readily accessible (50%) as a 1:1 mixture of E and Z isomers by reaction of triethyl diazophosphonoacetate (180) with 2-propanol in the presence of a catalytic amount of rhodium (II) acetate followed by an intermolecular Wadsworth-Emmons reaction with 4-t-butyldimethylsiloxybutanal (Scheme 90). The aldehyde was prepared in good yield (ca. 70%) by mono t-butyldimethylsilyl (TBS) protection of 1,4-butanediol followed by oxidation with pyridinium chlorochromate (PCC).

Scheme 90.
Removal of the silyl protecting group was readily effected by warming in 3:1:1 glacial acetic acid/THF/water mixture at 45-50°C (79%) (232, Scheme 91). On treatment with camphorsulphonic acid (CSA) in refluxing benzene, the isomeric mixture of enol ethers (232) cyclised to the dihydropyran (233) in a modest 47% yield (Scheme 91).

Scheme 91.

\[
\begin{align*}
\text{HOAc(aq)} & \quad \xrightarrow{\text{EtO\textsubscript{2}O\textsubscript{OTBS}}} \quad \text{EtO\textsubscript{2}O\textsubscript{OH}} \\
\text{CSA} & \quad \xrightarrow{\text{PhH, } \Delta} \quad \text{EtO\textsubscript{2}O} \\
\end{align*}
\]

A large amount of a single isomer, which was found to be the Z-isomer of the starting material, was recovered after reaction and the reaction yield is actually 86% based on recovered starting material. In an analogous manner the tetrahydro-oxepin (236) was prepared from the enol ether (235) derived from reaction of triethyl 1-isopropoxyphosphonoacetate (192) with 5-t-butyldimethylsiloxypentanal (Scheme 92). This time the cyclisation reaction time was trebled in order to determine whether all of the starting material could be made to react. After three hours at reflux in the presence of a catalytic amount of camphorsulphonic acid, no starting material could be observed by TLC and an 81% yield of the cyclic ether (236) was isolated after work-up and chromatography.

An attempt was also made to apply this intermolecular Wadsworth-Emmons methodology to the synthesis of a tetrahydro-oxepin with a benzenesulphonyl group
in the 2-position through the use of the isopropyloxy insertion product (199) derived from benzenesulphonyl-ethoxy carbonyl-diazomethane (185) (Scheme 93).

Scheme 92.

\[
\begin{align*}
\text{EtO} & \quad \text{N} \quad \text{EtO} \\
\text{Rh}_2(\text{OAc})_4 & \quad \text{PrOH} \\
(180) & \quad \rightarrow \\
\text{EtO} & \quad \text{PrO} \\
(192) & \\
\text{NaH}, \text{THF} & \quad H \quad \text{C} \quad \text{H} \quad \text{O} \\
(235) & \quad \rightarrow \\
\text{HOAc(aq)} & \\
(234) & \\
\text{CSA} & \quad \text{PhH}, \text{reflux} \\
(236) & \\
\end{align*}
\]

The intermolecular Wadsworth-Emmons reaction with 5-t-butyldimethylsiloxypentanal afforded the enol ether (237) in 84% yield and subsequent removal of the silyl protecting group yielded the enol ether (238) in 85% yield (Scheme 93). However the acid catalysed cyclisation to the tetrahydro-oxepin (239) failed despite prolonged heating of the substrate in benzene (and also toluene).

The mechanism for the cyclisation reaction presumably proceeds via the formation of an oxonium ion reactive intermediate (Scheme 94) which is rapidly attacked by the pendant hydroxy group. Elimination of 2-propanol leads ultimately to the formation of the heterocycle. It appears therefore in the case of the sulphonyl derivative that the powerfully electron withdrawing benzenesulphonyl group is able
to pull enough electron density away from the olefin system to either inhibit the formation of the oxonium ion reactive intermediate (A) or reduce the electrophilicity of the carbon centre in the oxonium ion such that the pendant hydroxy group is insufficiently nucleophilic to effect cyclisation (Scheme 94).

Scheme 93.

It may be possible that the use of a very strong acid such as trifluoroacetic acid or a Lewis acid such as boron trifluoride-etherate might induce cyclisation although as yet these have not been tried.

3.3 Cyclic Ether Synthesis: The Intramolecular Wadsworth-Emmons Reaction Route

3.3.1 Initial Studies

The second α-diazo phosphonate based route to cyclic ethers that has been developed involves the use of the intramolecular variant of the Wadsworth-Emmons reaction. Reactions of this type have been used to prepare γ-lactones, tetra-
hydropyridines,\textsuperscript{127} cyclopentanones\textsuperscript{128} and various macrocycles\textsuperscript{129,130} but as far as we are aware, has not been applied to medium ring cyclic ether synthesis.

Scheme 94.

It was found that treatment of triethyl diazophosphonoacetate (180) and 1-t-butylidimethylsiloxy-4-hydroxybutane in refluxing benzene with a catalytic amount of rhodium (II) acetate led to the formation of the alkoxy-phosphonate (240) in good yield (78%) (Scheme 95).

Scheme 95.

Facile removal of the silyl protecting group in good yield (90\%) to give (241) was achieved using the glacial acetic acid/water/THF protocol described previously
Functional group conversion of the resulting alcohol using pyridinium dichromate (PDC) (or alternatively under Swern conditions) \(^{131}\) led to the formation of the aldehyde (242) (Scheme 96).

Scheme 96.

Although this aldehyde could be isolated pure after silica gel chromatography, it was not found to be particularly stable; a gradual disappearance of the aldehydic peak in the \(^1\)H NMR was observed on standing at room temperature for several hours. In order to minimise the effect of aldehyde decomposition in subsequent reactions the crude aldehyde was used without purification. On slow addition of this substrate to relatively dilute (4.7 mM) suspension of sodium hydride in THF at 0°C, an intramolecular Wadsworth-Emmons reaction took place leading to the formation of the dihydropyran (233) in a modest 46% yield (Scheme 97).

Scheme 97.

The sequence was successfully repeated using 1-t-butyldimethysiloxy-3-hydroxypropane and 1-t-butyldimethylsiloxy-5-hydroxypentane affording the dihydrofuran (243) and the tetrahydro-oxepin (236) derivatives respectively (Scheme 103).
The formation of the tetrahydro-oxepin (236) was particularly satisfying in relation to our general interest in preparing seven membered ring oxygen heterocycles. Although the aldehyde of the phosphonate derived from insertion with 1-t-butyldimethyldimethyloxysilox-6-hydroxyhexane (242, n=4) could be prepared, none of the eight membered ring cyclic ether could be isolated on treatment with sodium hydride. Scheme 98.

The results of Schemes 97 and 98, illustrate some of the obstacles faced in the synthesis of medium rings; namely entropy loss, undesirable transannular interactions, torsional strain and angle deformation in transition states and products.
It appears that the formation of the eight membered ring is unfavourable in our case as the entropy of the system outweighs the enthalpic factors which on the whole favour cyclisation. As a result dimerisation routes are presumably preferred. In the case of five-, six- and seven-membered rings, the situation is reversed; these heterocycles possess lower free energy relative to their acyclic derivatives. This finely balanced enthalpy/entropy relationship explains why in contrast to the wealth of facile, high yielding methods available for five- and six-membered rings, there are comparatively far fewer synthetic methods for the formation of seven-, eight- and larger membered rings. It is precisely for this reason that we felt justified in spending time developing the methodology for the formation of seven-membered ring cyclic ethers through our two Wadsworth-Emmons reaction methodologies outlined so far, in addition to our interest in developing the methodology involving the intramolecular rhodium (II) catalysed O-H insertion reactions of diazo alcohols.

This intramolecular Wadsworth-Emmons route methodology could also be applied to other α-diazo phosphonates. Using acetyl-ethoxy carbonyl-diazoacetate (184) as opposed to triethyl diazophosphonoacetate (180) as our diazo substrate, the formation of the acetyl substituted dihydropyran (247) and acetyl substituted tetrahydro-oxepin (248) was possible (Scheme 99).

We were interested in probing some of the chemical characteristics of this tetrahydro-oxepin system (248) and so some simple experiments were performed. Hydrogenation over a palladium-charcoal catalyst afforded the reduced product (249) in 71% yield. This reduced substrate behaved as a simple ketone undergoing a Grignard reaction with methylmagnesium bromide to furnish the alcohol (250) in 84% yield (Scheme 100) and undergoing alkylithium reactions with phenyllithium to yield the alcohol (251) in 92% yield (Scheme 101). The tetrahydro-oxepin (248) itself behaved just as typical enone system undergoing purely 1,2-addition with phenyllithium at -78°C to afford the unsaturated alcohol (252) in 99% yield. Lack of material precluded any attempt to carry out a selective 1,4-addition with an organocuprate reagent although one would not envisage difficulties with such a reaction on the basis of the results just outlined (Schemes 100 and 101).
Scheme 99.

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{N} & \quad \text{2} & \quad \text{2} & \quad \text{2} & \quad \text{2} \\
\end{align*}
\]

(184) \rightarrow \text{Rh}_2\text{(OAc)}_4 \rightarrow \text{PhH, reflux} \rightarrow \text{HO-} \text{-} \text{OTBS}

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

(244) \rightarrow \text{HOAc(aq)}

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

(246) \rightarrow \text{PDC, DCM}

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

(245) \rightarrow \text{NaH, THF}

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

(247) n=2, 46% \quad (248) n=3, 32%

Scheme 100.

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

(248) \rightarrow \text{Pd-C, H}_2 \rightarrow \text{EtOAc}

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

(249) 71%

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

(249) \rightarrow \text{MeMgBr} \rightarrow \text{Et}_2\text{O, 0°C}

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

(250) 84%

106
The intramolecular Wadsworth-Emmons route methodology could also be applied when using secondary alcohols as opposed to simple primary alcohols. Those alcohols investigated were prepared by reaction of the Grignard reagents, methylmagnesium bromide and phenylmagnesium bromide respectively, with 1,5-t-butyldimethylsiloxypentanal. Rhodium (II) mediated O-H insertion followed by deprotection, oxidation and treatment with sodium hydride, as before, afforded the 7-substituted tetrahydro-oxepins (256) and (257) respectively (Scheme 102). This illustrates the point that rhodium carbenoids will generally react with all but the most highly hindered alcohols depending on the substrate. \(^{118,119,132}\)

3.3.2 The Intramolecular Wadsworth-Emmons Route: The Use of Terminal Alkenols and Alkynols

Amongst the many drawbacks of this methodology was the requirement to monoprotect the starting diol. This is obviously necessary to prevent the formation of double insertion/addition products. We hoped to circumvent this protection/deprotection problem by going directly to the carbonyl compound from the insertion product through the use of terminal alkenols.

Treatment of triethyl diazophosphonoacetate (180) and 5-hexen-1-ol in refluxing benzene with a catalytic amount of rhodium (II) acetate led to the formation of one major product which was that arising from O-H insertion (66%) (258) (Scheme
No product arising from cyclopropanation was observed. This was in agreement with observations made by Teyssie in competition experiments between the O-H and olefin functions of allyl alcohols with α-diazo ketones in the presence of rhodium (II) acetate; it was noted that O-H insertion products were almost invariably obtained even in the most sterically demanding environments although the reaction rate was significantly slower in these cases. A shift to cyclopropane formation could be
effected by the use of highly electron rich olefins or by using copper catalysts.\textsuperscript{118,132} These results illustrate the reluctance of electrophilic metallocarbenoids to add to electron poor double bonds.

Surprisingly however, all attempts to convert the alkoxy-phosphonate (258) to the aldehyde (259) by ozonolysis in dichloromethane failed in our hands (Scheme 103).

Scheme 103.

\[ \text{Scheme 103.} \]

Rhodium (II) catalysed insertion of triethyl diazophosphonoacetate (180) into the O-H bond of the terminal alkynol, 5-hexyn-1-ol, led to the formation of the alkoxy-phosphonate (260, n=3) in preference to formation of the cyclopropene. This was in agreement with observations made by Teyssié with respect to the rhodium (II) acetate catalysed reactions of α-diazo ketones with propargylic alcohols. In these cases, formation of the propargylic ether was again preferred although the reaction was far more sensitive to steric effects than the reaction with allyl alcohols. Cyclopropanation could therefore become the dominant reaction in
certain situations.\textsuperscript{118,119}

The alkyne (260, $n=3$) was found to be easily converted to the ketone functionality by mercury (II) catalysed hydration and this ketone (261, $n=3$) itself underwent the corresponding intramolecular Wadsworth-Emmons reaction on treatment with sodium hydride, leading to the formation of the 3-substituted tetrahydro-oxepin (264) in 47\% yield (Scheme 104).

Scheme 104.

In the same way the 3-substituted dihydrofuran (262) and the 3-substituted dihydropyran (263) could be prepared from the reaction products of triethyl diazophosphonoacetate (180) with 3-butyn-1-ol and 4-pentyn-1-ol respectively (Scheme 104).

5-Hexyn-1-ol was found to smoothly insert into acetyl-ethoxy carbonyldiazomethane (184) as well, yielding the alkoxy-phosphonate (265) in 66\% yield. However, on addition of sodium hydride to the derived ketone, no reaction appeared to
occur and the starting material was recovered unchanged.

3.3.3 The Intramolecular Wadsworth-Emmons Route: The Use of Amide, Sulphono and Phosphono α-Substituted Diazo Phosphonates

Although we were now in a position to prepare 3- and 7-substituted tetrahydro-oxepins using the intramolecular Wadsworth-Emmons route protocol, we were still rather limited in our choice of functional groups positioned in the 2-position; so far we had been able to incorporate the ethyl ester functionality (236, 256, 257 and 264), the acetyl functionality (248) and the carbinol (252) arising from the reaction of phenyllithium with the acetyl derivative (248). In order to expand the synthetic utility of the route, attempts were made to incorporate the CONMe(OMe) functionality, the so-called Weinreb amide,133 into the 2-position of the tetrahydro-oxepin. This functionality is an established pseudo-aldehyde equivalent since on reduction with lithium aluminium hydride an aldehyde is formed. It was hoped that a wide range of ketones (266) would then be available by means of a general route through the use of such a substituted tetrahydro-oxepin (267) (Scheme 105). The alternative was to proceed each time using the correct α-diazo phosphonate prepared by diazo transfer reaction with the phosphonate, prepared via the Michaelis-Arbusov reaction, with tosyl azide.

Scheme 105.

\[
\begin{align*}
\text{MeO, N-} & \quad \text{OAR}_3 \\
\text{(267)} & \quad \text{MeO, N-} \\
\text{OAR}_3 \\
\end{align*}
\]

Diazo transfer to the commercially available Weinreb phosphonate, diethyl (N-methoxy-N-methyl-carbomoylmethyl)phosphonate (268), was effected through the use of potassium hydride and tosyl azide, affording the desired α-diazo phosphonate (269) in a disappointing 36% yield (Scheme 106). Attempts to
prepare this α-diazo phosphonate using triethylamine as base led to no reaction at all whilst using sodium hydride as base led to the formation of unidentified reaction products.

The rhodium (II) catalysed O-H insertion reactions of the α-diazo amide (269) with 1-t-butyldimethylsiloxy-5-hydroxypentane and 5-hexyn-1-ol respectively were successful although the yields were extremely disappointing (32 and 39% respectively). This was surprising as these compounds appeared to be by far the major products by TLC (Scheme 107).

Scheme 106.

![Scheme 106](image)

Scheme 107.

![Scheme 107](image)

As a consequence of the low yielding formation of the insertion products (270) and (271) in addition to the low yielding diazo transfer reaction, it was felt that no synthetic advantage could be gained in continuing the sequence in relation to the
previous work and the idea was abandoned at this stage. Although the Weinreb amide could not be incorporated into the 2-position, we were able to incorporate the benzenesulphonyl and diethyl phosphono groups in this position through the use of the \(\alpha\)-benzenesulphonyl diazo phosphonate (185) (Scheme 108) and the \(\alpha\)-diethyl phosphono diazo phosphonate (186) (Scheme 109) respectively. However the yields of the Wadsworth-Emmons step were disappointingly low [24 (275) and 28% (279) respectively]. The rhodium (II) catalysed O-H insertion reaction of the \(\alpha\)-diazo bis-phosphonate (186) with the alcohol, 1-t-butyldimethylsiloxy-5-hydroxypentane, required the use of rhodium (II) trifluoroacetamide in order to ensure full decomposition of the diazo compound as no reaction was observed at all with rhodium (II) acetate (Chapter 2). The low yielding formation of the tetrahydro-oxepin (279) was particularly disappointing as we had hoped to be able to carry out subsequent Wadsworth-Emmons reactions with the reduced substrate to ultimately prepare spiroketals (in the fashion of Ley).\(^{134}\)

The \(\alpha\)-diazo phosphonate, diethyl diazomethylcyanophosphonate (223, Scheme 86) is known in the literature (although the yield of formation was poor). Therefore it appears that the tetrahydro-oxepin functionalised with a cyano group in the 2-position could also be synthesised, by analogy with our other previously prepared functionalised tetrahydro-oxepins.

### 3.4 Conclusions

We have successfully developed two novel routes leading to the formation of five-, six- and seven-membered ring oxygen containing heterocycles. With respect to our general interest in preparing seven membered ring cyclic ethers, a range of tetrahydro-oxepins functionalised in the 2-position were synthesised using these routes. However, the yields of formation of these compounds were generally low.

A substructure search in Chemical Abstracts and on the REACCS system revealed that although dihydrofurans and dihydropyrans substituted with a carbonyl group in the 2-position (of the type prepared in this work) are known in the literature, the
corresponding tetrahydro-oxepin is not known. Presumably, the same compound functionalised with other groups in the 2-position such as (275 and 279) are also unknown and thus it appears that a whole new class of seven-membered ring oxygen heterocycle has been prepared.

Studies into samarium (II) iodide catalysed cyclisations of suitably prepared insertion products have also been initiated, although this has so far met with little success.

Scheme 108.

\[
\begin{align*}
\text{Scheme 108.} \\
\text{(185)} \\
\end{align*}
\]
Scheme 109.

\[
\begin{align*}
\text{EtO} & \quad \text{PO} \quad \text{EtO} \\
\text{EtO} & \quad \text{PO} \quad \text{EtO} \\
\text{N}_2 & \quad \text{(186)} \\
\end{align*}
\]

\[
\text{Rh}_2(\text{NHCOCF}_3)_4 \quad \text{PhMe, reflux} \\
\]

\[
\begin{align*}
\text{EtO} & \quad \text{PO} \quad \text{EtO} \\
\text{EtO} & \quad \text{PO} \quad \text{EtO} \\
\text{H} & \quad \text{(276) 74\%} \\
\end{align*}
\]

\[
\text{HOAc} (\text{aq}) \\
\]

\[
\begin{align*}
\text{EtO} & \quad \text{PO} \quad \text{EtO} \\
\text{EtO} & \quad \text{PO} \quad \text{EtO} \\
\text{H} & \quad \text{(277) 82\%} \\
\end{align*}
\]

\[
\text{NaH, THF} \\
\]

\[
\begin{align*}
\text{C} & \quad \text{PO(OEt)}_2 \\
\text{PO(OEt)}_2 & \quad \text{(279) 28\%} \\
\end{align*}
\]
CHAPTER FOUR

ROUTES TO BICYCLIC Ethers: Elaboration of 2-Substituted 3-OxoOxepanes
4.1 **Introduction**

As has been mentioned several times already, the methodology leading to the formation of seven-membered ring oxygen heterocycles via the rhodium (II) catalysed decomposition of diazo alcohols has been previously developed in the group (Table 8).67

Table 8.

<table>
<thead>
<tr>
<th>R</th>
<th>Z</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a H C_O2But</td>
<td>48-56</td>
<td></td>
</tr>
<tr>
<td>b n-C_6H_13</td>
<td>CO2Bu^t</td>
<td>64</td>
</tr>
<tr>
<td>c H</td>
<td>Ac</td>
<td>62</td>
</tr>
<tr>
<td>d n-C_6H_13</td>
<td>Me_3Si(H)</td>
<td>56</td>
</tr>
<tr>
<td>e n-C_6H_13</td>
<td>SO2Ph</td>
<td>73</td>
</tr>
<tr>
<td>f n-C_6H_13</td>
<td>PO(OEt)_2</td>
<td>54</td>
</tr>
<tr>
<td>g H</td>
<td>PO(OEt)_2</td>
<td>52</td>
</tr>
</tbody>
</table>

Reaction Conditions: 1 mol% Rh_2(OAc)_4 in refluxing benzene.

Some of the chemistry of these 2-substituted 3-oxooxepanes has been previously investigated.67,68 The 2-phenylsulphonyl-3-oxooxepane (206) and the 2-diethyl phosphono-3-oxooxepane (208) (Scheme 110), in particular, were found to be versatile substrates for further elaboration and could be readily converted into substituted oxepanes. Some of the synthetic transformations that have been achieved by other workers with these types of system are illustrated in the sequence leading to the cis-2,7-disubstituted oxepane skeleton of the marine natural product,
isolaurepinnacin (280) (Scheme 110). This natural product skeleton could be prepared by means of three different routes from the oxepanes (206), (207) and (208) respectively (Scheme 110).

Scheme 110.


We were interested in investigating whether it would be possible to prepare bicyclic systems from intermediates such as (281) and (282) (Figure 2). These could theoretically be prepared by means of synthetic elaboration of 2-substituted 3-oxooxepane systems such as the ester (207), the sulphone (206) or the phosphonate (208).

Of the three possible starting materials (206), (207) and (208), the oxepane-phosphonate (208) was the most attractive to us. Not only can it be prepared fairly easily in good yield, but the phosphonate group is lost in the collapse of the
oxaphosphetane to the olefin in the course of the Wadsworth-Emmons olefination reaction, so negating the need for a separate defunctionalisation step.

Figure 2.

In contrast, the substrates (206) and (207) require an extra step to remove the ester and sulphonyl groups respectively. Moreover, the cyclisation substrate (282) would be more readily accessible through the oxepane-phosphonate by means of a Wadsworth-Emmons reaction than via synthetic elaboration of the oxepane-ester or sulphone.

4.2 The 2-Diethyl Phosphono 3-Oxooxepane Route

Thus, the oxepane-phosphonate (208) was prepared following the procedure of Davies, Moody and Taylor as depicted in Scheme 111.67 The ring opening of δ-lactones with anions such as diethyl lithiomethylphosphonate (or lithiomethyl phenyl sulphone) is not straightforward since the product β-keto compounds are more acidic than the substrates from which they are derived. Therefore, after addition of the δ-lactone to the anion, one equivalent of LDA is added followed by quenching with an excess of trimethylsilyl chloride.135 The resulting trimethylsilyl enol ether is readily hydrolysed on work-up and the crude product is then immediately subjected to the diazo transfer reaction. Acidic cleavage of the trimethylsilyl ether yielded the diazo alcohol in 55% overall yield which on heating in boiling benzene in the presence of a catalytic amount of rhodium (II) acetate afforded the desired oxepane-phosphonate in 54% yield (Scheme 111).

In contrast to 2-ester substituted 3-oxooxepanes which exist as a mixture of keto and enol forms in solution, the 2-diethyl phosphono substituted 3-oxooxepane
exists exclusively in the keto form.

It was known from previous work that this oxepane-phosphonate undergoes Wadsworth-Emmons olefination reactions with aldehydes and indeed, reaction with 1-dimethyloxybutanal afforded the oxepane (283) in 76% yield (Scheme 112).

Scheme 111.

Reagents: i. LiCH$_2$PO(OEt)$_2$, THF, -78°C; LDA (1 equiv.), Me$_3$SiCl (2 equiv.); ii. NH$_4$Cl (aq); iii. MsN$_3$, TEA, DCM; iv. H$_3$O$^+$; v. Rh$_2$(OAc)$_4$, PhH, reflux.

As had been observed earlier, the reaction gives largely (>90%) one geometrical isomer which on the basis of the chemical shift of the vinyl proton in the $^1$H NMR can be assigned as the Z-alkene.

The thexyldimethylsilyl (TDS) group was the hydroxyl protecting group of choice in this case since it has very similar properties to the t-butyldimethylsilyl (TBS)
group concerning conditions of introduction, stability and cleavage, but is less costly.\textsuperscript{136,137} As a guideline to stability, TDS ethers are about two to three times more stable to acidic hydrolysis and cleavage with fluoride ions compared to the corresponding TBS ethers.

Scheme 112.

\[
\begin{align*}
\text{R} & \quad \text{PO(OEt)}_2 \\
\text{NaH, THF} & \quad \text{OTDS} \\
\text{R} &= \text{n-C}_6\text{H}_{13} \ (208) \\
\end{align*}
\]

(283)

The silyl protecting group could be removed at this stage by stirring in 5\% ethanolic HCl, resulting in the formation of one of our two target cyclisation substrates (282, \(n=2\)) (56\%) (Scheme 113). However, attempted acid catalysed cyclisation in refluxing benzene which we hoped would lead to the spiro-acetal (284) was unsuccessful;\textsuperscript{134,138} a large number of reaction products were formed by TLC and consequently no attempt was made to purify the mixture (Scheme 113).

Scheme 113.

\[
\begin{align*}
\text{R} & \quad \text{OTDS} \\
\text{NaH, THF} & \quad \text{OTDS} \\
\text{R} &= \text{n-C}_6\text{H}_{13} \ (283) \\
\end{align*}
\]

(284)

Reagents: i. 5\% HCl/\text{EtOH}; ii. camphorsulphonic acid (CSA), PhH, reflux.

This was extremely disappointing as we had hoped that a process analogous to that leading to the formation of mono-cyclic ethers via our Wadsworth-Emmons/acid-catalysed cyclisation route (Chapter 3), would occur.\textsuperscript{139} However, in comparison, the olefin in this particular system (282) is rather unusual; not only is it a component of an exocyclic-enol ether system, it is additionally a component of an exocyclic-enone system. It was hoped that simplification of the cyclisation substrate
(282) by removal of the carbonyl function might minimise the possibility of deleterious side reactions and therefore lead to cyclisation. Selective reduction of the ketone to the alcohol through the use of the sodium borohydride/cerium chloride protocol was attempted. Surprisingly however, the reduction led to the formation of a large number of reaction products and again no attempt was made to purify the mixture. Attempted reduction with diisobutylaluminium hydride (Dibal) at -40°C led to a similarly disappointing result (Scheme 114).

It is therefore quite apparent that the electronics of this enol ether/enone system impart some rather unusual properties, and consequently some rather unexpected chemistry, to the substrate.

Scheme 114.

Reagents: i. NaBH₄/CeCl₃·7H₂O, MeOH and also Dibal, PhMe, -40°C.

In contrast to our failure to reduce selectively the carbonyl function of the oxepanone (283) (Scheme 114), selective reduction of the olefin by palladium catalysed hydrogenation was relatively simple, affording the oxepanone (285) as a mixture of cis- and trans-isomers in a ratio of ca. 2:1 (Scheme 115). Epimerisation of the mixture gave exclusively the thermodynamically more favourable cis-2,7-disubstituted oxepane diastereoisomer; that is the diastereoisomer with the n-hexyl and the 4-dimethylthexylsiloxybutyl chains in pseudo-equatorial positions. The yield over the two steps was 76%. Removal of the thexyldimethylsilyl group (TDS) was achieved using acidic alcoholic conditions as before (Scheme 113) to yield the oxepanone (281, n=2) in 71% yield. On treatment with trimethylsilyl triflate and triethylsilane in dichloromethane at 0°C, conditions developed by Olah and used to great effect by Nicolaou, the oxepanone (281, n=2) cyclised, leading to the
formation of the 7/7-fused bicyclic system (7-hexyl-2,3,4,5,5a,7,8,9,10,10a-decahydro-oxepino[3,2-b]oxepin) (286) in 51% yield as a ca. 3:1 mixture of trans/cis isomers (Scheme 115).

Scheme 115.

\[
\begin{align*}
R = \text{n-C}_6\text{H}_{13} & \quad (283) \\
\text{Roms} & \quad (285) \\
\text{Reagents:} & \quad \text{i. } \text{H}_2, \text{ Pd-C}, \text{ EtOAc}; \text{ ii. } \text{NaOMe (cat.)}, \text{ MeOH}; \text{ iii. } 5\% \text{ HCl/EtOH}; \text{ iv. } \text{Et}_3\text{SiH}, \text{ TMS-OTf}, \text{ DCM}, 0^\circ\text{C}.
\end{align*}
\]

Reagents: i. H₂, Pd-C, EtOAc; ii. NaOMe (cat.), MeOH; iii. 5% HCl/EtOH; iv. Et₃SiH, TMS-OTf, DCM, 0°C.

The isomeric ratio was determined by separating out the two isomers as far as possible by careful chromatography (and by comparing TLC staining intensities). The major product was the less polar component by TLC. The stereochemistry at the ring junction for this isomer was determined by NOE experiments. Pre-irradiation of the multiplet at \(\delta = 3.31-3.36\) (10a-CH) resulted only in enhancement of the signal at \(\delta = 3.62-3.76\) (2-CH₂) whilst pre-irradiation of the multiplet at \(\delta = 3.22-3.28\) (5a-CH) resulted only in enhancement of the multiplet at \(\delta = 3.41-3.46\) (7-CH) (Figure 3 and Spectrum 1).¹⁸⁰

In exactly the same fashion, the 7/6-fused bicyclic system (6-hexyl-3,4,4a,6,7,8,9,9a-octahydro-pyrano[3,2-b]oxepin) (287) could be prepared in 78% yield (trans/cis ratio ca. 3:1) from the oxepanone (281, n=1) derived from the Wadsworth-Emmons product (283, n=1). This itself was prepared by
reaction of the oxepane-phosphonate (208) with 1-dimethylthexyl-siloxopropanal (Scheme 116). However, the attempted cyclisation of the oxepanone (281, n=3) to the 7/8-fused bicyclic system led to the formation of a number of products by TLC, none of which could be identified as being the desired bicyclic ether (Scheme 116).

Figure 3.

The 7/7-fused bicyclic system (2,3,4,5,5a,7,8,9,10,10a-decahydro-oxepino[3,2-b]oxepin) (289) derived from diethyl-3-oxooxepane-2-phosphonate (290) [formed by the initial ring opening reaction of diethyl lithiomethylphosphonate with 8-valerolactone67 (Scheme 111, R=H)] was also successfully prepared [79%, trans/cis ratio ca. 2:1 (by 1H and 13C NMR)] (Scheme 116).180

The observed trans-selectivity in the triethylsilane/trimethylsilyl triflate reaction was fortunate as natural products containing 7/7- or 7/6-fused bicyclic ethers [such as hemibrevetoxin (Figure 4) and brevetoxin B (Figure 5)] invariably contain the trans-relationship at the ring junction as opposed to the cis. Natural products containing medium ring ethers are widespread and the two natural products shown (Figures 4 and 5) highlight some of the fascinating spectrum of structure that they often contain.

Figure 4.
Scheme 116.

Reagents: i. NaH, THF, 0°C, OHCCH₂(CH₂)ₙOTDS; ii. H₂, Pd-C, EtOAc; iii. NaOMe (cat.), MeOH; iv. 5% HCl/EtOH; v. Et₃SiH, TMS-OTf, DCM, 0°C.

Figure 5.
4.3 The 2-t-Butyl Ester 3-Oxooxepane Route

In addition to developing the chemistry of the 2-phosphono substituted 3-oxooxepane system, we were keen to develop the chemistry of other oxepane systems as part of our general investigations into chemical modifications of medium ring ethers. We therefore set upon trying to prepare the 7/6-fused bicyclic system (287) by means of the 2-t-butyl ester substituted 3-oxooxepane (207). We chose to look at the t-butyl ester rather than the ethyl ester derivative for the simple reason that the t-butyl ester group is removed more easily than the ethyl ester group.

The 2-t-butyl ester 3-oxooxepane (207) was prepared using the procedure of Davies, Moody and Taylor (Scheme 117).67 The procedure involved the ring opening of undecanoic acid δ-lactone with lithiated t-butyl diazoacetate9 followed by acetic acid quench. This gave, in essentially one step, the diazo alcohol precursor to cyclisation (204) in 60% yield (lit. yield 67%). Cyclisation in boiling benzene in the presence of a catalytic amount of rhodium (II) acetate led to the formation of the desired oxepane in 56% yield (lit. yield 64%)67 (Scheme 117).

Scheme 117.

Reagents: i. LiC(N₂)CO₂Bu, THF, -78°C; ii. AcOH; iii. Rh₂(OAc)₄, PhH, reflux.

Other diazo alcohols that have been prepared in this manner are those arising from reaction of the organolithium derivatives of ethyl diazoacetate, diazoacetone and trimethylsilyldiazomethane with undecanoic acid δ-lactone (or δ-valerolactone) respectively (Scheme 118).67 This technique, in conjunction with that involving the ring opening reactions of the organolithium derivatives of diethyl methylphosphonate and methyl phenyl sulphone, provides a powerful methodology
for the preparation of a wide range of functionalised diazo alcohols, leading in turn to a wide range of functionalised 2-substituted 3-oxooxepanes. The two complementary techniques are summarised in Scheme 118.

Although t-butyl diazoacetate (TBDA) (295) is not commercially available like ethyl diazoacetate (EDA), it can be easily prepared by diazotisation of t-butyl acetoacetate followed by deacetylation of the β-keto ester (294) (Scheme 119).  

**Scheme 118.**

Reagents: i. Z(Li)C=N₂, THF, -78°C; ii. ZCH₂Li, THF, -78°C; LDA (1 equiv.), Me₃SiCl (2 equiv.); iii. MsN₃, TEA, DCM; iv. 0.5 M HCl, THF; v. Rh₂(OAc)₄, PhH, reflux.

**Scheme 119.**

Reagents: i. TsN₃, TEA, MeCN, 0°C; ii. NaOMe, MeOH, -10°C.

Following the work of Davies and Moody, allylation in the 2-position was possible by treatment of the sodium salt of the oxepane-ester (207) with allyl acetate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (296,
86%) (Scheme 120). Removal of the t-butyl ester could be effected by heating at 150°C in the presence of a catalytic amount of 4-toluenesulphonic acid. This gave predominantly the cis-isomer (297) [by TLC and 1H NMR (NOE)]. Epimerisation as before with sodium methoxide effected complete conversion to the more favourable cis-2-7-disubstituted oxepane arrangement (59%) (Scheme 120).

Scheme 120.

Reagents: i. NaH, THF, allyl acetate, Pd(PPh₃)₄; ii. p-TSA, Δ; iii. NaOMe (cat.), MeOH.

Two methods were ultimately used for the preparation of the desired cyclisation precursor.

Method 1.

After protecting the ketone functionality by means of an ketal group (63%), the oxepane (298) was subjected to a hydroboration reaction with borane-tetrahydrofuran complex which afforded the oxepane (299) in 61% yield after oxidative work-up and chromatography (Scheme 121).

The ketal was subsequently hydrolysed back to the ketone by treatment with acid yielding the precursor to cyclisation, the oxepane (281, n=1), in 74% yield. This could be cyclised to the isomeric mixture of bicyclic ethers (287) using the Olah/Nicolaou protocol as before (Scheme 121).¹⁴²,¹⁴³ The cis-relationship between alkyl substituents in the substrates (298) and (299) was maintained throughout the sequence as monitored by NOE experiments.
Method 2

The oxepanone (281, n=1) was also accessible from the oxepane (297) by a second alternative route (Scheme 122). This involved reduction of the ketone using sodium borohydride to give the oxepane (300) as a mixture of diastereoisomers in 94% yield. Hydroboration using borane-tetrahydrofuran complex followed by oxidative work-up as before, afforded the diol (301) in 70% yield which was treated with t-butyldimethylsilyl chloride and triethylamine in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane. These conditions have been shown to lead to selective protection of primary hydroxyl groups in the presence of secondary hydroxyl groups\(^{144}\) but in our hands only a poor yield (57%) of the desired primary hydroxyl TBS protected oxepane (302) was isolated. However, the secondary hydroxyl group could be oxidised to the ketone (303) in good yield (88%) using pyridinium chlorochromate (PCC) and subsequent removal.
of the silyl protecting group could be readily effected by warming in an acidic medium to yield the oxepanone (281, n=1) (82%) (Scheme 122). Reagents such as Cl₂-pyridine,¹⁴⁵ (Bu₃Sn)₂O·Br₂,¹⁴⁶ NaBrO₃-CAN¹⁴⁷ and NaOCl in HOAc¹⁴⁸ have been shown to oxidise selectively secondary hydroxyl groups in the presence of primary hydroxyl groups. Therefore in theory, it should be possible to convert the diol (301) to the oxepanone (281, n=1) in one step so removing the need for the protection/deprotection sequence. However, such an oxidation step has not as yet been attempted.

4.4 Conclusions

We have successfully prepared 7/7- and 7/6-fused bicyclic ethers from 2-phosphono and 2-t-butyl ester substituted 3-oxooxepanes. In the case of the 2-phosphono substituted 3-oxooxepanes, the reaction sequence involves only seven steps from commercially available starting materials. We have therefore shown that rhodium (II) mediated intramolecular O-H insertion reactions can be used to prepare both monocyclic systems and bicyclic systems. The work highlights the fact that the 2-t-butyl ester 3-oxooxepane (207) and the 2-diethyl phosphono 3-oxooxepanes (208 and 290) are extremely versatile substrates for synthetic transformations. In addition, it appears very likely, on the basis of these and other results, that the 2-phenylsulphonyl 3-oxooxepane (206) could also be used to prepare such bicyclic systems.
Reagents: i. NaBH₄, CeCl₃·7H₂O, MeOH; ii. BH₃-THF, NaOH, H₂O₂, THF; iii. TBS-Cl, TEA, DMAP, DCM; iv. PCC, DCM; v. THF/HOAc/H₂O; vi. Et₃SiH, TMS-OTf, DCM, 0°C.
CHAPTER FIVE

ROUTES TO BICYCLIC ETHERS: THE DIANION APPROACH
5.1 Introduction

Although a range of fused bicyclic ethers had been successfully prepared by means of synthetic manipulation of functionalised 2-substituted 3-oxooxepanes, these bicyclic compounds by themselves were of little synthetic interest. The reason for this was due to their lack of functionalisation making further elaboration virtually impossible. We therefore set our sights on trying to prepare functionalised bicyclic ethers by use of intramolecular rhodium (II) carbenoid O-H insertion reaction methodology. We hoped that should we be able to prepare systems such as the diester (304) or the diphosphonate (305) (Figure 6), we would be able to use the chemistry just described in Chapter 4 to prepare tricyclic or even tetracyclic systems (Scheme 123).

Figure 6.

Scheme 123.

R = CO₂Bu⁺ or PO(OEt)₂
5.2 The Dianion Approach: β-Keto Esters

With a view to preparing bicyclic ethers such as (304) and (305), a retrosynthetic analysis was in order. The most obvious and logical disconnection appeared to be at the bonds a and b (Scheme 124) giving the diazo diol (306). However there is an immediate problem with this disconnection as there are two theoretically possible products of a rhodium (II) carbenoid mediated O-H insertion reaction involving such a substrate; (i) cyclisation to give the desired 7/7-fused bicyclic system (307) (Scheme 124) or (ii) cyclisation to give the 6/6-bicyclic system (308). It was known from previous work in our group that diazo alcohols undergo rhodium (II) catalysed O-H insertion reactions to give pyrans, but competitive pyran/oxepane forming rhodium (II) catalysed O-H insertion reactions in environments such as (306) had not been encountered before.

Scheme 124.

![Scheme 124](image)

It seemed likely that the formation of the pyran system would be favoured over the desired oxepane system purely as a consequence of rate considerations but we were intrigued to see what would actually occur in what was a potential "double diazo"
insertion system and so we decided to attempt a synthesis of the diol (306).

This diol could theoretically be derived from the olefin (309) (Scheme 125). The stereochemistry needed to ensure a requisite trans-arrangement in the bicyclic compound (307) on rhodium (II) catalysed cyclisation could be introduced at the diol stage by specific trans-dihydroxylation of the olefin (309). We envisaged being able to introduce the double diazo component of the substrate by standard diazo transfer methods. It was hoped that the diazo precursor (310) could be prepared using chemistry based on some previous work carried out in this group.

Scheme 125.

In 1987, Heslin and Moody reported the first intramolecular rhodium (II) acetate catalysed O-H insertion reaction of a diazo alcohol leading to the formation of a 2-methyl ester 3-oxooxepane. The method used to prepare their diazo alcohol (311) involved the alkylation of the dianion of methyl acetoacetate with a t-butyldimethylsilyl (TBS) protected hydroxy-iodoalkane, followed by introduction of the diazo function by means of the diazo transfer reaction and deprotection of the hydroxyl group under acidic conditions (Scheme 126).

Although the formation of diazo alcohols such as (311) by this method has now been superceded by the technique involving ring opening of 6-lactones with lithiated ethyl diazoacetate (Chapter 4), it was realised that this method would be ideal for the preparation of our diazo precursor (310) as not only would the diester (310, R = ester) be accessible to us but so would the diphosphonate (310, R = phosphonate).
and the disulphone (310, \( R = \) sulphone). This was because literature precedent suggested that dianion reactions of \( \beta \)-keto phosphonates and \( \beta \)-keto sulfoxides take place with alkyl halides in exactly the same way as the dianions of \( \beta \)-keto esters.\(^{151,152}\)

Scheme 126.

\[ \text{Reagents: i. NaH, n-BuLi, THF, 0°C, } (\text{CH}_2)_3\text{OTBS;} \text{ ii. TsN}_3, \text{ TEA, MeCN;} \text{ iii. HOAc/THF/H}_2\text{O} \]

The preparation of the diester derivative (310, \( R = \) ester) was attempted first as the methodology was already well known. Reaction of two equivalents of the dianion of ethyl acetoacetate with 1,4-dichlorobut-2-ene afforded a 24% yield of the desired disubstituted compound (312) as well as large amount of the mono-substituted product. However, using four equivalents of the dianion led to the isolation of 41% of the disubstituted compound (312) (Scheme 127).

Scheme 127.

\[ \text{Reagents: i. NaH, n-BuLi, THF, 0°C, } 1,4\text{-dichlorobut-2-ene.} \]

The subsequent diazo transfer step was smoothly effected through treatment with two equivalents of tosyl azide, furnishing the double diazo compound (313) in a
In order to introduce the *trans*-dihydroxy arrangement into the system, we decided to use the classical epoxide approach. The epoxy derivative (314) was first prepared using a urea-hydrogen peroxide method but this was found to be rather slow and inefficient. In contrast, m-chloroperbenzoic acid (m-CPBA) was found to be a far better reagent for the transformation. The product epoxide (314) was not isolated at this stage as it was found to have a tendency to ring open during silica gel chromatography and so was immediately cleaved under controlled conditions using perchloric acid in aqueous tetrahydrofuran. This yielded the desired diol (315) in 45% yield over the two steps (Scheme 129).

**Scheme 129.**

*Reagents: i. m-CPBA, DCM, NaHCO₃; ii. HClO₄, H₂O/THF*

After four relatively simple steps, the substrate required for our competitive...
rhodium (II) catalysed "double diazo" insertion reaction was now available.

However, slow addition of the diazo compound (315) to a dilute suspension of rhodium (II) acetate in dichloromethane led to an appalling streak when subsequently viewed by TLC. A low energy chemical ionisation mass spectrum of the crude product revealed no evidence of a product corresponding to a molecular weight of 342 [the 7/7- or 6/6-bicyclic systems, (316) and (308), R = ester] or 398 [the starting material (315)].

Scheme 130.

On the basis of this result, it was felt that a less complex system should be studied and it struck us that the most obvious candidate for further investigation would be the mono-diazo diester (317) (Figure 7). Rather than trying to synthesise ambitiously two carbon-oxygen bonds in one step as before, we wanted to see whether we could get any sort of observable single ring formation on treating this particular substrate with rhodium (II) acetate. If so, a repeat diazo transfer, O-H insertion step would in theory lead to the formation of the second ring.

Figure 7.

The double dianion displacement reaction was carried out in exactly the same way as before to give the olefin (312) (Scheme 131). Treatment with one equivalent of tosyl azide afforded a 50% yield of the mono-diazo diester (316). This is not a synthetically attractive step as half of the compound is lost as a combination of...
starting material and double-diazo product, purely as a consequence of the symmetrical nature of the compound. However, this was itself to be of little subsequent importance since whereas the subsequent epoxidation/cleavage step with the double-diazo compound (313) had been relatively clean and efficient, the same reaction with the mono-diazo compound (316) proved to be very messy and inefficient. A number of products were formed by TLC and no attempt was made to purify the mixture (Scheme 131). It is possible that in this system, the theoretical Baeyer-Villiger reaction competes with the epoxidation reaction leading to deleterious side reactions and undesirable reaction products.

Scheme 131.

\[ \begin{align*}
C_2H_5CO_2Et & \xrightarrow{i} C_2H_5CO_2Et \\
[EtO_2C \begin{array}{c}
\text{N}_2 \\
\text{EtO}_2C
\end{array}] & \xrightarrow{ii} [EtO_2C \begin{array}{c}
\text{N}_2 \\
\text{EtO}_2C
\end{array}] \\
\xrightarrow{iii} & \xrightarrow{iv}
\end{align*} \]

Reagents: i. NaH, n-BuLi, THF, 0°C; 1,4-dichlorobut-2-ene; ii. TsN₃ (1 equiv.), TEA, MeCN; iii. m-CPBA, DCM; iv. HClO₄, THF/H₂O
5.3 The Dianion Approach: \(\beta\)-Keto Phosphonates and Sulphoxides

From our previous investigations into the intermolecular rhodium (II) acetate catalysed O-H insertion reactions of various functionalised diazo compounds (Chapter 2), it was well established that \(\alpha\)-diazo phosphonates react slower than corresponding \(\alpha\)-diazo esters. We hoped that the rhodium (II) catalysed intramolecular O-H insertion reaction of the diphosphonate (306, \(R =\) phosphonate) might consequently be more selective than the reaction involving the diester (306, \(R =\) ester) thus leading to ring formation to at least some extent. As the bicyclic ether formed from the diphosphonate (305) would be just as or even more amenable to further synthetic elaboration in comparison to the bicyclic ether diester (304), in terms of functionalisation, it was not felt in any way that there would be any synthetic disadvantage in preparing this compound.

The synthesis of (305) was found not to be trivial. The dianion precursor we initially required was diethyl 2-oxopropylphosphonate (318). This compound (318) is not commercially available but can be prepared by means of the Michaelis-Arbusov reaction (Scheme 132).\textsuperscript{155} However, despite repeated distillations the required compound (318) could not be satisfactorily purified from its main contaminants, namely triethyl phosphite and the olefin arising from the Perkov reaction (319) (Scheme 132). Purification could not be achieved by chromatography either since the desired product could not visualised on TLC by either UV or by use of various developing agents.

Scheme 132.
We therefore used the procedure of Mathey and Savignac to prepare the desired β-keto phosphonate (318). The procedure involves lithiation of diethyl methylphosphonate with n-butyllithium in THF at low temperature followed by addition of copper(I) iodide which effects transmetallation to the organocuprate. On addition of acetyl chloride, a classical organocuprate reaction occurs leading to the formation of the desired β-keto phosphonate in 70% yield (95% literature yield) (Scheme 133).

Scheme 133.

\[ \text{Me-PO} \quad \text{OEt} \quad \text{OEt} \quad \underset{i}{\text{\rightarrow}} \quad \left[ \text{Li} \quad \text{P} \quad \text{OEt} \quad \text{OEt} \right] \quad \underset{ii}{\text{\rightarrow}} \quad \left[ \text{Cu} \quad \text{P} \quad \text{OEt} \quad \text{OEt} \right] \quad \underset{iii}{\text{\rightarrow}} \quad \text{Me-PO} \quad \text{OEt} \quad \text{OEt} \quad (318) \]

Reagents: i. n-BuLi, THF, -78°C; ii. Cul; iii. MeCOCI

However, the dianion reaction of the β-keto phosphonate with 1,4-dichlorobut-2-ene, the first step of the reaction sequence (Scheme 134), was totally unsuccessful. Most of the mass balance appeared to be lost in the aqueous phase on work-up and there was no evidence for any of the desired diphosphonate (320) in the recovered organics. The use of DMPU as a co-solvent did not improve the situation nor did use of 1,4-dibromobut-2-ene as the alkyl halide. It appears that there is some kind of "intermolecular communication" occurring such that elimination processes are favoured over the displacement reaction (Scheme 135) although no substituted phosphonate products such as [(322), (323) or (324)] were isolated from the reaction mixture. Such reactions might also explain the poor reaction yields obtained in the analogous ester reaction. Thus, although the diester diol (315) had been successfully prepared, the same
procedure could not be used to prepare the diphosphonate diol (321, Scheme 134).

Scheme 134.

Reagents: i. NaH, n-BuLi, THF, 0°C; 1,4-dichlorobut-2-ene; ii. TsN₃ (2 equiv.), TEA, DCM; iii. m-CPBA, DCM; iv. HClO₄, THF/H₂O.

Scheme 135.
Literature research revealed that β-keto sulfoxides undergo dianion reactions with alkyl halides in analogy to β-keto esters and β-keto phosphonates.\textsuperscript{152} It was decided to investigate whether the procedure would successfully yield the disulphone diol (327, Scheme 137).

The preparation of the dianion precursor, phenyl 2-oxopropylsulphoxide (325), was achieved using the method of Johnson and Keiser.\textsuperscript{157} This involved a displacement reaction of the sodium salt of thiophenol with chloroacetone followed by oxidation with sodium periodate in aqueous ethanol (Scheme 136).

**Scheme 136.**

\[
\text{Cl} - \overset{\text{Me}}{\text{C}} - \overset{\text{O}}{\text{Me}} \xrightarrow{\text{PhSH, NaOEt, EtOH}} \overset{\text{Me}}{\text{PhS} - \overset{\text{O}}{\text{C}}} - \overset{\text{Me}}{\text{O}} \xrightarrow{\text{NaIO}_4, \text{EtOH/H}_2\text{O}} \overset{\text{O}}{\text{PhS}^+ - \overset{\text{C}}{\text{Me}}} \]

(325)

**Scheme 137.**

\[
\overset{\text{O}}{\text{PhSO_2N}_2} \xrightarrow{i} \overset{\text{O}}{\text{PhSO_2N}_2} \overset{\text{O}^+}{\text{Ph}} \xrightarrow{\text{ii, iii}} \overset{\text{O}}{\text{PhSO_2N}_2} \overset{\text{O}^+}{\text{Ph}} \]

(326)

\[
\overset{\text{O}}{\text{PhSO_2N}_2} \xrightarrow{\text{iv}} \overset{\text{O}}{\text{PhSO_2N}_2} \overset{\text{O}^+}{\text{Ph}} \]

(327)
Reagents: i. NaH, n-BuLi, THF, 0°C; 1,4-dichlorobut-2-ene; ii. TsN₃ (2 equiv.), TEA, DCM; iii. Oxone, MeOH/H₂O; iv. HClO₄, THF/H₂O

The dianion reaction of the β-keto sulfoxide, as with the β-keto phosphonate, with 1,4-dichlorobut-2-ene was not a success. Again, an "intermolecular communication" effect appeared to dominate. A large number of products were formed by TLC but a small amount (18%) of the disulphoxide derivative (326, Scheme 137) was isolated [δH (250 MHz; CDCl₃) 2.16-2.36 (4 H, m, CH₂CO), 2.50-2.57 (4 H, m, CH₂CH=), 3.75 (2 H, d, J 13.6, PhSOCHH), 3.85 (2 H, d, J 13.7, PhSOCHH), 5.33-5.36 (2 H, m, CH=CH) and 7.27-7.65 (5 H, m, C₆H₅)]. Use of DMPU as co-solvent and 1,4-dibromobut-2-ene as the alkyl halide had a negligible effect on the yield of the disulphoxide (326) compared to the same reaction with 1,4-dichlorobut-2-ene. In view of the poor reaction yield of this first step, it was felt there was little point in progressing with the sequence (Scheme 137).

It had occurred to us more than once that our experimental procedure for the formation of the dianions of diethyl 2-oxopropylphosphonate (318) and phenyl 2-oxopropylsulphoxide (325) might be at fault. Therefore, some simple model studies were carried out (Scheme 138). Formation of the dianion of the β-keto phosphonate (318) under the usual experimental conditions followed by quenching with ethyl iodide or allyl bromide led to the formation of the substituted β-keto phosphonates (328) and (329) in 38 and 41% yield respectively. Although the yields were less than impressive, this demonstrated to us that the experimental aspect of our work was not totally at fault. The diazo function could be successfully introduced into these compounds by means of the diazo transfer reaction with mesyl azide affording the diazo derivatives (330) and (331) in 47 and 67% yield respectively.

Scheme 138.
Reagents: i. NaH, n-BuLi, THF, 0°C; ii. EtI (328) or allyl bromide (329); iii. MsN₃, piperidine, DCM.

On heating in 2-propanol in the presence of a catalytic amount of rhodium (II) acetate, these compounds (330) and (331) furnished the expected O-H insertion products (332) and (333) in reasonable yields (46 and 42% respectively) (Scheme 139). It should be noted that these intermolecular O-H insertion products were the major products of reaction as opposed to the theoretical intramolecular C-H insertion reaction products leading to cyclopentanones [or additionally the intramolecular cyclopropanation product in the case of (333)] (see Chapter 1).

Scheme 139.

In the same way, the dianion of the phenyl 2-oxopropylsulphoxide (325) reacted with ethyl iodide and allyl bromide to yield the substituted β-keto sulfoxides (334) and (335) in yields of 58 and 55%, respectively (Scheme 140). Oxidation of the sulfoxide to the sulphone could be realised through the use of Oxone (50 and 100%, respectively) and diazo transfer proceded reasonably well with mesyl azide to afford the diazo derivatives (338) and (339) in 42 and 47% yield, respectively (Scheme 140). Monteiro has reported that the addition of β-keto sulphones to aqueous-alcoholic solutions of sodium azide, sodium acetate and 1-ethyl-2-chloro-pyridinium tetrafluoroborate affords superior yields of diazo derivatives than normal diazo transfer conditions (tosyl azide/triethylamine), so it appears that improved yields of the diazo sulphones (338) and (339) may be possible, although this is a route yet to be explored.
Scheme 140.

![Scheme 140](image)

Reagents: i. NaH, n-BuLi, THF, 0°C; ii. EtI (334) or allyl bromide (335); iii. Oxone, MeOH/H₂O (336)/(337); iv. MsN₃, TEA, DCM (338)/(339).

5.4 Cyclic Ether Formation

As so much time had been invested in studying the dianion reactions of β-keto esters, β-keto phosphonates and β-keto sulfoxides, we thought it might be worth trying to expand the methods already known leading to the formation of 2-substituted phosphonate- and 2-substituted sulphone-cyclic ethers. The work would be based on that carried out by Heslin and Moody for β-keto esters involving rhodium (II) catalysed intra-molecular O-H insertion reactions of diazo alcohols (Scheme 126). It was hoped in an analogous way to prepare 2-phosphono and 2-sulphono substituted pyrans, oxepanes and oxecanes. The formation of the phosphono derivatives of these substrates was particularly appealing as it complemented well with the work that had been previously carried out involving 2-phosphono substituted 3-oxooxepanes (Chapter 4).

Thus, reaction of the dianion of diethyl 2-oxopropylphosphonate (318) with a range of t-butyldimethylsilyl (TBS) protected hydroxy-iodoalkanes of various chain lengths led to the formation of the substituted β-keto phosphonates (340, n= 1-3) in reasonable yields (Scheme 141). The alkyl iodides themselves were prepared by
literature procedure usually involving t-butyldimethylsilyl (TBS) protection of chloro-alcohols followed by Finkelstein reaction with sodium iodide in acetone.\textsuperscript{150}

Scheme 141.

Reagents: i. NaH, n-BuLi, THF, 0°C; ii. ICH\textsubscript{2}(CH\textsubscript{2})\textit{n}OTBS; iii. NaH, TsN\textsubscript{3}, THF, 0°C; iv. HOAc/THF/H\textsubscript{2}O; v. Rh\textsubscript{2}(OAc)\textsubscript{4}, PhH, reflux.

The substituted \(\beta\)-keto phosphonates (340, \(n = 1-3\)) could be smoothly diazotised (341, \(n = 1-3\)) with tosyl azide using sodium hydride to form the requisite formal anion. Initially triethylamine had been used as the base to effect the diazo transfer
reaction but it was found that using sodium hydride led to much faster and cleaner reactions in addition to superior yields. Deprotection could be effected under acidic conditions using aqueous acetic acid, furnishing the cyclisation precursors (342, n= 1-3) in good yields (Scheme 141). The phosphonate (342, n= 2) was found to smoothly cyclise in refluxing benzene in the presence of a catalytic amount of rhodium (II) acetate to yield the oxepane (344) but surprisingly both the phosphonates (342, n= 1) and (342, n= 2) failed to give identifiable cyclic ether products. In contrast, these afforded complex mixtures of products. In the case of the phosphonate (342, n= 3), a major product was isolated which was tentatively assigned by $^1$H NMR as being a cyclopentanone product arising from C-H insertion (346) (Scheme 142). However, this compound was found to be unstable, decomposing rapidly to mixtures of products so preventing full analysis from being obtained.

Scheme 142.

![Scheme 142](image)

As a whole, these were very disappointing results. Although Heslin and Moody had reported that they were unable to prepare 2-ester substituted pyrans by this method, they had been successful in preparing 2-ester substituted oxecanes in significant yield.\textsuperscript{150} We had been unable to isolate either any of the 2-phosphonate substituted pyran (343) or 2-phosphonate substituted oxecane (345).

Moody and Taylor later found that 2-ester substituted pyrans could be formed by rhodium (II) catalysed O-H insertion reactions of diazo alcohols although it was noted that in general the pyrans formed were less stable than the analogous oxepanes.\textsuperscript{149,159}

Although we were unable to prepare 2-phosphono substituted pyrans and oxecanes
using this methodology, we were able to demonstrate that it is possible to form 2-phosphono substituted oxepanes in this way. A range of 2-phosphono substituted oxepanes could therefore be theoretically accessible by this route by analogy with the Heslin/Moody work\(^ {150} \) (Scheme 143) and the technique would complement the diethyl lithiomethylphosphonate/\( \delta \)-lactone ring opening methodology described previously.

Scheme 143.

\[
\begin{align*}
\text{Me} & \overset{\text{PO(OEt)}_2}{\text{P}} \overset{\text{OEt}}{\text{OEt}} \quad \text{Rh(II)} \\
\begin{array}{c}
\text{Me} \\
\text{P} \\
\text{O(OEt)}_2
\end{array} & \quad \begin{array}{c}
\text{OH} \\
\text{N}_2
\end{array} & \quad \begin{array}{c}
\text{PO(OEt)}_2
\end{array}
\end{align*}
\]

In a similar fashion, an attempt was made to prepare the diazo alcohol which we hoped would cyclise to give us the 2-sulphono substituted 3-oxooxepane.

The dianion reaction of phenyl 2-oxopropylsulphoxide (325) with 1-t-butyldimethylsiloxy-3-iodopropane\(^ {150} \) afforded the substituted \( \beta \)-keto sulfoxide (347) in 46% yield (Scheme 144).\(^ {152} \) However, attempted oxidation to the sulphone derivative with Oxone\(^ {160} \) led to the formation of a number of products, none of which corresponded to the desired compound (348) (Scheme 144). From analysis of the reaction products, it was suspected that this might be due to the acidity of the Oxone reagent effecting removal of the silyl protecting group and consequently leading to further side reactions. The oxidation reaction was repeated again in systems buffered to pH 4 and pH 7 but in both cases clean reactions were not observed.

We therefore decided to use a different protecting group and the one chosen was the triisopropylsilyl (TIPS) group. This silyl protecting group is significantly more stable than the t-butyldimethylsilyl (TBS) group towards acid as a result of its
increased bulk although not it is not as stable as the t-butyldiphenylsilyl (TBDPS) group.\textsuperscript{137,161}

Scheme 144.

![Scheme 144](image)

Reagents: i. NaH, n-BuLi, THF, 0°C; ii. ICH\textsubscript{2}CH\textsubscript{2}OTBS; iii. oxone, MeOH/H\textsubscript{2}O

Although the TIPS substituted β-keto sulphoxide could be prepared in good yield (51\%) \textsuperscript{(349)} (Scheme 145), the oxidation reaction with Oxone again led, surprisingly, to a mixture of products.

Scheme 145.

![Scheme 145](image)

Reagents: i. NaH, n-BuLi, THF, 0°C; ii. ICH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}OTIPS; iii. Oxone, MeOH/H\textsubscript{2}O

It was finally decided to use another oxidising agent and the first one tried, m-
chloroperbenzoic acid, afforded the desired sulphone (350) in a satisfactory 100% yield (Scheme 146). We had not used this reagent initially as it had been feared that the reaction medium would be too acidic for the silyl groups to remain intact. The diazo group could be introduced through the use of mesyl azide which afforded the diazo derivative (351) in 50% yield.

Scheme 146.

Removal of the silyl protecting group was attempted using the acetic acid/THF/water protocol that had been so successful for us previously, but under these conditions the formation of two major products was observed. It was found by $^1$H NMR analysis that the reaction products appeared to be a mixture of the cyclised and open chain forms of the $\beta$-keto sulphone (352) (Scheme 146). This was not too surprising given the powerfully electron withdrawing strength of the benzenesulphonyl group but we knew from previous work that the substrate (203) derived by ring opening of undecanoic $\alpha$-lactone with lithiomethyl phenyl sulphone does exist in open chain form in solution (Scheme 147).$^{67}$ Attempted were made to remove the silyl protecting group under less acidic conditions using the very mild hydrogen fluoride-pyridine complex$^{162}$ but a similar result was obtained as before. Additionally, we tried using tetrabutylammonium fluoride...
(TBAF) to remove the silyl group but this reagent is far too basic for the diazo group to remain intact and the result is invariably destruction of the compound. Whether the cyclisation of the substrate occurs purely as a result of the presence of acid in the system or whether there is an natural equilibrium between the open chain and cyclised forms is uncertain but we decided in view of other on-going work that investigating the use of other protecting groups for the system or other solvent systems would not be a profitable exercise and so the work in this area was curtailed.

Scheme 147.

![Scheme 147](image)

**Reagents:**

i. MeSO₂Ph, n-BuL, THF, -78°C; LDA (1 equiv.), Me₃SiCl (2 equiv.), THF, -78°C; ii. NH₄Cl (aq); iii. MsN₃, TEA, EtOH; iv. H⁺

### 5.5 Conclusions

A number of routes leading to functionalised monocyclic and bicyclic ethers have been investigated involving the dianion chemistry of β-keto esters, β-keto phosphonates and β-keto sulphoxides. The attempted formation of a bicyclic system by means of novel competitive "double diazo" insertion reactions was unsuccessful. However, it has been shown that such dianion chemistry can be used in reaction sequences to prepare a range of α-diazo phosphonates and α-diazo sulphones and can be ultimately used to prepare 2-phosphono substituted 3-oxooxepanes.
CHAPTER SIX

ROUTES TO BICYCLIC ETHERS: FURTHER SYNTHETIC STRATEGIES
6.1 Introduction

With respect to our continued interest in preparing functionalised bicyclic ethers such as (353), we decided to investigate some other synthetic routes.

Scheme 148.

The disconnection which seemed most obvious to us was at bond a (Scheme 148), as before (Chapter 5). The formation of this bond could theoretically be achieved by two different methods (i) a rhodium (II) catalysed intramolecular O-H insertion reaction (path 1, Scheme 148) or (ii) the triethylsilane/TMS-triflate cyclisation route (path 2). The rhodium (II) catalysed route was much more attractive for the important reason that we would be able to dictate the stereochemistry of the resulting bicyclic ether by controlling the stereochemistry of the cyclisation precursor. In the case of the triethylsilane/TMS-triflate route, the bicyclic ether formed would always be obtained as a mixture of isomers (Chapter 4). Although we knew that the chirality of the rhodium (II) cyclisation precursor (354) would make its synthesis relatively more difficult, this was not seen as a major handicap especially as we more interested in developing the rhodium chemistry in any case.

Two routes to the rhodium (II) cyclisation precursor (354) were considered. The first was very much a step-wise building block approach (Scheme 149, Disconnection route A) but contained a feature that was particularly appealing to us.
This was the involvement of a competitive rhodium (II) catalysed O-H insertion reaction step. We were very interested in seeing what would be the preferred outcome of such a reaction as this would provide us with a useful comparison with our rate work (Chapter 2) and our previous unsuccessful competitive rhodium (II) catalysed O-H insertion reaction (Scheme 130) (Chapter 5).

Scheme 149.

**Disconnection Route A**

![Chemical diagram of Disconnection Route A](image)

The second route that was considered (Scheme 150, Disconnection route B) involved chemistry that had been successfully developed previously, featuring the Wadsworth-Emmons olefination reactions of 2-diethyl phosphono substituted 3-oxooxepanes with aldehydes (Chapter 4). Although the bicyclic ether that we hoped to prepare using this route was not as highly functionalised as the bicyclic ether we hoped to prepare by means of Disconnection route A [compare the cyclisation product]
of (363) with (368)], it would at least allow us an entry point into bicyclic systems should disconnection route A (which was considered much more of a gamble) fail.

Scheme 150.
Disconnection Route B

![Chemical Structures]

Analysis of Scheme 149: We envisaged being able to build up the phosphonate side chain by carrying out some dianion chemistry involving diethyl 2-oxopropylphosphonate (318) and the aldehyde (362) (Scheme 149). The aldehyde (362) itself would be prepared by simple elaboration of the oxepane (361) which we hoped would be accessible by means of the competitive rhodium (II) catalysed O-H insertion reaction of the diazo diol (360). Of course, as mentioned already, it was uncertain what would be the outcome of this reaction. It was hoped that the diazo diol (360) could in turn be prepared through the use of the dianion chemistry of ethyl acetoacetate. The alkyl halide (358) would be derived from 2-butene-1,4-diol (356) which is commercially available. The acetonide (357) is commercially
available (at great cost) in a non-benzylated form [(-)-2,3-O-isopropyldene D-threitol and its enantiomer (+)-2,3-O-isopropyldene L-threitol] but these have the "wrong" stereochemistry; a cis-configuration in the acetonide was required in order to ensure an ultimate trans-configuration in the bicyclic ether.

Analysis of Scheme 150: The rhodium (II) cyclisation precursor (367) was to be prepared by elaboration of the aldehyde (366). It was hoped that this aldehyde would be accessible through the Wadsworth-Emmons chemistry that had been developed previously using diethyl 7-hexyl-3-oxooxepane-2-phosphonate (208). One of the less attractive points of this synthesis was the inescapable need to differentiate, selectively, hydroxyl functions; this could only be achieved through the use of different protecting groups resulting in a much more step-wise and less convergent synthesis.

6.2 The Dianion Approach: Disconnection Route A

The mono-protected benzyl ether of 2-butene-1,4-diol (370) was prepared by the initially forming the benzylidene acetal (369) by refluxing 2-butene-1,4-diol with benzaldehyde in toluene in the presence of a catalytic amount of 4-toluenesulphonic acid under Dean-Stark conditions. Treatment of the acetal with two equivalents of Dibal at 0°C afforded the alcohol (370) in 90% yield (Scheme 151).163,164

Scheme 151.

Reagents: i. Dibal, toluene, 0°C; ii. TIPS-Cl, imidazole, DMF.
The same alcohol (370) could also be prepared by treating a large stoichiometric excess of 2-butene-1, 4-diol (356) with potassium hydride in THF and then adding benzyl bromide. This method is shorter, a lot less experimentally demanding than the Dibal reduction route and also less costly. However, the yields are poorer and the method is undoubtedly less synthetically elegant.

The alcohol could be converted to its triisopropylsilyl (TIPS) ether (371) in quantitative yield by treatment with triisopropyl chloride and imidazole in dichloromethane (Scheme 151).137 As we hoped to prepare a diol in the next step, it was thought advantageous to incorporate a highly non-polar group in order to increase the overall lipophilicity of the molecule and for this reason the large and bulky TIPS group was selected.

Subsequent hydroxylation of the olefin using a catalytic amount of osmium tetroxide in the presence of N-methylmorpholine-N-oxide (NMNO) in t-butanol led to the formation of the cis-diol (372) in 76% yield (Scheme 152). The diol was then simply protected as an acetonide (373) by treatment with 2,2-dimethoxypropane and 4-toluene sulfonic acid in dichloromethane (68%).

Scheme 152.

\[
\begin{align*}
\text{TIPS} & \quad \text{Ph} \\
(371) & \quad \text{Ph} \\
\text{HO} & \quad \text{HO} \\
(372) & \quad \text{Ph} \\
\text{HO} & \quad \text{HO} \\
(373) & \quad \text{Ph}
\end{align*}
\]

Reagents: i. OsO₄, NMNO, t-BuOH; ii. Me₂C(OMe)₂, p-TSA, DCM.

Removal of the triisopropylsilyl group could be smoothly effected through the use of t-butyrammonium fluoride (TBAF) which afforded the alcohol (374) in 86% yield (Scheme 153). On adding tosyl chloride, triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP), conversion to the tosyl derivative (375) could be achieved. However this compound was not found to be very stable; decomposition to a mixture of products occurring over several hours at room temperature.
Scheme 153.

\[
\begin{align*}
\text{OTIPS} & \quad \text{(373)} \\
\rightarrow & \quad \text{Ph} \\
\text{Reagents: } \text{i. TBAF, THF, 0°C; ii. p-TsCl, TEA, DMAP, DCM.}
\end{align*}
\]

We were not too surprised then that attempts to convert the tosyl derivative to the iodo-analog (376) failed on heating with sodium iodide in acetone\(^{165}\)-decomposition presumably occurring more rapidly at higher temperature (Scheme 154). It is worth noting that the conditions required to prepare a similar iodo-derivative with trans-geometry at the acetonide are particularly harsh (sodium iodide, acetone, sealed tube, 100°C, 3 h).\(^{165}\)

Scheme 154.

\[
\begin{align*}
\text{Nal, acetone, } \Delta & \quad \text{(375)} \\
\rightarrow & \quad \text{Ph} \\
\text{Efforts were made to prepare the iodo-derivative by treating the alcohol (374) with triphenylphosphine, imidazole and iodine (a particularly good method for converting primary and secondary hydroxy groups to iodo groups in carbohydrates).}^{166,167}\end{align*}
\]

Although a large amount of triphenylphosphine oxide was recovered after reaction, none of the desired iodo-derivative could be isolated (Scheme 155).

As a result of our lack of success in forming the halide, it was felt that the best way to incorporate the ester side chain into the molecule, since it was plainly not going to be possible by the dianion route, was by means of Wittig or Wadsworth-Emmons type chemistry.
However, in order to carry out such a reaction, the aldehyde analogue (377) of the alcohol (376) had to be prepared. Using pyridinium chlorochromate (PCC) as the oxidant (with sodium acetate, in view of our acetonide function), very slow consumption of the starting material was observed (>24 h at rt) and a number of by-products were formed in addition to the aldehyde. The Swern methodology is known to be a particularly effective for the oxidation of hindered alcohols and it was found by TLC that under these conditions, the alcohol could be converted to the aldehyde much more efficiently and effectively than with PCC (Scheme 156).\textsuperscript{131}

**Scheme 156.**

\[
\begin{array}{c}
\text{Reagents: CICOCOCl, DMSO, DCM, -60°C; TEA.}
\end{array}
\]

In order to test the potential of the Wittig route, the aldehyde was heated in toluene with methyl (triphenylphosphoranylidene)acetate.\textsuperscript{168} This furnished an excellent 97% of the $\alpha,\beta$-unsaturated ester (378) as a mixture of cis- and trans-isomers (Scheme 157). The equivalent Wadsworth-Emmons reaction was carried out in comparison using trimethyl phosphonoacetate. This afforded a lower yield (66%) of the $\alpha,\beta$-unsaturated ester but exhibited much higher trans-isomeric selectivity (Scheme 157). The olefin (378) could be hydrogenated over a platinum (IV) oxide
catalyst to yield the reduced compound (379) in 81% yield (NOE studies show a clear cis-arrangement for the ring protons) (Scheme 158).

Scheme 157.

\[
\begin{align*}
\text{Reagents: Wittig: } & \text{Ph}_3\text{PCHCO}_2\text{Me, PhMe, } \Delta; \text{ Wadsworth-Emmons: } \text{NaH, THF, 0°C, MeO}_2\text{CCH}_2\text{PO(OMe)}_2 \\
\end{align*}
\]

Scheme 158.

Obviously, the choice of catalyst was critical in this step as the use of a palladium catalyst for example, would have additionally led to cleavage of the benzyl group and perhaps hydrogenation of the benzene ring, in addition to reduction of the olefin.

On the basis of these encouraging results, it appeared that this Wittig route might be applicable to the synthesis of our target substrate. However, in contrast to the Wittig reactions of methyl (triphosphoranylidene)acetate, the analogous reactions of the homologated derivative, (3-methoxycarbonyl-2-oxopropylidene)triphenyl-phosphorane are far less well known.

Pietrusiewicz and Monkiewic reported several years ago that this reagent does not
react with aldehydes even after prolonged heating.\textsuperscript{169} However, they found that when equimolar amounts of the ylide and an aldehyde were mixed together with two equivalents of sodium hydride in wet THF, reaction did occur, leading to conjugated \( \beta \)-keto esters. The yields ranged from poor to excellent and there was considerable preference for the formation of the \( Z \)-(cis)-isomer. Other workers have reported that heating the same ylide, \([(3\text{-methoxycarbonyl-2-oxopropylidenetriphenylphosphorane, in toluene with aldehydes in the presence of benzoic acid, also leads to good yields of conjugated \( \beta \)-keto esters.\textsuperscript{170} We selected to proceed by way of the sodium hydride method as we were not keen to expose our acetonide (377) to acidic reaction media. Additionally, the reaction times using the sodium hydride method appeared to be significantly shorter and the reaction conditions appeared to be considerably milder in comparison to the latter method (50 h reflux in toluene).

The required phosphorane, \((3\text{-methoxycarbonyl-2-oxopropylidene)}\text{-triphenylphosphorane, is not commercially available and was prepared by literature procedure. This involved heating triphenyl phosphine and methyl 4-chloroacetate in toluene and then treating the resulting gum with sodium bicarbonate solution. Recrystallisation in benzene afforded the pure phosphorane as a white solid.\textsuperscript{171}

However, reaction of the ylide with the aldehyde (377), under the conditions developed by Pietrusiewicz and Monkievic,\textsuperscript{169} afforded the desired \( \beta \)-keto ester (380) in a very disappointing yield of 35\% (Scheme 159). Hydrogenation over platinum (IV) oxide as before, yielded the reduced derivative (381) in 58\% yield (NOE studies showed a clear cis-arrangement for the two ring protons).

This reduced product was then diazotised by standard diazo transfer methods with tosyl azide to furnish the diazo derivative (382) in excellent 93\% yield (still cis by \(^1\text{H NMR}) (\text{Scheme 160}). On treatment with a 3:1:1 mixture of glacial acetic acid, THF and water, the cyclisation precursor (383) was isolated in a very disappointing yield of 34\% (Scheme 160). No product (383) was observed in the aqueous extracts (it is a diol). The acetic acid/THF/water mixture was chosen to unmask the diol as we wanted the mildest acidic conditions necessary to effect the transformation. We feared that too acidic conditions would result in lactol formation
in analogy with the diazo sulphone (Chapter 5).}

Scheme 159.

\[
\begin{align*}
\text{(377)} & \overset{i}{\rightarrow} \text{(380)} \\
\text{(381)} & \overset{ii}{\rightarrow} \\
\end{align*}
\]

Reagents: i. \(\text{Ph}_3\text{P} = \text{CHCOCH}_2\text{CO}_2\text{Me},\ \text{NaH}, \ \text{THF}, \ \text{H}_2\text{O}\); ii. \(\text{PtO}_2, \ \text{H}_2, \ \text{EtOAc}\).

Scheme 160.

\[
\begin{align*}
\text{(381)} & \overset{i}{\rightarrow} \text{(382)} \\
\text{(383)} & \overset{ii}{\rightarrow} \\
\end{align*}
\]

Reagents: i. \(\text{TsN}_3, \ \text{TEA}, \ \text{MeCN}\); ii. \(\text{HOAc}/\text{THF}/\text{H}_2\text{O}\).
However, it was also known from working precedent that the individual alcohol derivatives themselves (methyl 2-diazo-6-hydroxy-3-oxohexanoate and methyl 2-diazo-7-hydroxy-3-oxoheptanoate (311) exist in open chain forms. (These alcohols had been subsequently successfully cyclised to give 2-ester substituted pyrans and oxepanes respectively).\textsuperscript{149,150} The deprotection sequence was carried out a number of times under various conditions but in every case low yields of the desired product were obtained. Adding to our problems, it was found that the diol (383) was unstable; decomposition occurred rapidly even at low temperatures and this precluded any attempt to obtain a full spectral analysis.

On addition of the diol (383) to a dilute suspension of rhodium (II) acetate in dichloromethane (Scheme 161), an horrific streak was obtained by TLC, redolent of the TLC obtained on the attempted double-diazo insertion reaction of the diol (315, Scheme 130) (Chapter 5). As in that particular experiment, a low energy chemical ionisation mass spectrum revealed that although all of the starting material had been consumed, there was no evidence for any oxepane (384) or pyran being present in the reaction mixture.

Scheme 161.

\[
\begin{align*}
\text{HO} & \quad \text{O} & \quad \text{N}_2 & \quad \text{OMe} \\
\text{HO} & \quad \text{Obn} & \quad & \\
\text{Rh}_2(\text{OAc})_4 & \rightarrow & \text{HO} & \quad \text{Obn} & \quad \text{CO}_2\text{Me} \\
\text{DCM, rt} & & \text{(383)} & \rightarrow & \text{(384)}
\end{align*}
\]

6.3 The Wadsworth-Emmons Route: Disconnection Route B

The reaction of diethyl 7-hexyl-3-oxooxepane-2-phosphonate (208) with 1-benzyloxypropanal afforded the oxepanone (364) in a disappointing 29% yield (Scheme 162). It is almost certain that should this reaction be repeated, a much better yield of the olefin would be isolated. The aldehyde itself was prepared in a route similar to that used to prepare the aldehyde derivative of the alcohol (370). Heating 1,3-propanediol with benzaldehyde in toluene in the presence of 4-
toluenesulphonic acid under Dean-Stark conditions yielded the acetal which on treatment with two equivalents of Dibal in toluene at 0°C afforded the mono-protected alcohol. Oxidation with PCC furnished the required aldehyde.\textsuperscript{172,173}

The low yielding first step was not repeated because it was found the subsequent hydrogenation/epimerisation sequence took place in an equally poor yield (385, 32\%) (steps ii. and iii., Scheme 162). This was very surprising bearing in mind that the silyl protected derivatives of the oxepane (364) furnish very high yields of the cis-2,7-disubstituted oxepane. The problem appeared to lie with the necessity to use a platinum catalyst as opposed to a palladium catalyst as a consequence of the presence of the benzyl group in the molecule although we had not envisaged problems with such a catalytic substitution.

Subsequent reduction of the oxepanone (385) using the sodium borohydride/cerium chloride protocol afforded the alcohol (386) as a mixture of diastereoisomers (ca. 1:1) in good yield (82\%) (Scheme 163). Although the high yield of the reaction was pleasing, the poor diastereoselectivity posed a stereochemical problem. A trans-configuration in the alcohol at this point was necessary in order to ensure a trans-ring junction relationship in the product bicyclic ether.

Scheme 162.

\[
\begin{align*}
\text{Reagents: i. } & \text{NaH, OHCCH}_2\text{CH}_2\text{OCH}_2\text{Ph, THF, } 0^\circ\text{C}; \\
\text{ii. } & \text{PtO}_2, \text{H}_2, \text{EtOAc}; \\
\text{iii. } & \text{NaOMe (cat.), MeOH.}
\end{align*}
\]
It was known from previous work with similar systems (Chapter 4) that a mixture of diasteromers was likely to arise using sodium borohydride as the reducing agent but it was also known that 7-hexyl 2-phenylsulphonyl-3-oxooxepane (206) is reduced under the exact same conditions to afford a near quantitative yield of the β-hydroxy sulphone with apparent total cis-diastereoselectivity. The origin of the diastereoselectivity in this case is ascribed to the presence of the bulky benzenesulphonyl group, forcing the approach of the reducing agent from the least hindered side.

Scheme 163.

![Chemical structure](attachment:image.png)

**Reagents:** i. NaBH₄, CeCl₃.7H₂O, MeOH; ii. TBS-OTf, 2,6-lutidine, DCM, -20°C.

The less polar isomer from the reduction reaction could be isolated pure by means of careful chromatography. On treatment with t-butyldimethylsilyl triflate using 2,6-lutidine as base in DCM at -20°C, the t-butyldimethylsiloxy derivative (387) was formed (97%) (Scheme 163). NOE difference spectroscopy suggested that that the isomer that had been obtained was the cis-isomer i.e. the wrong diastereomer.

As a consequence of the sequence of poor yields obtained in the initial Wadsworth-Emmons and hydrogenation/epimersiation steps (Scheme 162), lack of material prevented us from continuing the synthesis. Rather than remaking more of the oxepanone (385), it was felt that we would be better served by the thexyldimethylsilyl protected derivative (285) which we knew we could make without difficulties.

Once this substrate had been prepared, the question of diastereoselectivity in the
reduction step of the ketone to the aldehyde was addressed first (Scheme 164). The sodium borohydride/cerium chloride protocol afforded the alcohol as an approximately 1:1 mixture of cis- and trans-diastereomers by TLC (89%). The more bulky reducing agent, Red-Al (sodium bis(2-methoxyethoxy)aluminium hydride), showed a distinct preference for the cis-diastereomer (388) over the trans-diastereomer (389) (ca. 3:1 by TLC, 78%) and on going to the even more bulky reducing agent, L-Selectride (lithium tri-sec-butyldihyride), complete conversion to the cis-isomer (388) was observed by TLC (100%).

Scheme 164.

Thus, as would be expected, increasing the bulk of the reducing agent favours approach from the least hindered side of the oxepane and consequently results in increased diastereoselectivity. Although the alcohol could now be prepared with apparent total diastereoselectivity, this diasteromer was in fact the "wrong" diastereomer. However, we anticipated being able to convert this to our required trans-diasteromer under Mitsunobu conditions (triphenyl phosphine/DEAD).174 The alcohol [as a mixture of diastereomers (388) and (389)] could be converted to a number of derivatives by conventional means in varying yields (Scheme 165); the acetate (390), the benzyl ether (391) and the TBS and TIPS silyl ethers (392) and (393) were ultimately prepared.
Reagents: i. X= Ac, Ac₂O, py, DMAP (390, 81%); ii. X= Bn, NaH, DMF, 0°C; PhCH₂Br, TBAI (391, 39%); iii. X= TBS, TBS-OTf, 2,6-lutidine, DCM, -20°C (392, 100%); iv. X= TIPS, TIPS-OTf, 2,6-lutidine, DCM, -20°C (393, 100%).

The benzyl protected substrate (391) was of particular interest as it would potentially allow us to deprotect selectively the primary alcohol in the presence of the secondary alcohol. The benzyl group itself could be removed later by palladium catalysed hydrogenolysis. However, the yield of formation of this compound (391) was disappointingly low despite using tetra-butylammonium iodide to convert the alkylating agent, benzyl bromide, to its iodo derivative in situ.¹⁷⁵,¹⁷⁶

Our other alternative was to use the disilylated oxepane (393) which could be prepared very simply in excellent yield. It was hoped that the bulk of the TIPS group in conjunction with its attachment to a secondary alcohol might make it sufficiently stable to withstand the conditions needed to remove the trimethylsilyl (TDS) group and indeed it was found that heating the disilylated compound (393) in a 3:1:1 mixture of glacial acetic acid, water and THF at 70°C led to smooth removal of the TDS group in good yield without removal of the TIPS group (394, 92%) (Scheme 166).

We were slightly worried that the stability of the TIPS group might be such that we would unable to remove it at a later stage but a test reaction with the disilylated oxepane (393) allayed our fears (Scheme 167).
Treatment with hydrogen fluoride-pyridine complex in THF at 0°C led rapidly (within 1 h) to the removal of the thexydimethylsilyl group (TDS) (394, 73%) and on further stirring (24 h) it was found that the TIPS group was also removed (51%) (395) (Scheme 167).

**Scheme 167.**

Reagents: 1. Hydrogen fluoride-pyridine complex, THF, rt, 24 h

With the knowledge that it would be possible to remove the TIPS group, the reaction sequence was progressed. Firstly, the alcohol (394) was converted to the aldehyde (396) under Swern conditions (Scheme 168).

**Scheme 168.**

Reagents: 1. CICOCl, DMSO, DCM, -60°C; TEA.
It was then immediately added without purification to a solution of diethyl lithiummethylphosphonate in THF at \(-78^\circ\text{C}\). On work-up, a product corresponding to the alcohol (397) was isolated in 47% yield (Scheme 169). This was then successfully oxidised to the ketone (398) using pyridinium chlorochromate although in a disappointingly low yield (45%) (65% based on recovered starting material).\(^{177}\) Oxidation under Swern conditions may have resulted in a more efficient reaction.

Scheme 169.

Reagents: i. n-BuLi, MePO(OEt)\(_2\), THF, \(-78^\circ\text{C}\); ii. PCC, DCM, rt.

The remaining steps of the sequence to be carried should be relatively straightforward since much of the groundwork has already been established. This would firstly involve diazotisation of the ketone (398) to the \(\alpha\)-diazo phosphonate (399). Removal of the silyl group with hydrogen fluoride-pyridine complex should yield the diazo alcohol (400) (Scheme 170). Heating this cyclisation precursor in benzene in the presence of a catalytic amount of rhodium (II) acetate would be expected to finally furnish the functionalised bicyclic ether (401).
Reagents: i. NaH, TsN₃, THF, 0°C; ii. Hydrogen fluoride-pyridine complex, THF; iii. Rh₂(OAc)₄, PhH, Δ.

6.4 Conclusions

Two routes to functionalised bicyclic ethers have been investigated and in the course of the work a great deal of synthetic chemistry has been carried out. Both routes feature a second intramolecular rhodium (II) mediated O-H insertion reaction in which the diazo function and the alcohol are already incorporated into the oxepane containing molecule. The first route also features a competitive 6/7-intramolecular rhodium (II) catalysed O-H insertion reaction. Although this particular reaction failed to yield any isolable products and hence resulted in an early end to the reaction sequence, the second route has been developed to the point where the substrate for the second rhodium (II) catalysed intramolecular O-H insertion reaction has almost been prepared. There are great hopes that this substrate will cyclise to furnish the desired bicyclic ether.
CHAPTER SEVEN

EXPERIMENTAL SECTION
At the time of submission, spectral analysis for the compounds (177), (191), (193), (225), (283, n=3), (332), (338), (350) and (395) was still incomplete due to equipment problems at the SERC Mass Spectrometry Service (Swansea). These compounds have been marked with an asterisk in the text. Consequently, the missing data will be included in Appendix B, as and when it is obtained.

# [and (330), (334) and (349)]
7.1 General Information

Solvents and Reagents- Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. 'Light petroleum' refers to the fraction of petroleum ether boiling between 40°C and 60°C and was distilled through a 36 cm Vigreux column before use. 'Ether' refers to diethyl ether; this together with benzene and toluene, was dried where necessary by standing over sodium wire for several days. THF was distilled from sodium benzophenone ketyl under nitrogen, prior to use. Dichloromethane and carbon tetrachloride were dried where necessary by distillation from phosphorous pentoxide. DMSO and DMF were stirred for 15 h over barium oxide, decanted, and distilled under reduced pressure before storing over activated 4Å molecular sieves under nitrogen. Pyridine, triethylamine and diisopropylamine were each distilled from, and stored over, potassium hydroxide pellets.

Chromatographic Procedures- Analytical thin layer chromatography (TLC) was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under uv light (at 254 and / or 360 nm) or by staining with molybdate and permanganate dips. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Sorbsil C 60 silica gel. Pressure was applied at the column head with either hand bellows or an aquarium pump. Gravity chromatography was carried out using Merck Kieselgel 60 (70-230 mesh) silica. Samples were applied pre-adsorbed on silica or as a saturated solution in an appropriate solvent.

Spectroscopic techniques- Infra red spectra were recorded in the range 4000-600 cm⁻¹ using a Pye-Unicam PU 9516 linked to an IBM computer or a Nicolet FT-205 spectrometer, both with internal calibration. Spectra were recorded as either solutions in chloroform, as thin films or as nujol mulls. Thin films and nujol mulls were recorded between sodium chloride plates.

¹H NMR spectra were recorded using Bruker AC-250 (250 MHz), Bruker AC-360 (360 MHz), Bruker WH-400 (400 MHz) (courtesy of the SERC NMR Spectroscopy Centre, Warwick) and Varian EM360A (60 MHz) instruments. ¹³C NMR spectra were recorded on a Bruker AC-250 (62.9 MHz), Bruker AC-360 (92.6 MHz) or a
Bruker WH-400 (125 MHz). $^1$H NMR spectra are referenced against tetramethylsilane at 0.0 ppm when using the continuous wave machine and against residual undeuterated solvent when using the Fourier transform machines. In the case of deuterochloroform, this is 7.260 ppm. Signals are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), double doublets (dd) etc.

High and low resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG Analytical ZAB-E instrument (courtesy of the SERC mass spectometry service, Swansea).

Other data and instrumentation- Melting points were measured on a Reichert-Kofler hot stage apparatus or an Electrothermal digital melting point apparatus and are uncorrected.

NOTE: All of the following experimental reactions were carried out under an atmosphere of nitrogen except in cases where it was obviously unnecessary.

7.2 Experimental for Chapter Two

\[
\begin{align*}
\text{PhS}(-OEt) & \quad \text{PhSO}_2(-OEt) \\
(212) & \quad (177)
\end{align*}
\]

Ethyl phenylthioacetate (212)

A solution of sodium ethoxide was prepared by adding finely cut pieces of sodium (1.20 g, 53 mmol) to absolute ethanol (90 ml) and leaving until all the sodium had reacted. Thiophenol (5.20 ml, 5.50 g, 50 mmol) was then added dropwise from a dropping funnel (CAUTION). After 30 min, ethyl bromoacetate (5.55 ml, 8.35 g, 50 mmol) was added dropwise and the reaction mixture then allowed to stir for 12 h. Ether (100 ml) and water (100 ml) were added and the aqueous layer extracted with ether (2 x 150 ml). The combined ethereal extracts were washed successively with water (100 ml), aqueous sodium hydroxide (5%, 100 ml) and brine (100 ml) and then dried (MgSO$_4$). Evaporation of the solvent gave an oil which was Kugelrohr distilled to give the title compound (7.8 g, 80%) (b.p. 156-158°C/14 mmHg).
This displayed identical spectral properties to those described in references 111 and 115.

**Ethyl phenylsulphonylacetate**

A solution of ethyl phenylthioacetate (212) (10.0 g, 0.051 mol) in methanol (200 ml) was cooled to -10°C and a solution of Oxone (46.0 g, 0.072 mol) in water (200 ml) was added dropwise. After stirring the reaction mixture at room temperature for 12 h, water (200 ml) and dichloromethane (200 ml) were added. The aqueous layer was extracted with dichloromethane (3 x 200 ml) and the combined organic extracts washed successively with water (200 ml) and brine (200) and then dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the *title compound* (10.7 g, 92%), which displayed identical spectral properties to those described in references 111 and 115.

*Benzenesulphonyl-ethoxy carbonyl-diazomethane* (177)

A mixture of ethyl phenylsulphonylacetate (5.0 g, 0.022 mol), tosyl azide (4.75 g, 0.024 mol) and triethylamine (3.35 ml, 2.4 g, 0.024 mol) in dichloromethane (100 ml) was stirred for two days at room temperature. Most of the solvent was then removed by evaporation. Ether (100 ml) and sodium hydroxide (5%, 75 ml) were added and the organic layer washed successively with sodium hydroxide (5%, 75 ml), water (2 x 75 ml) and brine (75 ml). After drying (MgSO₄), the solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the *title compound* as a yellow solid (3.91 g, 70%); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \): 2129, 1720, 1344, 1291, 1216, 1160, 1073 and 611; \( \delta_\text{H} \) (250 MHz; CDCl₃) 1.25 (3 H, t, J 7.1, OCH₂Me), 4.22 (2 H, q, J 7.1, OCH₂Me) and 7.53-8.05 (5 H, m, C₆H₅S); \( \delta_\text{C} \) (62.9 MHz; CDCl₃) 14.16 (OCH₂Me), 62.37 (OCH₂Me), 127.85 (C₆H₅), 129.43 (C₆H₅), 133.68 (C₆H₅), 141.60 (C₆H₅) and 159.58 (C=O). CN₂ not observed.
Triethyl phosphonodiazooacetate (180)

Triethyl phosphonoacetate (30.0 g, 0.134 mol) was added dropwise to a suspension of sodium hydride (80%, 4.42 g, 0.147 mol) in THF (400 ml) at 0°C. After stirring for 45 min, a solution of tosyl azide (26.4 g, 0.134 mol) in THF (50 ml) was added dropwise. The reaction was then left to stir for 1 h at 0°C and 2 h at room temperature. Ether (300 ml) and water (300 ml) were then added and the aqueous layer extracted with ether (3 x 200 ml). The combined ethereal extracts were washed successively with aqueous sodium hydroxide (5%, 200 ml), water (2 x 200 ml) and brine (200 ml). After drying (MgSO₄), the solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the title compound (20.94 g, 63%) as a yellow oil which displayed identical spectral properties to those described in reference 8.

Diethyl phenylsulphonylmethanephosphonate

A solution of Oxone (34.6 g, 0.056 mol) in water (150 ml) was added dropwise to a solution of diethyl phenylthiomethanephosphonate (9.75 g, 37.5 mmol) (Lancaster Synthesis) in methanol (150 ml) at -10°C. After stirring at room temperature for 12 h, water (200 ml) and dichloromethane (200 ml) were added. The aqueous layer was extracted with dichloromethane (3 x 200 ml) and the combined organic extracts were washed successively with water (200 ml) and brine (200 ml). After drying (MgSO₄), the solvent was removed by evaporation and the residue chromatographed on silica (ether-ethyl acetate) to yield the title compound. This displayed identical spectral properties to those described in reference 178.
**Benzenesulphonyl-diethyl phosphono-diazomethane (185)**

A solution of diethyl phenylsulphonylmethanephosphonate (2.0 g, 6.8 mmol) in benzene (CAUTION) (8 ml) was added dropwise over 15 min to a suspension of sodium hydride (80%, 0.23 g, 7.5 mmol) in benzene (CAUTION) (60 ml). The reaction was then stirred for 30 min at room temperature. During this time the anion precipitated out as a white solid. Tosyl azide (1.35 g, 6.8 mmol) was added dropwise to the solid which turned immediately orange and began to dissolve. After stirring the reaction mixture for 2 h at room temperature, water (100 ml) was added. The aqueous layer was extracted with benzene (CAUTION) (3 x 60 ml) and the combined organic extracts washed successively with aqueous sodium hydroxide (5%, 100 ml), water (2 x 50 ml) and brine (50 ml). After drying (MgSO4), the solvent was removed by evaporation and the residue chromatographed on silica (ether-ethyl acetate) to yield the title compound as a pale yellow oil (1.92 g, 88%), (Found: M+NH4+, 336.0783. C11H15N2O5PS+NH4 requires 336.0783); \( \nu_{\text{max}}^{\text{film}} / \text{cm}^{-1} \): 2987, 2115, 1338, 1266, 1156, 1087, 1014, 725, 629 and 574; \( \delta_{\text{H}} \) (60 MHz; CDCl3) 1.3 (6 H, t, J 8.0, OCH2Me), 3.9-4.4 (4 H, m, OCH2Me) and 7.5-8.1 (5 H, m, C6H5S); \( \delta_{\text{C}} \) (62.9 MHz; CDCl3) 15.90 (OCH2Me), 16.02 (OCH2Me), 63.92 (OCH2Me), 64.01 (OCH2Me), 127.18 (C6H5), 129.27 (C6H5), 133.86 (C6H5) and 142.78 (C6H5). CN2 not observed; m/z (EI+) 319 (MH+, 2%), 121 (56), 109 (100), 93 (32), 77 (97), 65 (84), 51 (63) and 43 (26).

![Chemical structure](attachment:image.png)

**Diethyl phosphono-diethyl phosphono-diazomethane (186)** [bis-(diethyl phosphono)]-

A solution of tetraethyl methylenediphosphonate (6.0 g, 0.021 mol) (Lancaster Synthesis) in THF (20 ml) was added dropwise to a suspension of sodium hydride (80%, 0.75 g, 0.025 mol) in THF (200 ml) at 0°C. After stirring for 30 min at 0°C, tosyl azide (4.92 g, 0.025 mol) was added dropwise and the reaction allowed to stir for 3 h at room temperature. Ether (200 ml) and water (200 ml) were then
added and the aqueous layer extracted with ether (3 x 100 ml). The combined organic extracts were washed with brine (200 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ethyl acetate) to yield the title compound as a pale yellow oil (5.10 g, 78%). This displayed identical spectral properties to those described in reference 8.

**General Procedure for Rhodium (II) Catalysed Intermolecular O-H Insertion Reactions**

\[ \text{Z} \text{N}_2 \text{OEt} \xrightarrow{\text{Rh}_2(\text{OAc})_4} \text{H} \text{N}=\text{C} \text{H} \xrightarrow{\text{OEt}} \text{Z} \text{N}_2 \text{OEt} \]

The appropriate diazo compound (1.0 mmol) was added to a suspension of rhodium (II) acetate (4.4 mg, 0.01 mmol) in a mixture of dichloromethane (2 ml) and 2-propanol (9.19 ml, 7.2 g, 0.12 mol). The reaction was stirred at room temperature until complete (as determined by TLC). The solvent was removed by evaporation and the residue chromatographed on silica to yield the respective insertion product. In the case of the various phosphonates where the reaction was very slow, the reaction mixture was heated to reflux temperature.

**Ethyl 2-isopropoxyacetate** (187) (64%), (Found: M+H⁺, 147.1021. C₇H₁₄O₃+H requires 147.1021; νmax(film)/cm⁻¹ 2972, 2936, 1756, 1380, 1370, 1278, 1204, 1126 and 1034; δH (250 MHz; CDCl₃) 1.20 (6 H, d, J 6.1, Me₂CH), 1.29 (3 H, t, J 7.1, OCH₂Me), 3.68 (1 H, h, J 6.1, Me₂CH), 4.07 (2 H, s, CH₂) and 4.23 (2 H, q, J 7.1, OCH₂Me); δC (62.9 MHz; CDCl₃) 14.25 (OCH₂Me), 21.83 (OCHMe₂), 60.70 (OCH₂Me), 65.85 (OCH₂), 72.59 (OCHMe₂)
and 170.934 (C=O); \textit{m/z} (\textit{El}+) 127 (8\%), 99 (26), 88 (7), 73 (25) and 43 (100).

\textbf{Ethyl 2-cyano-2-isopropoxyacetate} (188) (86\%), (\textit{Found: }M+H^+, 172.0970. C_{8}H_{13}O_{3}N+H requires 172.0974); \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 2983, 1770, 1751, 1299, 1284, 1213, 1183, 1142, 1114 and 1025; \delta_{\text{H}} (250 \text{ MHz}; \text{CDCl}_3) 1.23-1.38 (9 \text{ H, m, OCH}_2\text{Me and CHMe}_2), 3.97 (1 \text{ H, h, J 6.1, CHMe}_2), 4.34 (2 \text{ H, q, J 7.2, OCH}_2\text{Me}) and 4.81 (1 \text{ H, s, OCH}); \delta_{\text{C}} (62.9 \text{ MHz; CDCl}_3) 13.96 (\text{OCH}_2\text{Me}), 21.32 (\text{OCHMe}_2), 22.14 (\text{OCHMe}_2), 63.34 (\text{OCH}_2\text{Me}), 65.61 (\text{OCH}), 74.22 (\text{OCHMe})_2, 114.71 (\text{C=N}) and 163.79 (\text{C=O}); \textit{m/z} (\textit{Cl}^+) 189 (M+\text{NH}_4^+, 100\%), 172 (\text{MH}^+, 10), 118 (1), 102 (4), 85 (5) and 49 (27).

![](PhSO2.png)

![](Et.png)

\textbf{Ethyl 2-benzenesulphonyl-2-isopropoxyacetate} (189) (64\%), (\textit{Found: }M+\text{NH}_4^+, 304.1219. C_{13}H_{18}O_{5}S+\text{NH}_4 \text{ requires } 304.1219); \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 2980, 1746, 1326, 1310, 1232, 1186, 1154, 1108, 1080 and 688; \delta_{\text{H}} (250 \text{ MHz; CDCl}_3) 1.15-1.32 (9 \text{ H, m, OCH}_2\text{Me and Me}_2\text{CH}), 3.99 (1 \text{ H, h, J 6.1, Me}_2\text{CH}), 4.23 (2 \text{ H, q, J 7.1, OCH}_2\text{Me}), 4.94 (1 \text{ H, s, OCH}) and 7.53-7.93 (5 \text{ H, m, C}_6\text{H}_5\text{S}); \delta_{\text{C}} (62.9 \text{ MHz; CDCl}_3) 13.94 (\text{OCH}_2\text{Me}), 21.41 (\text{OCHMe}_2), 22.04 (\text{OCHMe}_2), 62.65 (\text{OCH}_2\text{Me}), 76.85 (\text{OCH}), 92.47 (\text{OCH}), 128.85 (\text{C}_6\text{H}_5), 129.96 (\text{C}_6\text{H}_5), 134.44 (\text{C}_6\text{H}_5), 135.80 (\text{C}_6\text{H}_5) and 164.30 (\text{C=O}); \textit{m/z} (\textit{Cl}^+) 287 (\text{MH}^+-\text{OC}_3\text{H}_7, 16\%), 185 (76), 143 (40), 125 (37), 103 (100), 78 (53) and 43 (65).

\textbf{Diethyl 2-isopropoxyxymalonate} (190) (66\%), (\textit{Found: }M+\text{NH}_4^+, 236.1498. C_{10}H_{18}O_{5}+\text{NH}_4 \text{ requires } 236.1498); \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 2980, 2936, 1764, 1740, 1466, 1384, 1370, 1322, 1224, 1180 and 1032; \delta_{\text{H}} (250 \text{ MHz; CDCl}_3) 1.24-1.33 (12 \text{ H, m, OCH}_2\text{Me and Me}_2\text{CH}), 3.77 (1 \text{ H, h, J 6.2, Me}_2\text{CH}), 4.20-
4.31 (4 H, m, OCH₂Me) and 4.54 (1 H, s, OCH); δC (62.9 MHz; CDCl₃) 14.07 (OCH₂Me), 21.91 (OCHMe₂), 61.64 (OCH₂Me), 73.39 (OCHMe₂), 77.25 (COCH) and 167.24 (C=O); m/z (Cl⁺) 236 (M+NH₄⁺, 100%), 219 (MH⁺, 25), 194 (44), 177 (22) and 161 (35).

 Ethyl 2-isopropyloxy-2-diethyl phosphonoacetate (192) (83%), (Found: M+H⁺, 283.1311. C₁₁H₂₃O₆P+H requires 283.1311); νmax(nujol)/cm⁻¹ 1728, 1438, 1282, 1188, 1162, 1124 and 1074; δH (250 MHz; CDCl₃) 1.03 (3 H, t, J 7.1, OCH₂Me), 3.49 (2 H, d, J 14.9, CH₂), 4.00 (2 H, q, J 7.1, OCH₂Me) and 7.41-7.87 (10 H, m, C₆H₅P).

 Ethyl 2-isopropyloxy-3-phenylpropanoate (193) (32%); δH (250 MHz; CDCl₃) 0.94 (3 H, d, J 6.1, Me₂CH), 1.15 (3 H, d, J 6.1, Me₂CH), 1.23 (3 H, t, J 7.1, OCH₂Me), 2.89-3.05 (2 H, m, PhCH₂), 3.50 (1 H, h, J 6.1, OCHMe₂).
4.02-4.08 (1 H, m, OCH), 4.13-4.22 (2 H, m, OCH₂Me) and 7.24-7.26 (5 H, m, C₆H₅); m/z (El⁺) 176 (16%), 163 (20), 121 (100), 103 (36), 91 (44), 75 (13), 43 (31) and 39 (9).

Dimethyl 2-isopropyloxymalonate (194) (58%), (Found: M+NH₄⁺, 208.1185. C₈H₁₄O₅+NH₄ requires 208.1185); νmax(film)/cm⁻¹ 2976, 1744, 1436, 1384, 1332, 1288, 1234, 1168, 1114 and 1024; δH (250 MHz; CDCl₃) 1.23 (6 H, d, J 6.2, Me₂CH), 3.80 (6 H, s, OCH₃), 3.80 (1 H, m, Me₂C!::!.2Me) and 4.59 (1 H, s, OCH); δC (62.9 MHz; CDCl₃) 21.87 (OCHMe₂), 52.83 (CO₂Me), 73.44 (OCHMe₂), 76.93 (COCH) and 167.63 (C=O); m/z (El⁺) 89 (14), 59 (19), 43 (100) and 39 (9).

Diethyl 1-(isopropyloxy)-2-oxopropylphosphonate (195) (71%), (Found M+H⁺, 253.1205. C₁₀H₂₁O₅P+H requires 253.1205); νmax(film)/cm⁻¹ 2976, 1716, 1384, 1376, 1356, 1258, 1166, 1140, 1094, 1052, 1026 and 974; δH (250 MHz; CDCl₃) 1.20-1.29 (6 H, m, Me₂CH), 1.34 (6 H, m, OCH₂Me), 2.32 (3 H, s, Ac), 3.70 (1 H, h, J 6.0, Me₂CH), 4.17-4.24 (4 H, m, OCH₂Me), 4.26 (1 H, d, J 20.0, OCHP); δC (62.9 MHz; CDCl₃) 16.08-16.42 (2 C, m, OCH₂Me), 20.90 (Me), 22.16 (Me), 27.28 (MeCO), 63.33-63.81 (2 C, m, OCH₂Me), 74.77 (1 C, d, J 9.9, OCHMe₂), 81.59 (1 C, d, J 151.6, OCHP) and 205.34 (1 C, d, J 2.7, C=O); m/z (El⁺) 210 (10), 167 (100), 139 (44), 111 (74), 65 (12) and 43 (21).

\[
\begin{align*}
\text{PhSO}_2 & \quad \text{O}
\end{align*}
\]

Diethyl 1-(isopropyloxy)-1-phenylsulphonylmethane phosphonate (199)

A mixture of benzenesulphonyl-diethyl phosphono-diazomethane (185) (0.50 g, 1.57 mmol), 2-propanol (0.6 ml, 0.47 g, 7.86 mmol) and rhodium (ii) acetate (6.9 mg, 0.016 mmol) in toluene (30 ml) was refluxed for 72 h. The solvent was
removed by evaporation and the residue chromatographed on silica (ether-ethyl acetate) to yield the title compound as a colourless oil (0.37 g, 67%), (Found $M+\text{NH}_4^+$, 368.1300. $\text{C}_14\text{H}_{23}\text{O}_6\text{PS+NH}_4$ requires 368.1297); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1322, 1311, 1260, 1157, 1142, 1098, 1073, 1050 and 1024; $\delta_H$ (250 MHz; CDCl$_3$) 1.14-1.37 (12 H, m, OCH$_2$Me and OCH$_2$Me), 4.03-4.25 (5 H, m, OCH$_2$Me and OCH$_2$Me), 4.73 (1 H, d, J 12.5, OCHP) and 7.52-8.04 (5 H, m, C$_6$H$_5$); $\delta_C$ (62.9 MHz; CDCl$_3$) 16.28 (2 C, m, OCH$_2$Me), 21.27 (OCH$_2$Me), 22.15 (OCH$_2$Me), 64.09 (2 C, m, OCH$_2$Me), 77.89 (1 C, d, J 6.0, OCHMe$_2$), 90.34 (1 C, d, J 169.2, OCHP), 128.61 (C$_6$H$_5$), 130.21 (C$_6$H$_5$), 134.20 (C$_6$H$_5$) and 137.02 (C$_6$H$_5$); $m/z$ (CI$^+$) 368 (M$+\text{NH}_4^+$), 351 (MH$^+$, 6), 228 (44), 211 (7), 184 (19), 170 (4) and 156 (16).

**Rhodium (II) Trifluoroacetamide Catalysed O-H Insertion Reactions**

In general, these were carried out in exactly the same fashion as the corresponding rhodium (II) acetate catalysed reactions.

\[
\begin{array}{c}
\text{EtO} & \text{O} & \text{P} & \text{O} & \text{Et} \\
\text{EtO} & \text{P} & \text{O} & \text{Et} \\
\text{N}_2
\end{array}
\rightarrow
\begin{array}{c}
\text{EtO} & \text{O} & \text{P} & \text{O} & \text{Et} \\
\text{EtO} & \text{P} & \text{O} & \text{Et} \\
\text{PrO}
\end{array}
\]

(186) \quad (202)

**Diethyl 1-(isopropoxy)-1-diethyl phosphonomethane phosphonate (202)**

A mixture of diethyl phosphono-diethyl phosphono-diazomethane [bis-(diethyl phosphono-diazomethane)] (186) (1.0 g, 3.18 mmol), 2-propanol (1.22 ml, 0.96 g, 0.016 mol) and rhodium (II) trifluoroacetamide (21 mg, 0.032 mmol) was refluxed for 2 h in dry toluene (60 ml). The solvent was removed by evaporation and the residue chromatographed on silica (dichloromethane-methanol) to yield the title compound (0.89 g, 81%), (Found: $M+\text{H}^+$, 347.1390. $\text{C}_{12}\text{H}_{28}\text{O}_7\text{P}_2\text{H}$ requires 347.1389); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2981, 1255, 1165, 1097, 1049, 1026 and 975; $\delta_H$ (250 MHz; CDCl$_3$) 1.21 (6 H, d, J 6.1, CHMe$_2$), 1.35 (6 H, t, J 7.1, OCH$_2$Me), 1.36 (6 H, t, J 7.1, OCH$_2$Me), 3.98 (1 H, h, J 6.1, CHMe$_2$), 4.07 (1 H, t, J 17.7, OCHP) and 4.18-4.30 (8 H, m, OCH$_2$Me); $m/z$ (CI$^+$) 347 ($\text{MH}^+$, 100%), 319 (3), 305 (3), 288 (6), 261 (3), 167 (8) and 152 (3).
A solution of the diazo alcohol (1.0 mmol) in dichloromethane (10 ml) was added dropwise over 15 min to a suspension of rhodium (II) trifluoroacetamide (6.5 mg, 0.01 mmol) in dichloromethane (30 ml). The reaction was then left to stir until complete as determined by TLC. The solvent was removed by evaporation and the residue chromatographed on silica to yield the respective 2-substituted 3-oxooxepane.

7-Hexyl-2-phenylsulphonyloxepan-3-one (206) (55%), Melting point 61-62°C; δH (250 MHz; CDCl₃) 0.83 (3 H, t, J 6.7, Me), 0.90-1.85 (12 H, m, (CH₂)₅ and 5-CH₂), 1.85-2.04 (2 H, m, 6-CH₂), 2.49 (1 H, dd, J 5.4, 11.1, 4-CHH), 2.86 (1 H, ddd, J 2.2, 8.9, 13.4, 4-CHH), 3.12-3.25 (1 H, m, 7-CH), 4.67 (1 H, s, 2-CH), 7.48-7.93 (5 H, m, C₆H₅). Rest of data already reported in reference 67.

t-Butyl-7-hexyl-3-oxooxepane-2-carboxylate (207) (57%); δH (250 MHz; CDCl₃) 0.80-0.90 (3 H, m, Me, keto and enol), 1.44 and 1.50 (9 H, 2 s, t-Bu, keto, axial and equatorial), 1.55 (9 H, s, t-Bu, enol), 1.22-2.01 (14 H, m, (CH₂)₅, 5-CH₂ and 6-CH₂), 2.19-2.32 (1 H, dd, J 5.0, 16.0, 4-CHH, enol), 2.36-2.49 (1 H, dd, J 5.0, 13.0, 4-CHH, keto), 2.59-2.80 (1 H, m, 4-CHH, keto), 2.87-3.01 (1 H, dt, J 2.5, 16.0, 4-CHH, enol), 3.17-3.30 (1 H, m, 7-CH), 4.29 and 4.58 (1 H, 2 s, 2-CH, keto, axial and equatorial) and 11.15 (1 H, s,
OH, enol), ca. 50% enol form. Rest of data reported in reference 67.

**Diethyl-7-hexyl-3-oxooxepane-2-phosphonate (208)** (24%); $\delta_H$ (250 MHz; CDCl$_3$) 0.85 (3 H, J 6.7, Me), 1.18-1.84 (18 H, m, (CH$_2$)$_5$, 5-CH$_2$ and OCH$_2$Me), 1.89-2.04 (2 H, m, 6-CH$_2$), 2.44 (1 H, dd, J 6.2, 15.0, 4-CHH), 3.02-3.20 (2 H, m, 4-CHH and 7-CH) and 4.09-4.28 (5 H, m, OCH$_2$Me and 2-CH). Rest of data reported in reference 67.

**Insertion Reactions with other Alcohols**

The compounds (209-211) were prepared in exactly the same manner as the isopropyloxy derivatives (187-195). Where reaction was very slow, as outlined in Chapter 2, the reaction mixture was heated to reflux temperature.

![Chemical structures](image)

**Ethyl 2-benzenesulphonyl-2-methoxyacetate (209)** (92%), (Found: $M+\text{NH}_4^+$, 276.0906. $C_{11}H_{14}O_5S+\text{NH}_4$ requires 276.0906); $v_{\text{max}}$(film)/cm$^{-1}$ 1748, 1446, 1324, 1310, 1196, 1154, 1122, 1078, 1024 and 688; $\delta_H$ (250 MHz; CDCl$_3$) 1.25 (3 H, t, J 7.2, OCH$_2$Me), 3.73 (3 H, s, OMe), 4.21 (2 H, q, J 7.1, OCH$_2$Me), 4.83 (1 H, s, SCH) and 7.54-7.93 (5 H, m, C$_6$H$_5$SO$_2$); $\delta_C$ (62.9 MHz; CDCl$_3$) 13.90 (OCH$_2$Me), 61.39 (OMe), 62.75 (OCH$_2$Me), 95.78 (OCH), 129.00 (C$_6$H$_5$), 129.75 (C$_6$H$_5$), 134.59 (C$_6$H$_5$), 135.64 (C$_6$H$_5$) and 165.42 (C=O); m/z (El$^+$) 157 (5%), 125 (35), 117 (100), 102 (5), 89 (11), 61 (15) and 45 (8).

**Ethyl 2-benzenesulphonyl-2-t-butyloxyacetate (210)** (90%), (Found: $M+\text{NH}_4^+$, 318.1375. $C_{14}H_{20}O_5S+\text{NH}_4$ requires 318.1375); $v_{\text{max}}$(film)/cm$^{-1}$ 1724, 1324, 1312, 1264, 1152, 1106 and 1078; $\delta_H$ (250 MHz; CDCl$_3$) 1.12 (9
H, s, t-Bu), 1.30 (3 H, t, J 7.1, OCH₂Me), 4.31 (2 H, q, J 7.1, OCH₂Me), 5.00 (1 H, s, SCH) and 7.50-7.99 (5 H, m, C₆H₅SO₂); δC (62.9 MHz; CDCl₃) 13.98 (OCH₂Me), 27.32 (t-Bu), 62.57 (OC₂H₅), 79.54 (OC₃Me₃), 88.02 (OCH), 128.70 (C₆H₅), 130.25 (C₆H₅), 134.37 (C₆H₅), 135.89 (C₆H₅) and 165.53 (C=O).

Ethyl 2-t-butyloxy-2-diethyl phosphonacetate (211) (63%), (Found: M+H⁺, 297.1467. C₁₂H₂₅O₆P+H requires 297.1467); ν max(film)/cm⁻¹ 2980, 1752, 1256, 1184, 1164, 1100, 1050, 1028 and 976; δH (250 MHz; CDCl₃) 1.20-1.38 (18 H, m, t-Bu and OCH₂Me), 4.20-4.28 (6 H, m, OCH₂Me) and 4.45 (1 H, d, J 21.0, OCHP); δC (62.9 MHz; CDCl₃) 14.10 (OCH₂Me), 16.37 (OCH₂Me), 16.47 (OCH₂Me), 27.31 (t-Bu), 61.60 (OCH₂Me), 63.70 (2 C, m, OCH₂Me), 70.09 (1 C, d, J 159.7, OCHP), 77.67 (OC₃Me₃) and 169.32 (1 C, d, J 3.9, C=O); m/z (El⁺) 297 (MH⁺, 21%), 241 (100), 194 (5), 167 (24), 138 (21), 111 (13), 57 (11) and 29 (9).

**General Procedure for Photolysis Experiments**

![Diagram](image)

A solution of benzenesulphonyl-diethyl phosphono-diazomethane (185) (0.15 g, 0.47 mmol) in dry alcohol (methanol or 2-methyl-2-propanol) (10 ml), in a quartz test-tube, was degassed and simultaneously put under an atmosphere of nitrogen by bubbling nitrogen through it, via a syringe needle, for 30 min. The reaction was irradiated for varying periods of time with a medium pressure mercury vapour lamp. When the reaction was complete (as determined by TLC), the solvent was removed by evaporation and the residue chromatographed on silica (ether-ethyl acetate) to yield the insertion products as clear oils.
Diethyl 1-methoxy-1-phenylsulphonylmethane phosphonate (196) (63%), (Found: M+H+, 323.0718. C_{12}H_{19}O_{6}PS+H requires 323.0718); v_{\text{max}}(\text{film})/\text{cm}^{-1} 1446, 1324, 1312, 1264, 1158, 1102, 1078, 1046, 980, 732 and 688; δ_H (250 MHz; CDCl3) 1.21-1.37 (6 H, m, O CH_{2}Me), 3.68 (3 H, s, OCH_{3}), 4.07-4.21 (4 H, m, OCH_{2}Me), 4.53 (1 H, d, J 12.6, SCHP) and 7.36-8.02 (5 H, m, C_{6}H_{5}S); m/z (EI+) 323 (MH+, 42%), 291 (5), 182 (5), 121 (100), 91 (5), 77 (23), 51 (11) and 29 (5).

Diethyl 1-(t-butyloxy)-1-phenylsulphonylmethane phosphonate (197) (44%), (Found: M+H+, 365.1188. C_{15}H_{25}O_{6}SP+H requires 365.1188); v_{\text{max}}(\text{film})/\text{cm}^{-1} 2980, 1370, 1322, 1310, 1260, 1174, 1158, 1092, 1070, 1052, 1024, 978 and 688; δ_H (250 MHz; CDCl3) 1.15-1.39 (15 H, m, O CH_{2}Me and t-Bu), 4.03-4.20 (4 H, m, OCH_{2}Me), 4.95 (1 H, d, J 11.2, SCHP) and 7.51-8.01 (5 H, m, C_{6}H_{5}S); m/z (EI+) 365 (MH+, 6%), 309 (10), 167 (100), 139 (23), 111 (23), 77(13), 57 (17) and 41 (11).

2-benzenesulphonyl-2-methoxy styrene (198)
A solution of diethyl 1-methoxy-1-phenylsulphonylmethane phosphonate (196) (0.1 g, 0.31 mmol) in THF (2 ml) was added dropwise to a suspension of sodium hydride (80%, 10 mg, 0.34 mmol) in THF (15 ml) at 0°C. After stirring the reaction for 30 min, a solution of benzaldehyde (33 mg, 0.31 mmol) in THF (1 ml) was added. The reaction was then allowed to stir overnight at room temperature.
Ether (20 ml) and water (20 ml) were added and the aqueous layer extracted with ether (3 x 20 ml). The combined ethereal extracts were washed with brine (20 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound (48 mg, 56%, E:Z ca. 95:5), (Found: M⁺, 274.0664. C₁₅H₁₄S0₃ requires 274.0664); νₓₙₓ₁(CCl₄)/cm⁻¹ 1446, 1348, 1322, 1308, 1158, 1094, 1062, 718, 688 and 616; δₕ (250 MHz; CDCl₃) 3.67 (3 H, s, OCH₃) and 7.23-7.55 (11 H, m, C₆H₅S, C₆H₅C and CH); m/z (EI⁺) 274 (M⁺, 34%), 149 (16), 118 (100), 90 (42), 71 (17) and 51 (12).

![Chemical structures](image)

**Ethyl phenylsulphinylacetate (213)**

A solution of ethyl phenylthioacetate (212) (10.0 g, 51.0 mmol) in ethanol (50 ml) was added dropwise to a solution of sodium metaperiodate (11.5 g, 54.0 mmol) in water (75 ml). After stirring for 18 h at room temperature, the insoluble sodium iodate was filtered off and the aqueous solution extracted with dichloromethane (3 x 75 ml). The combined organics were washed successively with water (100 ml) and brine (100 ml) and then dried (MgSO₄). The solvent was removed by evaporation yielding the title compound as a colourless oil (8.76 g, 81%) which was used without further purification. This displayed identical spectral properties to those described in reference 115.

**Phenyl thiodiethylacetal (218)**

A solution of sodium ethoxide was prepared by adding finely cut pieces of sodium (2.3 g, 0.1 mol) to ethanol (180 ml) and leaving until all the sodium had reacted. After putting the reaction under an atmosphere of nitrogen, thiophenol (CAUTION) (10.25 ml, 11.0 g, 0.1 mol) was added dropwise via a dropping funnel. After stirring for 30 min, bromoacetaldehyde diethylacetal (15 ml, 19.7 g, 0.1 mol) was added dropwise. The reaction was stirred for 1 week at room temperature. Ether (200 ml) and water (200 ml) were added and the aqueous layer extracted with ether.
(2 x 200 ml). The combined ethereal extracts were washed successively with water (2 x 200 ml), aqueous sodium hydroxide (5%, 200 ml) and brine (200 ml) and then dried (MgSO₄). Evaporation of the solvent followed by Kugelrohr distillation of the residue yielded the title compound (15.9 g, 70%). This displayed identical spectral properties to those described in reference 115.

Phenyl thioacetaldehyde (219)

Removal of the acetal group was carried out by refluxing a solution of phenyl thiodiethylacetal (218) (2.0 g, 8.8 mmol) in THF (5 ml) with 2 M hydrochloric acid (10 ml) for 5 hours. After allowing to cool, the acid solution was poured into water (20 ml) and extracted with ether (3 x 20 ml). The combined ethereal extracts were washed successively with saturated sodium bicarbonate solution (2 x 40 ml) and brine (40 ml) and then dried (MgSO₄). Evaporation of the solvent yielded the crude title product which was used without further purification. This displayed identical spectral properties to those described in reference 115.

\[
\text{PhS} \quad \text{O} \\
\text{(219)} \\
\rightarrow \\
\text{PhS} \quad \text{O} \\
\text{Et} \\
\text{(220)}
\]

Ethyl 4-phenylthio-but-2-enoate (220)

A solution of triethyl phosphonoacetate (1.47 g, 6.6 mmol) in THF (5 ml) was added dropwise to a suspension of sodium hydride (80%, 0.22 g, 7.2 mmol) in THF (30 ml) at 0°C. After stirring the reaction for 45 min at 0°C, a solution of phenyl thioacetaldehyde (219) (1.0 g, 6.6 mmol) in THF (5 ml) was added dropwise. The reaction was stirred for 1 h at 0°C and subsequently allowed to warm to room temperature. Ether (50 ml) and water (50 ml) were added and the aqueous layer extracted with ether (3 x 50 ml). The combined ethereal extracts were washed with brine (50 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound (0.76 g, 52%), (Found: M⁺, 222.0715. C₁₂H₁₄O₂S requires 222.0715); \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1}\) 2980, 1734, 1718, 1648, 1478, 1314, 1266.
1196, 1026, 740 and 690; \( \delta_H \) (250 MHz; CDCl\(_3\)) 1.19-1.31 (3 H, m, OCH\(_2\)Me), 3.15-3.63 (2 H, m, SCH\(_2\)C), 4.12-4.22 (2 H, m, OCH\(_2\)Me), 5.78-6.02 (1 H, m, CH\(_2\)CH), 6.27-7.00 (1 H, m, CHCO) and 7.22-7.37 (5 H, m, C\(_6\)H\(_5\)S); \( m/z \) (El\(^+\)) 222 (M\(^+\), 100%), 177 (21), 149 (66), 135 (26), 109 (42), 103 (54) and 29 (40).

Ethyl 4-phenylsulphinyl-but-2-enoate (221)

To a solution of sodium periodate (1.78 g, 8.32 mmol) in water (20 ml) was added a solution of the sulphide (220) (1.76 g, 7.9 mmol) in ethanol (20 ml). After stirring the reaction for 18 h, the insoluble sodium iodate was filtered off and dichloromethane (20 ml) added. The aqueous layer was extracted with dichloromethane (3 x 20 ml) and the combined organic extracts washed with brine (50 ml) and dried (MgSO\(_4\)). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound (0.95 g, 51%), (Found: M\(^+\), 239.0742. C\(_{12}\)H\(_{14}\)O\(_3\)S requires 239.0742); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2980, 1718, 1648, 1318, 1270, 1198, 1146, 1084, 1072, 1046, 750 and 692; \( \delta_H \) (250 MHz; CDCl\(_3\)) 1.27 (3 H, t, J 7.1, OCH\(_2\)Me), 3.54-3.75 (2 H, dq, J 7.9, SCH\(_2\)C), 4.18 (2 H, q, J 7.1, OCH\(_2\)Me), 5.89 (1 H, d, J 15.6, CH\(_2\)CH), 6.69 (1 H, dq, J 7.9, CHCO) and 7.51-7.65 (5 H, m, C\(_6\)H\(_5\)SO); \( m/z \) (El\(^+\)) 125 (39%), 109 (29), 85 (31), 78 (29), 69 (35), 57 (22), 51 (39) and 30 (100).

Ethyl 4-diazo-4-phenylsulphinyl-but-2-enoate (222)

A mixture of the sulphonyl (221) (0.50 g, 2.1 mmol), tosyl azide (0.46 g, 2.3
mmol) and triethylamine (0.58 ml, 0.42 g, 4.2 mmol) in acetonitrile (10 ml) was stirred for 24 h at room temperature. The solvent was removed by evaporation and ether (20 ml) and aqueous sodium hydroxide (5%, 20 ml) added. The ethereal layer was washed successively with water (20 ml) and brine (20 ml) and then dried (MgSO$_4$). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound as a yellow oil (0.34 g, 60%). (Found: $M+H^+$, 265.0647. C$_{12}$H$_{12}$N$_2$O$_3$S+H requires 265.0647); $\nu_{\text{max}}$(film)/cm$^{-1}$: 2980, 2100, 1702, 1596, 1370, 1330, 1308, 1200, 1182, 1124, 1104, 1084, 1048, 1022 and 750; $\delta_{\text{H}}$ (250 MHz; CDCl$_3$) 1.31 (3 H, t, J 7.1, OCH$_2$Me), 4.30 (2 H, q, J 7.1, OCH$_2$Me), 6.37 (1 H, d, J 15.2, CCH), 6.95 (1 H, d, J 15.2, CHCO) and 7.50-7.62 (5 H, m, C$_6$H$_5$SO); m/z (El$^+$) 265 (MH$^+$, 7%), 216 (10), 163 (32), 147 (18), 125 (77), 111 (100), 77 (47) and 51 (47).
7.3 Experimental for Chapter 3

**General Procedure for the Preparation of 2-Disubstituted Styrenes**

![Chemical structure](image)

A suspension of sodium hydride (80%, 0.031 g, 1.03 mmol) in THF (20 ml) at 0°C was treated dropwise with a solution of the phosphonate (192, 199 or 202, respectively) (0.86 mmol) in THF (5 ml). After stirring for 45 min at 0°C, benzaldehyde (0.10 g, 0.95 mmol) was added. The reaction was allowed to stir for 2 h at room temperature after which ether (60 ml) and water (60 ml) were added. The aqueous phase was extracted with ether (3 x 40 ml) and the combined organic extracts washed with brine (80 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica to yield the respective title compound as a colourless oil.

*Ethyl 2-isopropoxy-3-phenyl-2-propenoate (225) (64%, E/Z ratio ca. 3:2); ν₂max (film)/ cm⁻¹ 2976, 1716, 1630, 1372, 1246, 1204, 1178, 1150, 1108 and 696; δH (250 MHz; CDCl₃) 1.06-1.40 (9 H, m, OCH₂Me and OCHMe₂), 4.08-4.45 (3 H, m, OCH₂Me and OCHMe₂) and 7.18-7.83 (6 H, m, CHPh and C₆H₅).

2-Benzene sulphonyl-2-isopropoxy-styrene (226) (72%) (Analysis carried out on dominant E isomer), (Found: M+NH₄⁺, 320.1320. C₁₇H₁₈O₃S+NH₄⁺ requires 320.1320); ν₂max (film)/ cm⁻¹ 1448, 1319, 1306, 1154, 1095,
1052, 752, 688 and 641; $\delta_H$ (250 MHz; CDCl$_3$) 1.23 (6 H, d, J 6.1, CHMe$_2$), 4.43 (1 H, h, J 6.1, CHMe$_2$) and 7.29-7.81 (11 H, m, C=CH, C$_6$H$_5$ and C$_6$H$_5$SO$_2$); $\delta_C$ (62.9 MHz; CDCl$_3$) 22.12, 78.02, 123.44, 128.20, 128.46, 129.07, 129.41, 130.03, 132.22, 133.45, 139.01 and 150.02; m/z (Cl$^+$) 320 (M+NH$_4^+$, 100%), 260 (6), 177 (3), 152 (9), 118 (27) and 107 (5).

2-Diethyl phosphono-2-isopropyloxy-styrene (227) (85%, E/Z ratio ca. 3:2), (Found: M+H$^+$, 299.1410. C$_{15}$H$_{23}$O$_4$P+H requires 299.1412); $\nu_{\max }$ (film)/cm$^{-1}$ 2981, 1247, 1164, 1148, 1107, 1049, 1025, 969, 733 and 696; $\delta_H$ (250 MHz; CDCl$_3$) 1.07-1.40 (12 H, m, OCH$_2$Me and OCHMe$_2$), 3.86-4.67 (5 H, m, OCH$_2$Me and OCHMe$_2$), 6.41-6.75 (1 H, m, CHPh) and 7.21-7.78 (5 H, m, C$_6$H$_5$); $\delta_C$ (62.9 MHz; CDCl$_3$) 15.92-16.42 (2 C, m, OCH$_2$Me), 21.71 (CHMe$_2$), 22.62 (CHMe$_2$), 62.28-62.62 (2 C, m, OCH$_2$Me), 71.39 (1 C, d, J 7.8, CHMe$_2$), 74.03 (1 C, d, J 25.7, =CHPh), 127.08-134.64 (5 C, m, C$_6$H$_5$) and 141.76-143.93 (2 C, m, =CPO(OEt)$_2$); m/z (Cl$^+$) 299 (MH$^+$, 100%), 256 (29), 228 (18), 200 (3), 138 (10), 118 (62) and 90 (14).

**General Procedure for the Preparation of t-Butyldimethylsilyloxy-alkanols**

\[
\begin{align*}
\text{HO} & \quad (\gamma_n \text{OH}) \quad \longrightarrow \quad \text{HO} & \quad (\gamma_n \text{OTBS})
\end{align*}
\]

A solution of t-butyldimethylsilyl chloride (5.00 g, 33 mmol) in DMF (20 ml) was added dropwise over 30 min to a stirred solution of the 1, n-diol (132 mmol) and imidazole (5.65 g, 83 mmol) in DMF (45 ml). After stirring for 48 h at room temperature, ether (60 ml) and water (60 ml) were added. The aqueous layer was extracted with ether (3 x 50 ml) and the combined ethereal extracts washed with water (2 x 30 ml) and brine (50 ml) and then dried (MgSO$_4$). Evaporation of the solvent followed by Kugelrohr distillation of the residue yielded the desired mono-protected diol.
<table>
<thead>
<tr>
<th>mono-protected TBS diol</th>
<th>yield</th>
<th>boiling point (approx.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO(CH₂)₃OTBS</td>
<td>78%</td>
<td>110°C/6 mmHg</td>
</tr>
<tr>
<td>HO(CH₂)₄OTBS</td>
<td>70%</td>
<td>120°C/6 mmHg</td>
</tr>
<tr>
<td>HO(CH₂)₅OTBS</td>
<td>75%</td>
<td>140°C/6 mmHg</td>
</tr>
<tr>
<td>HO(CH₂)₆OTBS</td>
<td>75%</td>
<td>150°C/4 mmHg</td>
</tr>
</tbody>
</table>

**General Procedure for the Preparation of t-Butyldimethylsiloxy-alkylaldehydes**

A solution of the mono-protected diol (11.5 mmol) in dichloromethane (10 ml) was added to a suspension of pyridinium chlorochromate (PCC) (3.72 g, 17.3 mmol) in dichloromethane (30 ml). After stirring for 90 min at room temperature, ether (20 ml) was added and the reaction mixture stirred for a further 30 min. The suspension was then filtered through a pad of silica under suction. The silica was washed with ether and the filtrate and washings were then combined. The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the t-butyldimethylsiloxy-alkylaldehyde which was used immediately without further purification or characterisation.

**General Procedure for the Preparation of Enol Ethers**

A solution of triethyl isopropylxy-phosphonoacetate (192) (1.95 g, 6.9 mmol) in THF (5 ml) was added dropwise to a suspension of sodium hydride (80%, 0.23 g, 7.6 mmol) in THF (30 ml) at 0°C. After stirring for 20 min at 0°C, a solution of the t-butyldimethylsiloxyalkylaldehyde (6.9 mmol) in THF (5 ml) was added. The reaction was stirred for a further 1 h at 0°C and then allowed to warm to room
temperature. Ether (50 ml) and water (50 ml) were added and the aqueous layer extracted with ether (3 x 50 ml). The combined ethereal extracts were washed with brine (75 ml) and then dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the pure enol ether derivative as a mixture of cis- and trans-isomers.

![Chemical structures](image)

Ethyl 6-(t-butyldimethylsiloxy)-2-isopropyloxy-hex-2-enoate (231) (50%, E:Z ratio ca. 1:1), (Found: M+H⁺, 331.2305. C₁₇H₃₄SiO₄+H, 331.2305); νₘₐₓ (film)/ cm⁻¹ 2956, 2928, 2856, 1720, 1642, 1370, 1258, 1148, 1104, 836 and 776; Z isomer: δ_H (250 MHz; CDCl₃) 0.04 (6 H, s, SiMe₂), 0.89 (9 H, s, t-BuSi), 1.24 (6 H, d, J 6.1, Me₂CH), 1.32 (3 H, t, J 7.0, OCH₂Me), 1.60-1.67 (2 H, m, CH₂), 2.47 (2 H, q, J 7.6, CH₂), 3.64 (2 H, t, J 6.3, OCH₂), 4.14-4.29 (3 H, m, OCH₂Me and Me₂CH) and 6.28 (1 H, t, J 7.6, =CH); E isomer: δ_H (250 MHz; CDCl₃) 0.04 (6 H, s, SiMe₂), 0.89 (9 H, s, t-BuSi), 1.23 (6 H, d, J 6.1, Me₂CH), 1.31 (3 H, t, J 7.0, OCH₂Me), 1.59-1.67 (2 H, m, CH₂), 2.29 (2 H, q, J 7.6, CH₂), 3.64 (2 H, t, J 6.3, OCH₂), 4.06-4.29 (3 H, m, OCH₂Me and Me₂CH) and 5.48 (1 H, t, J 7.7, =CH); m/z (EI⁺) 273 (M⁺-C₄H₉, 11%), 231 (32), 157 (M⁺-C₆H₁₅OSi-C₃H₆, 100), 129 (22), 101 (28), 75 (98), 55 (31) and 43 (72).

Ethyl 7-(t-butyldimethylsiloxy)-2-isopropyloxy-hept-2-enoate (234) (76%, E:Z ratio ca. 1:1), (Found: M+H⁺, 345.2461. C₁₈H₃₆SiO₄+H requires 345.2461); νₘₐₓ (film)/ cm⁻¹ 2952, 2928, 2856, 1720, 1640, 1254, 1182, 1100, 836, 776 and 734; Z isomer: δ_H (250 MHz; CDCl₃) 0.04 (6 H, s, SiMe₂), 0.89 (9 H, s, t-BuSi), 1.23 (6 H, d, J 6.1, Me₂CH), 1.33 (3 H, t, J 7.2, OCH₂Me), 1.46-1.55 (4 H, m, CH₂CH₂), 2.43 (2 H, q, J 7.4, CH₂), 3.61 (2 H, m, OCH₂), 4.01-4.26 (3 H, m, OCH₂Me and Me₂CH) and 6.25 (1 H, t, J 7.6,
$E$ isomer: $\delta_H$ (250 MHz; CDCl$_3$) 0.04 (6 H, s, SiMe$_2$), 0.89 (9 H, s, t-BuSi), 1.23 (6 H, d, J 6.1, Me$_2$CH), 1.31 (3 H, t, J 7.2, OCH$_2$Me), 1.45-1.55 (4 H, m, CH$_2$CH$_2$), 2.25 (2 H, q, J 7.5, CH$_2$), 3.61 (2 H, t, J 6.3, OCH$_2$), 4.01-4.26 (3 H, m, OCH$_2$Me and Me$_2$CH) and 5.47 (1 H, t, J 7.7, =CH); m/z (EI$^+$) 345 ($M^+$, 17%), 303 (37), 287 ($M^+-C_4$H$_9$, 38), 245 (50), 171 ($M^+-OC_6$H$_{15}$Si-C$_3$H$_6$, 100), 75 (24) and 43 (30).

$1$-Benzenesulphonyl-$6$-($t$-butyldimethylsiloxy)-$1$-isopropoxy-hex-$1$-enoate (237)

A suspension of sodium hydride (80%, 0.12 g, 4.11 mmol) in THF (80 ml) at 0°C was treated dropwise with a solution of diethyl $1$-isopropoxy-$1$-phenylsulphonylmethane phosphonate (199) (1.20 g, 3.43 mmol) in THF (20 ml). After stirring for 45 min at 0°C, 5-$t$-butyldimethylsiloxy-pentanal (1.48 g, 6.86 mmol) was added. The reaction was allowed to stir for 2 h at room temperature after which ether (100 ml) and water (100 ml) were added. The aqueous phase was extracted with ether (3 x 50 ml) and the combined organic extracts washed with brine (100 ml) and dried (MgSO$_4$). The solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the title compound as a mixture of cis- and trans-isomers (1.19 g, 84%), (E/Z ratio ca. 5:1), (Found $M^+$NH$_4^+$, 430.2447. C$_{21}$H$_{36}$O$_4$SSi+NH$_4$ requires 430.2447); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 2954, 2930, 2858, 1322, 1308, 1158, 1143, 1101, 1085, 837 and 777; Major trans-isomer $\delta_H$ (250 MHz; CDCl$_3$) 0.05 (6 H, s, SiMe$_2$), 0.89 (9 H, s, t-Bu), 1.14 (6 H, d, J 6.1, CHMe$_2$), 1.42-1.56 (4 H, m, (CH$_2$CH$_2$), 2.67-2.75 (2 H, m, CHCH$_2$), 3.59-3.65 (2 H, m, CH$_2$OSi), 4.27 (1 H, h, J 6.1, CHMe$_2$), 5.44 (1 H, t, J 8.1, CHCH$_2$) and 7.49-7.94 (5 H, m, C$_6$H$_5$); $\delta_C$ (62.9 MHz; CDCl$_3$) -5.290 (SiMe$_2$), 18.30 (C-Si), 21.54 (CHMe$_2$), 25.17 (CH$_2$), 25.95 (t-Bu), 26.30 (CH$_2$), 32.28 (CHCH$_2$), 62.77 (CH$_2$OSi), 75.46 (CHMe$_2$), 122.04 (C=CH), 128.17 (C$_6$H$_5$), 128.77 (C$_6$H$_5$), 133.37...
(C₆H₅), 139.99 (C₆H₅) and 150.02 (C=CH); m/z (Cl⁺) 430 (M+NH₄⁺, 100%), 413 (MH⁺, 32), 290 (6), 246 (7), 230 (13), 229 (19), 158 (8) and 132 (20).

**General Procedure for the Preparation of Hydroxy Enol Ether Derivatives**

A mixture of the enol ether [(231) or (234)] (4.4 mmol), THF (8 ml), water (4 ml) and glacial acetic acid (12 ml) was heated at 45-50°C for 30 min. After allowing to cool, dichloromethane (20 ml) and water (20 ml) were added. The aqueous layer was extracted with dichloromethane (3 x 20 ml) and the combined organic extracts washed successively with saturated sodium bicarbonate solution (5 x 25 ml) and brine (50 ml) and then dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the respective hydroxy enol ether derivative as a colourless oil.

**Ethyl 6-hydroxy-2-isopropoxy-hex-2-enoate (232) (79%)**

(Found: M+NH₄⁺, 234.1705. C₁₁H₂₀O₄+NH₄ requires 234.1705); νmax (film)/ cm⁻¹ 3416, 2976, 2932, 1718, 1640, 1372, 1256, 1182 and 1106; Z isomer: δH (250 MHz; CDCI₃) 1.24 (6 H, d, J 6.2, Me₂CH), 1.30-1.36 (3 H, m, OCH₂Me), 1.65-1.75 (2 H, m, CH₂), 2.51 (2 H, q, J 7.6, CH₂), 3.61-3.66 (2 H, m, OCH₂), 4.18-4.31 (3 H, m, OCH₂Me and Me₂Cl), and 6.26 (1 H, t, J 7.8, =CH); OH not observed; E isomer: δH (250 MHz; CDCI₃) 1.23 (6 H, d, J 6.2, Me₂CH), 1.30-1.36 (3 H, m, OCH₂Me), 1.65-1.75 (2 H, m, CH₂), 2.33 (2 H, q, J 7.6,
CH₂), 3.61-3.66 (2 H, m, OCH₂), 4.05 (1 H, J 6.1, Me₂CH), 4.18-4.31 (2 H, m, OCH₂Me), and 5.43 (1 H, t, J 8.5, =CH); OH not observed; m/z (El⁺) 216 (M⁺, 13%), 171 (M⁺-OCH₂H₅, 10), 157 (M⁺-OC₃H₇, 100) and 82 (9).

_Ethyl 7-hydroxy-2-isopropyloxy-hept-2-enoate_ (235) (60%), (Found: M⁺, 230.1518. C₁₂H₂₂O₄ requires 230.1513); νmax (film)/ cm⁻¹ 3416, 2976, 2932, 1718, 1640, 1370, 1248, 1180 and 1106; Z isomer: δH (250 MHz; CDCl₃) 1.23 (6 H, d, J 6.2, Me₂CH), 1.33 (3 H, t, J 7.1, OCH₂Me), 1.50-1.61 (4 H, m, CH₂CH₂), 2.46 (2 H, q, J 7.3, CH₂), 3.64-3.69 (2 H, m, OCH₂) and 6.25 (1 H, t, J 7.9, =CH); OH not observed; E isomer: δH (250 MHz; CDCl₃) 1.23 (6 H, d, J 6.2, Me₂CH), 1.32 (3 H, t, J 7.1, OCH₂Me), 1.50-1.61 (4 H, m, CH₂CH₂), 2.38 (2 H, q, J 7.3, CH₂), 3.64-3.68 (2 H, m, OCH₂), 4.00-4.27 (3 H, m, OCH₂Me and Me₂CH) and 5.48 (1 H, t, J 8.1, =CH). OH not observed; m/z (El⁺) 230 (M⁺, 10%), 171 (100), 142 (21), 115 (32), 97 (35), 70 (62), 55 (52), and 41 (30).

\[\text{PhSO}_2\overset{O'Pr}{\rightarrow}\overset{\text{OTBS}}{\longrightarrow}\text{PhSO}_2\overset{O'Pr}{\rightarrow}\overset{\text{OH}}{\longrightarrow}\]

(237)  (238)

_1-Benzencesulphonyl-6-hydroxy-1-isopropyloxy-hex-1-enoate_ (238)

The procedure used for the preparation of the ethyl ester derivatives [(232) and (235)] was followed (0.61 g, 85%) [Chromatographed on silica (ether)]; νmax (film)/ cm⁻¹ 3392, 2979, 2935, 1637, 1448, 1319, 1307, 1143, 1082, 734 and 689; E isomer: δH (250 MHz; CDCl₃) 1.14 (6 H, d, J 6.1, CHMe₂), 1.52-1.67 (4 H, m, CH₂CH₂), 2.22 (1 H, s, OH), 2.67-2.76 (2 H, m, CHCH₂), 3.69 (2 H, m, CH₂OH), 4.26 (1 H, h, J 6.1, CHMe₂), 5.44 (1 H, t, J 8.2, CHCH₂) and 7.50-7.94 (5 H, m, C₆H₅); δC (62.9 MHz; CDCl₃) 21.49 (CHMe₂), 25.04 (CH₂), 26.16 (CH₂), 31.83 (CHCH₂), 62.20 (CH₂OH), 75.48 (CHMe₂), 121.25 (C=CH), 124.18 (C₆H₅), 128.85 (C₆H₅), 133.51 (C₆H₅), 139.71 (C₆H₅) and 152.12 (C=CH); m/z (Cl⁺) 316 (M+NH₄⁺, 89%), 192 (10), 176 (20), 157 (100), 132 (82), 116 (55), 114 (27), 98 (9) and 78 (5).
General Procedure for Cyclisation of Hydroxy Enol Ethers

A mixture of the hydroxy enol ether [(232) or (235)] (2.2 mmol) and camphorsulphonic acid (0.05 g, 0.22 mmol) was heated under reflux in benzene (CAUTION) (15 ml) for 2 h. After allowing to cool, ether (20 ml) and water (20 ml) were added. The aqueous layer was extracted with ether (3 x 20 ml) and the combined ethereal extracts washed with brine (20 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the respective cyclic enol ether as a colourless oil.

Ethyl 4,5-dihydropyran-2-carboxylate (233) (47%), (Found: M⁺, 156.0786. C₉H₁₂O₃ requires 156.0786); ʋ_max (film)/ cm⁻¹ 2980, 2932, 1722, 1644, 1368, 1300, 1264, 1222, 1190, 1112, 1070, 1056 and 924; δ_H (250 MHz; CDCl₃) 1.32 (3 H, t, J 7.2, OCH₂Me), 1.82-1.91 (2 H, m, 5-CH₂), 2.16-2.23 (2 H, m, 4-CH₂), 4.12 (2 H, t, J 4.2, 6-CH₂), 4.26 (2 H, q, J 7.2, OCH₂Me) and 6.07 (1 H, t, J 4.2, 3-CH); m/z (EI⁺) 156 (M⁺, 22%), 127 (M⁺-C₂H₅, 13), 111 (M⁺-OC₂H₅, 18), 83 (43), 55 (100), 43 (38) and 39 (23).

Ethyl 4,5,6,7-tetrahydro-oxepin-2-carboxylate (236) (81%), (Found: M⁺, 170.0943. C₉H₁₄O₃ requires 170.0943); ʋ_max (film)/ cm⁻¹ 2932, 1724, 1642, 1368, 1316, 1296, 1270, 1222, 1126, 1088, 1052 and 1036; δ_H (250 MHz; CDCl₃) 1.31 (3 H, t, J 7.0, OCH₂Me), 1.62-1.72 (2 H, m, 5- or 6-CH₂), 1.86-1.95 (2 H, m, 6- or 5-CH₂), 2.26-2.33 (2 H, m, 4-CH₂), 4.02 (2 H, t, J 5.4, 7-CH₂), 4.23 (2 H, q, J 6.9, OCH₂Me) and 6.39 (1 H, t, J 6.2, 3-CH);
m/z (EI+) 170 (M+, 32%), 141 (22), 125 (15), 97 (41), 69 (22), 55 (100) and 41 (60).

General Procedure for the Preparation of t-Butyldimethylsiloxy-alkyloxyphosphonates

A mixture of diazo compound [(180) or (184)] (20 mmol), the t-butyldimethylsiloxy mono-protected diol (20 mmol) and rhodium (II) acetate (88 mg, 0.20 mmol) was refluxed for 6-8 h in dry benzene (CAUTION) (30 ml). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the respective alkoxy-phosphonate as a colourless oil.

Ethyl 2-(3-t-butyldimethylsiloxy)propyloxy-2-diethyl-phosphonoacetate (240, n=1) (66%), (Found: M+H+, 413.2124. C_{17}H_{37}O_{7}PSi+H requires 413.2124); \( \nu_{\text{max}} \) (film)/ cm\(^{-1}\) 2928, 2856, 1748, 1258, 1118, 1054, 1026, 974, 838 and 778; \( \delta_{\text{H}} \) (250 MHz; CDCl\(_3\)) 0.04 (6 H, s, Me\(_2\)Si), 0.83 (9 H, s, t-BuSi), 1.25-1.33 (9 H, m, OCH\(_2\)Me), 1.80 (2 H, q, J 6.2, CH\(_2\)), 3.53-3.76 (4 H, m, OCH\(_2\) and CH\(_2\)OSi), 4.11-4.30 (6 H, m, OCH\(_2\)Me) and 4.26 (1 H, d, J 22.2, OCHP); m/z (EI+) 355 (M+-C\(_4\)H\(_9\), 57%), 297 (90), 269 (60), 195 (51), 167 (100), 147 (51) and 75 (84).

Ethyl 2-(4-t-butyldimethylsiloxy)butyloxy-2-diethyl-phosphonoacetate (240, n=2) (78%), (Found: M+H+, 427.2281. C\(_{18}\)H\(_{39}\)O\(_7\)PSi+H requires 427.2281);
\[ \nu_{\text{max}} \text{ (film) cm}^{-1} \quad 2952, 2932, 2856, 1748, 1258, 1100, 1026, 978, 836 \text{ and } 776; \delta_H \text{ (250 MHz; CDCl}_3) \quad 0.04 \text{ (6H, s, SiMe}_2), \quad 0.82 \text{ (9H, s, t-BuSi)}, \quad 1.23-1.33 \text{ (9H, m, OCH}_2\text{Me)}, \quad 1.53-1.67 \text{ (4H, m, CH}_2\text{CH}_2\text{)}, \quad 3.47-3.66 \text{ (4H, m, OCH}_2\text{ and CH}_2\text{OSi)}, \quad 4.11-4.30 \text{ (6H, m, OCH}_2\text{Me}) \text{ and } 4.26 \text{ (1H, d, J 22.8, OCHP)}; \quad m/z \text{ (El}^+) \quad 369 \text{ (M}^+-\text{C}_4\text{H}_9, \text{ 39\%), 241 (20), 167 (74), 139 (93), 109 (96) and 75 (100).}

\[
\begin{align*}
\text{EtO} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{OEt} & \quad \text{OTBS} \\
\text{O} & \quad \text{OEt}
\end{align*}
\]
(240, n=3)

\[
\begin{align*}
\text{EtO} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{OEt} & \quad \text{OTBS} \\
\text{O} & \quad \text{OEt}
\end{align*}
\]
(253, R=Me)

**Ethyl 2-((5-t-butyldimethylsiloxy)pentyloxy-2-diethyl-phosphonoacetate** (240, n=3) (80\%), (Found: M+H\(^+\), 441.2437. \(\text{C}_{19}\text{H}_{41}\text{O}_7\text{PSiP}+\text{H} \text{ requires 441.2437); \quad \nu_{\text{max}} \text{ (film) cm}^{-1} \quad 2932, 2856, 1750, 1258, 1122, 1056, 1030, 976, 838 \text{ and } 776; \delta_H \text{ (250 MHz; CDCl}_3) \quad 0.04 \text{ (6H, s, SiMe}_2), \quad 0.85 \text{ (9H, s, t-BuSi)}, \quad 1.25-1.69 \text{ (15H, m, OCH}_2\text{Me and CH}_2\text{CH}_2\text{CH}_2\text{)}, \quad 3.42-3.66 \text{ (4H, m, OCH}_2\text{ and CH}_2\text{OSi)}, \quad 4.11-4.29 \text{ (6H, m, OCH}_2\text{Me}) \text{ and } 4.25 \text{ (1H, d, J 21.5, OCHP); \delta_C \text{ (62.9 MHz; CDCl}_3) \quad -5.29 \text{ (SiMe}_2), \quad 14.15 \text{ (OCH}_2\text{Me)}, \quad 16.36 \text{ (OCH}_2\text{Me)}, \quad 16.45 \text{ (OCH}_2\text{Me), 18.35 \text{ (C-Si), 22.19 \text{ (OCH}_2\text{CH}_2\text{CH}_2\text{)}, 25.97 \text{ (t-BuSi), 29.28 \text{ (CH}_2\text{CH}_2\text{OSi)}, 32.54 \text{ (OCH}_2\text{CH}_2\text{)}, 61.72 \text{ (OCH}_2\text{Me)}, 63.05 \text{ (CH}_2\text{OSi)}, 63.63 \text{ (2C, m, OCH}_2\text{Me), 73.13 \text{ (1C, d, J 12.6, OCH}_2\text{)}, 77.07 \text{ (1C, d, J 157.4, OCHP) and 167.58 \text{ (1C, d, J 1.6, C=O); m/z (El}^+) \quad 383 \text{ (M}^+-\text{C}_4\text{H}_9, \text{ 2\%), 201 (13), 189 (16), 147 (65), 69 (100) and 41 (41).}

**Ethyl 2-((5-t-butyldimethylsiloxy-1-methyl)pentyloxy-2-diethyl-phosphonoacetate** (253, R=Me) (85\%), (Found: M+H\(^+\), 455.2594. \(\text{C}_{20}\text{H}_{43}\text{O}_7\text{PSiP}+\text{H} \text{ requires 455.2594); \quad \nu_{\text{max}} \text{ (film) cm}^{-1} \quad 2932, 2856, 1750, 1258, 1128, 1164, 1056, 1028, 974, 838 \text{ and } 776; \delta_H \text{ (250 MHz; CDCl}_3) \quad 0.04 \text{ (6H, s, SiMe}_2), \quad 0.89 \text{ (9H, s, t-BuSi)}, \quad 1.16-1.66 \text{ (18H, m, Me, CH}_2\text{CH}_2\text{CH}_2\text{ and OCH}_2\text{Me)}, \quad 3.46-3.62 \text{ (3H, m, OCH}_2\text{Me and CH}_2\text{OSi), 4.18-4.28 (6H, m, OCH}_2\text{Me}) \text{ and 4.42 (1H, d, J 19.8, OCHP); m/z (Cl}^+) \quad 455 \text{ (MH}^+, \text{ 100\%), 397 (52), 236 (100), 189 (74), 158 (44) and 41 (41).}

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241 (31), and 167 (6).

Ethyl 2-(5-t-butyldimethylsiloxyl-1-phenyl)pentyloxy-2-diethyl-phosphonoacetate (253, R=Ph) (46%), (Found: M+H+, 517.2750. C_{25}H_{45}O_7PSi+H requires 517.2750); ν_{max} (film)/ cm⁻¹ 2928, 1748, 1258, 1098, 1054, 1028, 978, 836, 776, 732 and 702; δ_H (250 MHz; CDCl₃) 0.04 (6 H, s, SiMe₂), 0.86 (9 H, s, t-BuSi), 1.24-1.66 (15 H, m, CH₂CH₂CH₂ and OCH₂Me), 3.54-3.59 (2 H, m, OCH₂Si), 4.07-4.30 (8 H, m, OCH₂Me, OCHPh and OCHP) and 7.26-7.34 (5 H, m, C₆H₅); m/z (CI⁺) 535 (M+NH₄⁺, 41%), 518 (37), 459 (7), 258 (100), 241 (37), 156 (29) 132 (82) and 90 (31).

Ethyl 2-(6-t-butyldimethylsiloxyl)hexyloxy-2-diethyl-phosphonoacetate (240, n=4) (61%), (Found: M+H+, 455.2594. C_{20}H_{43}O_7PSi+H requires 455.2594); ν_{max} (film)/ cm⁻¹ 2932, 2856, 1750, 1258, 1102, 1052, 1026, 976, 838 and 776; δ_H (250 MHz; CDCl₃) 0.04 (6 H, s, SiMe₂), 0.84 (9 H, s, t-BuSi), 1.25-1.34 (9 H, m, OCH₂Me), 1.44-1.63 (8 H, m, CH₂CH₂CH₂CH₂), 3.44-3.63 (4 H, m, OCH₂ and CH₂OSi), 4.14-4.29 (6 H, m, OCH₂Me) and 4.25 (1 H, d, J 21.4, OCHP); m/z (EI⁺) 397 (M⁺-C₄H₉, 3%), 241 (3), 167 (12), 118 (41), 90 (74), 63 (100), 51 (21) and 39 (84).

Diethyl 1-(4-t-butyldimethylsiloxyl)butyloxy-2-oxopropanephosphonate (244, n=2) (83%), (Found: M+H⁺, 397.2175. C_{17}H_{37}O_6PSi+H requires 397.2175);
$v_{\text{max}}$ (film) / cm$^{-1}$ 2952, 2932, 2856, 1736, 1254, 1094, 1032, 982, 838 and 776; $\delta_{\text{H}}$ (250 MHz; CDCl$_3$) 0.04 (6 H, s, SiMe$_2$), 0.84 (9 H, s, t-BuSi), 1.27-1.35 (6 H, m, OCH$_2$Me), 1.42-1.57 (4 H, m, CH$_2$CH$_2$), 2.38 (3 H, s, Ac), 3.53-3.63 (4 H, m, OCH$_2$ and CH$_2$OSi) and 4.10-4.19 (5 H, m, OCH$_2$Me and OCHP); $m/z$ (El$^+$) 339 ($M^+-$C$_4$H$_9$, 6%), 187 (8), 147 (16), 105 (75), 75 (100) and 41 (20).

Diethyl 1-(5-t-butyldimethylsiloxy)pentyloxy-2-oxopropanephosphonate (244, n=3) (67%), (Found: M+H$, 411.2330. C$_{18}$H$_{39}$O$_6$PSi+H requires 411.2332); $v_{\text{max}}$ (film) / cm$^{-1}$ 2932, 2856, 1256, 1100, 1052, 1030, 974, 836, 778 and 732; $\delta_{\text{H}}$ (250 MHz; CDCl$_3$) 0.04 (6 H, s, SiMe$_2$), 0.89 (9 H, s, t-BuSi), 1.30-1.49 (12 H, m, OCH$_2$Me and CH$_2$CH$_2$CH$_2$), 2.31 (3 H, s, Ac), 3.53-3.62 (4 H, m, OCH$_2$ and CH$_2$OSi) and 4.08-4.23 (5 H, m, OCH$_2$Me and OCHP); $m/z$ (CI$^+$) 411 (MH$^+$, 100%), 353 (11), 325 (8), 297 (52), 211 (10), and 167 (15).

**General Procedure for the Preparation of Hydroxyalkyloxyphosphonates**

A mixture of the insertion product (240, 244 or 253) (15 mmol), water (25 ml), THF (25 ml) and glacial acetic acid (70 ml) was heated at between 45-50°C for 1 h [the acetyl derivatives (244, n=2), (244, n=3) were heated for only 20 min]. After allowing to cool, dichloromethane (70 ml) and water (70 ml) were added. The aqueous layer was extracted with dichloromethane (3 x 50 ml) and the combined organic extracts washed successively with saturated sodium bicarbonate (5 x 50 ml) and brine (50 ml) and then dried (MgSO$_4$). The solvent was removed by evaporation and the residue chromatographed on silica (ethyl acetate-ether) to yield the respective title compound as a colourless oil.
Ethyl 2-(3-hydroxy)propyloxy-2-diethyl-phosphonoacetate (241, n=1) (70%), (Found: M+H+, 299.1260. C_{11}H_{23}O_{7}P+H requires 299.1260); ν_{max} (film)/ cm^{-1} 3428, 2980, 2932, 1746, 1254, 1164, 1126, 1048, 1024 and 978; δ_{H} (250 MHz; CDCl_{3}) 1.29-1.43 (9 H, m, OCH_{2}Me), 1.80-1.95 (2 H, m, CH_{2}), 3.77-3.83 (4 H, m, OCH_{2} and CH_{2}OH) and 4.14-4.35 (7 H, m, OCH_{2}Me and OCHP). OH not observed; m/z (El^+) 299 (MH^+, 10%), 197 (32), 111 (53), 87 (100), 81 (31), 65 (46), 59 (31) and 41 (31).

Ethyl 2-(4-hydroxy)butyloxy-2-diethyl-phosphonoacetate (241, n=2) (90%), (Found: M+H+, 313.1416. C_{12}H_{25}O_{7}P+H requires 313.1416); ν_{max} (film)/ cm^{-1} 3428, 2984, 2936, 1746, 1252, 1188, 1164, 1126, 1052 and 978; δ_{H} (250 MHz; CDCl_{3}) 1.29-1.38 (9 H, m, OCH_{2}Me), 1.65-1.80 (4 H, m, CH_{2}CH_{2}), 3.57-3.70 (4 H, m, OCH_{2} and CH_{2}OH), 4.21-4.34 (6 H, m, OCH_{2}Me) and 4.31 (1 H, d, J 18.8 Hz, OCHP). OH not observed; m/z (El^+) 239 (M^+-OC_{4}H_{9}, 2%), 197 (22), 171 (22), 152 (27), 111 (31), 65 (31), 55 (76) and 43 (100).

Ethyl 2-(5-hydroxy)pentyloxy-2-diethyl-phosphonoacetate (241, n=3) (83%), (Found: M+H+, 327.1573. C_{13}H_{27}O_{7}P+H requires 327.1573); ν_{max} (film)/ cm^{-1} 3436, 2936, 1746, 1256, 1186, 1164, 1126, 1054, 1026 and 980; δ_{H} (250 MHz; CDCl_{3}) 1.32-1.42 (9 H, m, OCH_{2}Me), 1.44-1.70 (6 H, m, CH_{2}CH_{2}CH_{2}), 3.47-3.73 (4 H, m, OCH_{2} and CH_{2}OH), 4.15-4.34 (6 H, m,
OCH₂Me) and 4.29 (1 H, d, J 21.6, OCHP). OH not observed; δC (62.9 MHz; CDCl₃) 13.8 (COOCH₂Me); 16.1 (2 C, m, POCH₂Me), 21.8 (OCH₂CH₂CH₂), 28.8 (CH₂CH₂OH), 32.0 (OCH₂CH₂), 61.5 (COOCH₂Me), 61.8 (CH₂OH), 63.4 (2 C, m, POCH₂Me), 72.8 (OCH₂), 76.3 (1 C, d, OCHP) and 167.2 (C=O); m/z (EI⁺) 239 (M⁺-OC₅H₁₁, 5%), 197 (35), 152 (24), 111 (34), 75 (100), 69 (60), 55 (24) and 41 (74).

**Ethyl 2-(5-hydroxy-1-methyl)pentyloxy-2-diethyl-phosphonoacetate** (254, R=Me) (74%), (Found: M+H⁺, 341.1729. C₁₄H₂₉O₇P+H requires 341.1729); v_max (film)/ cm⁻¹ 3436, 2980, 2932, 1748, 1258, 1180, 1164, 1112, 1050, 1028 and 978 cm⁻¹; δH (250 MHz; CDCl₃) 1.52 (3 H, d, J 6.1, Me), 1.27-1.37 (9 H, m, OCH₂Me), 1.46-1.59 (6 H, m, CH₂CH₂CH₂), 3.61-3.65 (3 H, m, OCH₂), 4.17-4.31 (6 H, m, OCH₂Me) and 4.43 (1 H, d, J 19.4, OCHP). OH not observed; m/z (EI⁺) 341 (M⁺, 4%), 197 (64), 167 (71), 139 (71), 111 (100), 65 (79), 55 (88) and 41 (76).

![Ethyl 2-(5-hydroxy-1-methyl)pentyloxy-2-diethyl-phosphonoacetate](image)

**Ethyl 2-(6-hydroxy)hexyloxy-2-diethyl-phosphonoacetate** (241, n=4) (90%), (Found: M+H⁺, 341.1729. C₁₄H₂₉O₇P+H requires 341.1729); v_max (film)/ cm⁻¹ 2932, 1748, 1254, 1164, 1098, 1054, 1026, 978, 704 and 664; δH (250 MHz; CDCl₃) 1.15 (3 H, t, J 7.1, OCH₂Me), 1.27-1.61 (12 H, m, (CH₂)₃ and OCH₂Me), 3.61-3.63 (2 H, m, CH₂OH), 4.04-4.34 (7 H, m, OCH₂Me and OCHP), 4.60-4.65 (1 H, m, OCHPh) and 7.26-7.33 (5 H, m, C₆H₅). OH not observed; m/z (CI⁺) 420 (M+NH₄⁺, 17%), 403 (MH⁺, 6), 258 (100), 241 (34), 180 (23) and 156 (24).

**Ethyl 2-(5-hydroxy-1-phenyl)pentyloxy-2-diethyl-phosphonoacetate** (254, R=Ph) (83%), (Found: M+H⁺, 403.1890. C₁₉H₃₁O₇P+H requires 403.1886); v_max (film)/ cm⁻¹ 2932, 1748, 1254, 1164, 1098, 1054, 1026, 978, 704 and 664; δH (250 MHz; CDCl₃) 1.15 (3 H, t, J 7.1, OCH₂Me), 1.27-1.61 (12 H, m, (CH₂)₃ and OCH₂Me), 3.61-3.63 (2 H, m, CH₂OH), 4.04-4.34 (7 H, m, OCH₂Me and OCHP), 4.60-4.65 (1 H, m, OCHPh) and 7.26-7.33 (5 H, m, C₆H₅). OH not observed; m/z (CI⁺) 420 (M+NH₄⁺, 17%), 403 (MH⁺, 6), 258 (100), 241 (34), 180 (23) and 156 (24).

**Ethyl 2-(6-hydroxy)hexyloxy-2-diethyl-phosphonoacetate** (241, n=4) (90%), (Found: M+H⁺, 341.1729. C₁₄H₂₉O₇P+H requires 341.1729); v_max (film)/
cm⁻¹ 3436, 2932, 2864, 1738, 1250, 1184, 1128, 1056, 976 and 732; δH (250 MHz; CDCl₃) 1.29-1.69 (17 H, m, OCH₂Me and CH₂CH₂CH₂CH₂), 3.50-3.69 (4 H, m, OCH₂ and CH₂OH), 4.15-4.33 (7 H, m, OCH₂Me and OCHP). OH not observed; m/z (Ei⁺) 239 (M⁺-OC₆H₁₃, 8%), 224 (28), 197 (60), 152 (50), 111 (42), 83 (53), 65 (37), 55 (100) and 41 (84).

Diethyl 1-(4-hydroxy)butyloxy-2-oxopropanephosphonate (245, n=2) (82%), (Found: M+H+, 283.1310. C₁₁H₂₃O₆P+H requires 283.1311); νmax (film)/cm⁻¹ 3428, 2940, 1722, 1250, 1104, 1052 and 974; δH (250 MHz; CDCl₃) 1.32-1.39 (6 H, m, OCH₂Me), 1.66-1.75 (4 H, m, CH₂CH₂), 2.32 (3 H, s, Ac), 3.62-3.71 (4 H, m, OCH₂ and CH₂OH) and 4.13-4.26 (5 H, m, OCH₂Me and OCHP). OH not observed; m/z (Cl⁻) 281 (M⁺-H, 100%), 263 (4), 220 (2), 195 (3), 172 (6), 156 (7), 144 (31) and 127 (48).

Diethyl (5-hydroxy)pentyloxy-2-oxopropanephosphonate (245, n=3) (87%), (Found: M+H+, 297.1470. C₂₁₂H₂₅O₆P+H requires 297.1467); νmax (film)/cm⁻¹ 3420, 2936, 1722, 1252, 1102, 1050 and 974; δH (250 MHz; CDCl₃) 1.31-1.39 (6 H, m, OCH₂Me), 1.44-1.73 (6 H, m, CH₂CH₂CH₂), 2.31 (3 H, s, Ac), 3.60 (2 H, t, J 6.3, OCH₂), 3.65 (2 H, t, J 6.1, CH₂O), and 4.13-4.27 (5 H, m, OCHP and OCH₂Me). OH not observed; m/z (Ei⁺) 297 (MH⁺, 35%), 254 (17), 211 (19), 193 (23), 167 (100), 139 (58), 111 (69), 81 (23), and 69 (44).
**General Procedure for the Preparation of Alkylloxyaldehyde-phosphonates**

![Chemical structure]

A solution of the alcohol (3.07 mmol) in dichloromethane (5 ml) was added to a suspension of pyridinium dichromate (PDC) (1.73 g, 4.6 mmol) in dichloromethane (15 ml). After stirring for 20-24 h, ether (15 ml) was added and the mixture then stirred for a further 30 min. The reaction mixture was filtered through a pad of silica under suction. The silica was washed well with ether and the filtrate and washings were then combined. The solvent was removed by evaporation to yield the crude aldehyde which was used directly in the next step without further purification or characterisation.

**General Procedure for Intramolecular Wadsworth-Emmons Olefination Reaction of Phosphonate Aldehydes to give Cyclic Ethers**

![Chemical structure]

A solution of the aldehyde (theoretical 0.93 mmol) in THF (100 ml) was added dropwise over 30 min to a suspension of sodium hydride (80%, 56 mg, 1.85 mmol) in THF (200 ml) at 0°C. After stirring for 2 h at 0°C, ether (200 ml) and water (200 ml) were added. The aqueous layer was extracted with ether (2 x 200 ml) and the combined ethereal extracts washed with brine (200 ml) and then dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the respective cyclic enol ether as a colourless oil.
Ethyl 3,4-dihydrofuran-2-carboxylate (243) (50%), (Found: $M^+$, 142.0630. $C_7H_{10}O_3$ requires 142.0630); $\nu_{\text{max}}$(film)/ cm$^{-1}$ 2980, 2924, 1726, 1628, 1378, 1320, 1266, 1210, 1174, 1124, 952, 936 and 738; $\delta_H$ (250 MHz; CDCl$_3$) 1.33 (3 H, t, J 7.2, OCH$_2$Me), 2.80 (2 H, dt, J 3.0, 9.8, 4-CH$_2$), 4.27 (2 H, q, J 7.2, OCH$_2$Me), 4.50 (2 H, t, J 9.8, 5-CH$_2$) and 5.97 (1 H, t, J 3.0, 3-CH); m/z (EI$^+$) 142 ($M^+$, 10%), 97 (23), 91 (24), 83 (15), 69 (40), 55 (43) and 41 (100).

Ethyl 4,5-dihydropyran-2-carboxylate (233) (46%). This displayed identical spectral properties to the same compound prepared previously. See above for data (page 198).

Ethyl 4,5,6,7-tetrahydro-oxepin-2-carboxylate (236) (43%). This displayed identical spectral properties to the same compound prepared previously. See above for data (page 198).

Ethyl 7-methyl-4,5,6,7-tetrahydro-oxepin-2-carboxylate (256) (47%), (Found: $M^+$, 184.1099. $C_{10}H_{16}O_3$ requires 184.1099); $\nu_{\text{max}}$(film)/ cm$^{-1}$ 2972, 2928, 1728, 1644, 1372, 1318, 1268, 1222 and 1120; $\delta_H$ (250 MHz; CDCl$_3$) 1.30 (3 H, t, J 7.1, OCH$_2$Me), 1.35 (3 H, d, J 6.4, Me), 1.50-1.92 (4 H, m, 5-CH$_2$, 6-CH$_2$), 2.21-2.30 (2 H, m, 4-CH$_2$), 3.85-3.93 (1 H, m, 7-CH), 4.22 (2 H, q, J 7.1, OCH$_2$Me) and 6.39 (1 H, t, J 5.9, 3-H); $\delta_C$ (62.9 MHz; CDCl$_3$) 14.26 (Me), 22.33 (OCH$_2$Me), 23.96 (5-CH$_2$), 26.07 (6-CH$_2$), 38.17
(4-CH₂), 60.93 (OCH₂Me), 79.51 (7-CH), 122.54 (3-CH), 148.72 (2-C) and 164.56 (C=O); m/z (El⁺) 184 (M⁺, 26%), 105 (24), 83 (34), 69 (24), 55 (100) and 41 (29).

Ethyl 7-phenyl-4,5,6,7-tetrahydro-oxepin-2-carboxylate (257) (46%), (Found: M+NH₄⁺, 264.1600. C₁₅H₁₈O₃+NH₄ requires 264.1600); ν max (film)/ cm⁻¹ 2932, 1722, 1644, 1312, 1264, 1216, 1120, 1076, 1050, 1032, 748 and 698; δH (250 MHz; CDCl₃) 1.29 (3 H, t, J 7.2, OCH₂Me), 1.65-2.42 (6 H, m, 4-CH₂, 5-CH₂ and 6-CH₂), 4.20 (2H, q, J 7.1, OCH₂Me), 4.76 (1 H, dd, J 2.6, 10.7, 7-CH), 6.51 (1H, t, J 6.0, 3-CH) and 7.26-7.50 (5 H, m, C₆H₅); δC (62.9 MHz; CDCl₃) 14.20 (OCH₂Me), 24.25 (5-CH₂), 25.91 (6-CH₂), 37.64 (4-CH₂), 60.89 (OCH₂Me), 84.03 (7-CH), 123.25 (3-CH), 125.78 (C₆H₅), 127.31 (C₆H₅), 128.22 (C₆H₅), 142.21 (C₆H₅), 149.29 (2-C) and 164.14 (C=O); m/z (Cl⁺) 264 (M+NH₄⁺, 100%), 246 (53), 229 (79), 190 (7), 173 (8), 155 (8), 145 (8) and 108 (14).

2-Acetyl-4,5-dihydropyran (247) (46%), (Found: M⁺, 126.0681. C₇H₁₀O₂ requires 126.0681); ν max (film)/ cm⁻¹ 2932, 1698, 1684, 1626, 1356, 1290, 1276, 1260, 1220, 1078, 1046, 912 and 624; δH (250 MHz; CDCl₃) 1.81-1.88 (2 H, m, 5-CH₂), 2.21-2.28 (2 H, m, 4-CH₂), 2.28 (3 H, s, Ac), 4.09 (2 H, t, J 5.3, 6-CH₂) and 5.99 (1 H, t, J 4.3, 3-CH); δC (62.9 MHz; 20.76 (5-CH₂), 21.47 (4-CH₂), 25.32 (Me), 66.29 (6-CH₂), 110.79 (3-CH), 152.05 (2-C) and 194.83 (C=O); m/z (El⁺) 126 (M⁺, 2%), 69 (25), 55 (29) and 41 (100).

2-Acetyl-4,5,6,7-tetrahydro-oxepin (248) (32%), (Found: M+H⁺, 141.0916. C₈H₁₂O₂+H requires 141.0916); ν max (film)/ cm⁻¹ 2932, 1698, 1684, 1626, 1356, 1310, 1264, 1250, 1220, 1120, 1082 and 612; δH (250
MHz; CDCl₃) 1.62-1.72 (2 H, m, 5-CH₂), 1.87-1.96 (2 H, m, 6-CH₂), 2.25-2.34 (2 H, m, 4-CH₂), 2.27 (3 H, s, Ac), 4.00 (2 H, t, J 5.4, 7-CH₂) and 6.27 (1 H, t, J 6.1, 3-CH); δC (62.9 MHz; CDCl₃) 24.71 (5-CH₂), 26.11 (Me), 26.28 (6-CH₂), 31.36 (4-CH₂), 72.67 (7-CH₂), 119.97 (3-CH), 156.82 (2-C) and 196.57 (C=O); m/z (Cl⁻) 158 (M+NH₄⁺, 100%), 154 (97), 139 (13), 127 (35), and 87 (22).

2-Acetyl-oxepane (249)
A mixture of the tetrahydro-oxepin (248) (0.48 g, 3.43 mmol) and palladium on charcoal (10%, 0.048 g) was hydrogenated at atmospheric pressure for 1 h in ethyl acetate (60 ml). After removing the catalyst by filtration, the solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound as a colourless oil (0.35 g, 71%), (Found: M⁺, 142.0990. C₈H₁₄O₂ requires 142.0994); νmax (film)/ cm⁻¹ 2930, 2858, 1718, 1353, 1130 and 1110; δH (250 MHz; CDCl₃) 1.57-1.79 (8 H, m, 3-CH₂, 4-CH₂, 5-CH₂ and 6-CH₂), 2.21 (3 H, s, Ac), 3.62-3.69 (1 H, m, 7-CHH) and 3.85-3.97 (2 H, m, 2-CH and 7-CHH); δC (62.9 MHz; CDCl₃) 25.76 (5-CH₂), 26.35 (Me), 26.95 (4-CH₂), 31.04 (6-CH₂), 31.73 (3-CH₂), 69.13 (7-CH₂), 84.80 (2-CH) and 210.79 (C=O); m/z (EI⁺) 99 (69%), 81 (77), 55 (92), 43 (100), 41 (32), 39 (20) and 27 (21).

2-(1-Hydroxy-1-methyl)-ethyl-oxepane (250) [2-(oxepan-2-yl)propan-2-ol]
Methyl magnesium bromide (3 M, 0.39 ml, 1.18 mmol) was added dropwise to a
solution of the oxepane (249) (0.14 g, 0.99 mmol) in ether (12 ml) at 0°C. After stirring at room temperature for 2 h, water (30 ml) and ether (30 ml) were added. The aqueous phase was extracted with ether (3 x 20 ml) and the combined organic extracts washed with brine and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the title compound as a colourless oil (0.13 g, 84%), (Found: M⁺, 158.1310. C₉H₁₈O₂ requires 158.1307); v_max (film)/ cm⁻¹ 3493, 2971, 2929, 2857, 1376, 1165, 1113, 1093, 1026 and 666; δ_H (250 MHz; CDCl₃) 1.13 (3 H, s, Me), 1.16 (3 H, s, Me), 1.43-1.64 (8 H, m, 3-CH₂, 4-CH₂, 5-CH₂ and 6-CH₂), 2.63 (1 H, s, OH), 3.21 (1 H, dd, J 2.8, 9.7, 7-CH₂H), 3.54-3.63 (1 H, m, 7-CHH) and 3.94-4.01 (1 H, m, 2-CH); δ_C (62.9 MHz; CDCl₃) 23.82 (Me), 25.78 (5-CH₂), 25.95 (Me), 26.86 (4-CH₂), 30.35 (6-CH₂), 30.82 (3-CH₂), 70.65 (7-CH₂), 72.58 (C-OH) and 86.50 (2-CH); m/z (EI⁺) 99 (38%), 81 (46), 71 (15), 59 (100), 55 (48), 43 (66) and 27 (17).

2-(1-Hydroxy-1-phenyl)-ethyl-oxepane (251)
Phenyllithium (2 M, 0.59 ml, 1.18 mmol) was added dropwise to a solution of the oxepane (249) (0.14 g, 0.99 mmol) in THF (12 ml) at -78°C. After stirring at -78°C for 30 min and at room temperature for 1 h, water (30 ml) and ether (30 ml) were added. The aqueous phase was extracted with ether (3 x 20 ml) and the combined organic extracts washed with brine and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the title compound as a colourless oil (0.20 g, 92%); v_max (film)/ cm⁻¹ 3464, 2978, 2929, 2857, 1447, 1107, 1068, 1022, 701 and 666; δ_H (250 MHz; CDCl₃) 1.33-1.78 (8 H, m, 3-CH₂, 4-CH₂, 5-CH₂ and 6-CH₂), 1.51 (3 H, s, Me), 3.12 (1 H, s, OH), 3.47-3.60 (2 H, m, 7-CH₂), 3.88-3.96 (1 H, m, 2-CH) and 7.21-7.51 (5 H, m, C₆H₅); δ_C (62.9 MHz; CDCl₃) 22.76 (Me), 25.69 (5-CH₂), 26.67 (4-CH₂), 29.72 (6-CH₂), 30.71 (3-CH₂),
70.48 (7-CH₂), 76.40 (C-OH), 86.57 (2-CH), 125.99 (C₆H₅), 126.81 (C₆H₅), 127.91 (C₆H₅) and 145.49 (C₆H₅); m/z (El⁺) 121 (57%), 99 (89), 84 (67), 55 (41), 49 (31) and 43 (100).

2-(1-hydroxy-1-phenyl)-ethyl-4,5,6,7-tetrahydro-oxepin (252)

Phenyllithium (2 M, 0.56 ml, 1.13 mmol) was added dropwise to a solution of the tetrahydro-oxepin (248) (0.15 g, 1.07 mmol) in THF (12 ml) at -78°C. After stirring at -78°C for 30 min and at room temperature for 1 h, water (30 ml) and ether (30 ml) were added. The aqueous phase was extracted with ether (3 x 20 ml) and the combined organic extracts washed with brine and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the title compound as a colourless oil (0.23 g, 99%), (Found: M⁺, 218.1310. C₁₄H₁₈O₂ requires 218.1307); νmax (film)/ cm⁻¹ 3428, 2976, 2869, 1670, 1447, 1354, 1307, 1110, 1077, 1070, 701; δH (250 MHz; CDCl₃) 1.55-1.67 (2 H, m, 5-CH₂), 1.59 (3 H, s, Me), 1.76-1.85 (2 H, m, 6-CH₂), 2.18-2.25 (2 H, m, 4-CH₂), 2.85 (1 H, s, OH), 3.80 (2 H, t, J 5.0, 7-CH₂), 5.27 (1 H, t, J 5.9, 3-CH) and 7.20-7.53 (5 H, m, C₆H₅); δC (62.9 MHz; CDCl₃) 25.42 (5-CH₂), 25.76 (6-CH₂), 27.99 (Me), 31.73 (4-CH₂), 73.03 (7-CH₂), 76.15 (C-OH), 106.65 (3-CH), 125.25 (C₆H₅), 126.81 (C₆H₅), 127.95 (C₆H₅), 146.47 (C₆H₅) and 162.22 (2-C); m/z (El⁺) 218 (M⁺, 34%), 203 (30), 121 (20), 105 (37), 77 (19), 55 (24) and 43 (100).
**Ethyl 2-(5-hexen-1-oxy)-2-diethyl-phosphonoacetate (258)**

A mixture of triethyl diazophosphonoacetate (180) (2.0 g, 8.0 mmol), 5-hexen-1-ol (0.80 g, 8.0 mmol) and rhodium (II) acetate (35 mg, 0.08 mmol) was refluxed for 5 h in benzene (CAUTION) (60 ml). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the *title compound* as a colourless oil (1.70 g, 66%). (Found: \(M^+\), 322.1545. \(C_{14}H_{27}O_6P\) requires 322.1545); \(\nu_{\text{max}}\) (film)/ cm\(^{-1}\) 2983, 2937, 1750, 1264, 1224, 1182, 1164, 1125, 1052, 1028 and 975; \(\delta_H\) (250 MHz; CDCl\(_3\)) 1.29-1.69 (9 H, m, OCH\(_2\)Me), 1.47-1.51 (2 H, m, CH\(_2\)), 1.63-1.69 (2 H, m, OCH\(_2\)CH\(_2\)), 2.06-2.09 (2 H, m, CH\(_2\)CH=CH\(_2\)), 3.50-3.54 (1 H, m, OCH\(_2\)H), 3.65-3.68 (1 H, m, OCHH), 4.17-4.33 (7 H, m, OCH\(_2\)Me and OCHP), 4.93-5.04 (2 H, m, CH\(_2\)CH=CH\(_2\)) and 5.71-5.85 (1 H, m, CH\(_2\)CH=CH\(_2\)) ; \(\delta_C\) (62.9 MHz; CDCl\(_3\)) 14.16 (OCH\(_2\)Me), 16.36 (OCH\(_2\)Me), 16.46 (OCH\(_2\)Me), 25.15 (OCH\(_2\)CH\(_2\)CH\(_2\)), 28.90 (OCH\(_2\)CH\(_2\)), 33.39 (CH\(_2\)CH=CH\(_2\)), 61.68 (OCH\(_2\)Me), 63.62 (2 C, m, OCH\(_2\)Me), 72.87 (1 C, d, J 12.1, OCH\(_2\)), 77.05 (1 C, d, J 157.4, OCHP), 114.65 (CH\(_2\)CH=CH\(_2\)), 138.50 (CH\(_2\)CH=CH\(_2\)) and 167.52 (1 C, d, J 1.8, C=O); \(m/z\) (El\(^+\)) 322 (\(M^+\), 2%), 224 (60), 197 (64), 139 (51), 111 (100), 81 (48), 65 (45), 55 (74) and 29 (79).

**General Method for the Preparation of Alkynyloxy Phosphonates**

![Reaction Scheme](image)

A mixture of triethyl diazophosphonoacetate (180) [or acetyl-ethoxy carbonyldiazomethane (184)] (8.0 mmol), the alkynol (8.0 mmol) and rhodium (II) acetate (35 mg, 0.08 mmol) was refluxed for 2-5 h in benzene (CAUTION) (30 ml). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the respective alkynloxy-phosphonate as a colourless oil.
Ethyl 2-(3-butyn-1-oxy)-2-diethyl-phosphonoacetate (260, n=1) (61%),
(Found: M+H+, 293.1154. C₁₂H₂₁O₆P+H requires 293.1154); ν_max (film)/
cm⁻¹ 3280, 2980, 2936, 2908, 2116, 1744, 1392, 1368, 1264, 1186, 1162,
1128, 1056, 978 and 632; δ_H (250 MHz; CDCl₃) 1.24-1.39 (9 H, m, OCH₂Me),
1.98 (1 H, t, J 2.6, C=CH), 2.56 (2 H, dt, J 2.6, 6.9, =CCH₂), 3.65-3.70 (1 H,
m, OCHH), 3.78-3.84 (1 H, m, OCHH), 4.21-4.36 (6 H, m, OCH₂Me) and 4.40 (1
H, d, J 18.8, OCHP); m/z (El⁺) 293 (MH⁺, 100%), 269 (23), 224 (71),
197 (62), 152 (48), 133 (44), 111 (65), and 83 (44).

Ethyl 2-(4-pentyn-1-oxy)-2-diethyl-phosphonoacetate (260, n=2) (74%),
(Found: M+H+, 307.1311. C₁₃H₂₃O₆P+H requires 307.1311); ν_max (film)/
cm⁻¹ 3284, 2980, 2112, 1746, 1264, 1196, 1164, 1128, 1024 and 976; δ_H
(250 MHz; CDCl₃) 1.25-1.39 (9 H, m, OCH₂Me), 1.81-1.91 (2 H, m, CH₂),
1.95 (1 H, t, J 2.7, C=CH), 2.35 (2 H, dt, J 2.7, 6.9, =CCH₂), 3.59-3.68 (1 H,
m, OCHH), 3.72-3.77 (1 H, m, OCHH) and 4.22-4.35 (7 H, m, OCH₂Me and
OCHP); δ_C (62.9 MHz; CDCl₃) 14.15 (OCH₂CH₂), 15.04 (OCH₂Me), 16.36
(OCH₂Me), 16.45 (OCH₂Me), 28.50 (CH₂C=CH), 61.80 (OCH₂Me), 63.660 (2 C,
m, OCH₂Me), 68.84 (CH₂C=CH), 71.34 (1 C, d, J 12.1, OCH₂), 77.12 (1 C, d, J
157.4, OCHP), 83.52 (CH₂C=CH) and 167.40 (1 C, d, J 1.7, C=O); m/z (Cl⁺)
307 (MH⁺, 100%), 224 (34), 197 (23), 152 (33), 121 (15), 97 (13), and
67 (13).
Ethyl 2-(5-hexyn-1-oxy)-2-diethyl-phosphonoacetate (260, n=3) (50%), (Found: M+H+, 321.1467. C₁₄H₂₅O₆P+H requires 321.1467); ν max (film)/cm⁻¹ 3280, 2980, 2112, 1746, 1260, 1164, 1128, 1098, 1052, 1026 and 976; δ H (250 MHz; CDCl₃) 1.29-1.38 (9 H, m, OCH₂Me), 1.65-1.77 (4 H, m, CH₂CH₂), 1.95 (1 H, t, J 2.6 Hz, C=CH), 2.24 (2 H, dt, J 2.6, 6.9, =CH₂), 3.44-3.59 (1 H, m, OCH), 3.60-3.76 (1 H, m, OCH) and 4.19-4.34 (7 H, m, OCH₂Me and OCHP); δ C (62.9 MHz; CDCl₃) 14.16 (OCH₂Me), 16.37 (OCH₂Me), 16.46 (OCH₂Me), 18.06 (OCH₂CH₂CH₂), 24.89 (OCH₂CH₂), 28.44 (CH₂=CH), 61.77 (OCH₂Me), 63.66 (2 C, m, OCH₂Me), 68.60 (CH₂C=CH), 72.40 (1 C, d, J 12.7, OCH₂), 77.04 (1 C, d, J 157.4, OCHP), 84.12 (CH₂C=CH) and 167.507 (1 C, d, J 1.7, C=O); m/z (EI⁺) 321 (MH⁺, 25%), 224 (96), 197 (88), 152 (87), 111 (100) and 81 (63).

Diethyl 1-(5-hexyn-1-oxy)-2-oxopropanephosphonate (265) (66%), (Found: M⁺, 290.1283. C₁₃H₂₃O₅ requires 290.1284); ν max (film)/cm⁻¹ 3284, 2112, 1720, 1258, 1116, 1050, 1026, 972 and 628; δ H (250 MHz; CDCl₃) 1.31-1.38 (6 H, m, OCH₂Me), 1.65-1.78 (4 H, m, CH₂CH₂), 1.95 (1 H, t, J 2.6 Hz, C=CH), 2.25 (2 H, dt, J 2.7, 6.9, =CH₂), 2.32 (3 H, s, Ac), 3.57-3.64 (2 H, m, OCH₂) and 4.15-4.24 (5 H, m, OCH₂Me and OCHP); m/z (EI⁺) 291 (MH⁺, 27%), 248 (22), 209 (10), 190 (6), 167 (49), 139 (51), 111 (100) and 81 (20).

General Procedure for the Preparation of Methyl Ketone Phosphonates

A mixture of the alkynylloxy phosphonate (1.56 mmol), mercury (II) sulphate (36 mg, 0.12 mmol), THF (5 ml) and water (10 ml) was heated at 60°C for 1 h. Ether (20 ml) was added and the aqueous layer extracted with ether (3 x 20 ml). The combined ethereal extracts were washed with brine (50 ml) and dried (MgSO₄). The
solvent was removed by evaporation to afford the crude ketone phosphonate which was used directly in the next step without further characterisation or purification.

**General Procedure for Intramolecular Wadsworth-Emmons Cyclisation Reaction of Ketones**

A solution of the methyl ketone phosphonate (0.63 mmol) in THF (10 ml) was added dropwise over 20 min to a suspension of sodium hydride (80%, 21 mg, 0.69 mmol) in dry THF (50 ml) at 0°C. The reaction was allowed to come to room temperature overnight. Ether (50 ml) and water (30 ml) were added and the aqueous layer extracted with ether (3 x 30 ml). The combined ethereal extracts were washed with brine (200 ml) and then dried (MgSO$_4$). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the respective cyclic enol ether.

**Ethyl 3-methyl-4,5-dihydrofuran-2-carboxylate (262)** (23%), (Found: $M^+$, 156.0786. C$_8$H$_{12}$O$_3$ requires 156.0786); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 2980, 1714, 1658, 1374, 1332, 1266, 1174, 1140 and 1078; $\delta_H$ (250 MHz; CDCl$_3$) 1.34 (3 H, t, $J$ 7.2, OCH$_2$Me), 2.07 (3 H, t, $J$ 1.6, Me), 2.77 (2 H, m, 4-CH$_2$), 4.28 (2 H, q, $J$ 7.2, OCH$_2$Me) and 4.34 (2 H, t, $J$ 9.7, 5-CH$_2$); $m/z$ (El$^+$) 156 ($M^+$, 65%), 127 (100), 111 (53), 83 (33), 55 (94), and 43 (30).

**Ethyl 3-methyl-4,5-dihydropyran-2-carboxylate (263)** (40%), (Found: $M^+$,
170.0940. C₉H₁₄O₃ requires 170.0943); νₘₐₓ (film)/ cm⁻¹ 2976, 2932, 1714, 1640, 1370, 1284, 1228, 1208, 1194, 1152, 1094 and 1024; δ_H (250 MHz; CDCl₃) 1.34 (3 H, t, J 7.2, OCH₂Me), 1.82-1.91 (2 H, m, 5-CH₂), 2.02 (3 H, t, J 1.1, Me), 2.15 (2 H, m, 4-CH₂), 4.01 (2 H, t, J 5.1, 6-CH₂) and 4.27 (2 H, q, J 7.1, OCH₂Me); m/z (El⁺) 170 (M⁺, 70%), 141 (100), 125 (32), 97 (35), 69 (49), 51 (63), and 41 (72).

Ethyl 3-methyl-4,5,6,7-tetrahydro-oxepin-2-carboxylate (264) (47%), (Found: M+H⁺, 185.1178. C₁₀H₁₆O₃+H requires 185.1178); νₘₐₓ (film)/ cm⁻¹ 2932, 1710, 1638, 1292, 1270, 1222, 1140, 1094, 1080, 1064 and 756; δ_H (250 MHz; CDCl₃) 1.31 (3 H, t, J 7.1, OCH₂Me), 1.52-1.61 (2 H, m, 5-CH₂), 1.83-1.92 (2 H, m, 6-CH₂), 2.11 (3 H, s, Me), 2.32-2.37 (2 H, m, 4-CH₂), 3.86 (2 H, t, J 5.3, 7-CH₂) and 4.22 (2 H, q, J 7.1, OCH₂Me); m/z (Cl⁻ ) 184 (M⁺, 9%), 183 (83), 155 (45), 127 (100), 88 (22), and 68 (21).

![Diethyl phosphono-N-methoxy-N-methy carbamoyl-diazomethane (269)](image)

Diethyl phosphono-N-methoxy-N-methyl carbamoyl-diazomethane (269)
A solution of diethyl (N-methoxy-N-methyl-carbamoylmethyl)phosphonate (Aldrich) (2.1 g, 8.8 mmol) in THF (15 ml) was added dropwise to a mixture of potassium hydride (0.42 g, 10.5 mmol) (prewashed with light petroleum) and tosyl azide (2.1 g, 10.5 mmol) in THF (60 ml) at 0°C. The mixture was stirred for 3 h at 0°C and then allowed to come to room temperature overnight. Ether (50 ml) and water (50 ml) were added and the aqueous layer extracted with ether (3 x 50 ml). The combined ethereal extracts were washed with brine (100 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether-ethyl acetate) to yield the title compound as a pale yellow oil (0.83 g, 36%), (Found: M+H⁺, 266.0906. C₈H₁₆N₃O₅P+H requires 266.0906); νₘₐₓ (film)/ cm⁻¹ 2980, 2112, 1636, 1408, 1368, 1258, 1180, 1026 and 978; δ_H
(250 MHz; CDCl$_3$) 1.34-1.40 (6 H, m, OCH$_2$Me), 3.22 (3 H, s, NMe), 3.71 (3 H, s, NMe) and 4.15-4.26 (4 H, m, OCH$_2$Me); $\delta_{C}$ (62.9 MHz; CDCl$_3$) 16.15 (OCH$_2$Me), 16.25 (OCH$_2$Me), 33.63 (N-Me), 61.51 (N-OMe), 63.60 (OCH$_2$Me), 63.70 (OCH$_2$Me) and 163.85 (C, d, J 11.6 Hz, C=O). CN$_2$ not observed; m/z (EI$^+$) 266 (MH$^+$, 100%), 234 (12), 197 (28), 177 (32), 137 (18), 109 (49), and 42 (33).

![Diethyl 1-(N-methoxy-N-methyl-carbamoyl)-1-(5-t-butyldimethylsiloxy)pentyloxymethane-phosphonate (270)](image)

**Diethyl 1-(N-methoxy-N-methyl-carbamoyl)-1-(5-t-butyldimethylsiloxy)pentyloxymethane-phosphonate (270)**

The procedure used for the preparation of the ethyl ester derivative (240) was followed (32%). [Chromatographed on silica (ethyl acetate)]; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2936, 2856, 1672, 1470, 1386, 1256, 1164, 1096, 1052, 978, 836 and 776; $\delta_{H}$ (250 MHz; CDCl$_3$) 0.04 (6 H, s, SiMe$_2$), 0.89 (9 H, s, t-BuSi), 1.30-1.71 (12 H, m, CH$_2$CH$_2$CH$_2$ and OCH$_2$Me), 3.21 (3 H, br s, NMe), 3.45-3.62 (4 H, m, OCH$_2$ and OCH$_2$Si), 3.78 (3 H, s, NMe) and 4.16-4.27 (5 H, m, OCH$_2$Me and OCHP); Satisfactory analytical data could not be obtained.

**Diethyl 1-(N-methoxy-N-methyl-carbamoyl)-1-(5-hexyn-1-oxy)methane-phosphonate (271)**

The procedure used for the preparation of the ethyl ester derivative (260) was followed (30%). [Chromatographed on silica (ethyl acetate)]; (Found: M+H$^+$, 336.1576. C$_{14}$H$_{26}$N$_6$O$_6$P+H requires 336.1576); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3284, 2980, 2936, 2112, 1670, 1442, 1388, 1258, 1166, 1124, 1052, 978 and 624; $\delta_{H}$ (250 MHz; CDCl$_3$) 1.30-1.39 (6 H, m, OCH$_2$Me), 1.60-1.66 (4 H, m, CH$_2$CH$_2$), 1.93 (1 H, t, J 2.6, =CCH), 2.23 (2 H, dt, J 2.6, 6.9, =CCH$_2$), 3.26 (3 H, br s, NMe), 3.47-3.63 (2 H, m, OCH$_2$), 3.78 (3 H, s, NMe) and 4.18-4.28 (5 H, m, OCH$_2$Me and OCHP); m/z (EI$^+$) 366 (MH$^+$, 19%), 304 (34), 179 (91), 139 (63), 111 (100), 81 (72), 65 (44), and 41 (44).
Diethyl 1-benzenesulphonyl-1-(5-t-butyldimethylsiloxyl)pentyloxymethane-phosphonate (272)

A mixture of benzenesulphonyl-diethyl phosphono-diazomethane (185) (1.0 g, 3.14 mmol), 1-(t-butyldimethylsiloxyl)-pentan-5-ol (2.06 g, 9.43 mmol) and rhodium (II) acetate (69 mg, 0.16 mmol) was refluxed for 72 h in dry toluene (60 ml). The solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the title compound (0.65 g, 41%); \( \nu_{\text{max}} \) (film)/ cm\(^{-1}\) 2952, 2932, 1325, 1258, 1159, 1100, 1078, 1052, 1025 and 837; \( \delta_H \) (250 MHz; CDCl\(_3\)) 0.04 (6 H, s, SiMe\(_2\)), 0.89 (9 H, s, t-BuSi), 1.20-1.59 (12 H, m, (CH\(_2\))\(_3\) and OCH\(_2\)Me), 3.58 (2 H, t, J 6.2, CH\(_2\)OSi), 3.75-3.90 (2 H, m, OCH\(_2\)), 4.10-4.23 (4 H, m, OCH\(_2\)Me), 4.60 (1 H, d, J 12.4, OCHP) and 7.52-8.01 (5 H, m, C\(_6\)H\(_5\)); \( \delta_C \) (62.9 MHz; CDCl\(_3\)) -5.29 (SiMe\(_2\)), 16.32 (2 C, m, OCH\(_2\)Me), 18.33 (C-Si), 22.07 (CH\(_2\)), 25.96 (t-BuSi), 29.37 (CH\(_2\)), 32.42 (CH\(_2\)), 62.89 (CH\(_2\)OSi), 64.15 (2 C, m, OCH\(_2\)Me), 76.54 (1 C, m, OCH\(_2\)), 92.57 (1 C, d, J 167.4, OCHP), 128.66 (C\(_6\)H\(_5\)), 130.09 (C\(_6\)H\(_5\)), 134.20 (C\(_6\)H\(_5\)) and 137.82 (C\(_6\)H\(_5\)); \( m/z \) (El\(^+\)) 147 (5%), 105 (100), 55 (16), 41 (35) and 31 (24).

Diethyl 1-benzenesulphonyl-1-(5-hydroxy)pentyloxymethane-phosphonate (273)

The procedure used for the preparation of the ethyl ester derivative (241) was followed (0.31 g, 80%). [Chromatographed on silica (ethyl acetate-ether)], (Found \( M+H^+ \), 395.1290. C\(_{16}\)H\(_{27}\)O\(_7\)PS+H requires 395.1293); \( \nu_{\text{max}} \) (film)/ cm\(^{-1}\) 3442, 2938, 2868, 1448, 1324, 1310, 1158, 1102, 1077, 1050 and 1024; \( \delta_H \)
(250 MHz; CDCl₃) 1.17-1.71 (12 H, m, (CH₂)₃ and OCH₂Me), 3.46-3.49 (2 H, m, CH₂OH), 3.61-3.63 (1 H, m, OCHH), 3.77-3.80 (1 H, m, OCH₂), 4.06-4.22 (4 H, m, OCH₂Me), 4.61 (1 H, d, J 12.5, OCHP) and 7.53-8.01 (5 H, m, C₆H₅). OH not observed; m/z (Cl⁺) 412 (M⁺NH₄⁺, 21%), 395 (MH⁺, 100), 253 (97), 184 (23), 167 (21), 139 (28) and 115 (35).

2-Benzensulphonyl-4,5,6,7-tetrahydro-oxepin (275)
A solution of dimethyl sulfoxide (0.12 ml, 0.13 g, 1.68 mmol) in dichloromethane (0.5 ml) was added dropwise to a solution of oxalyl chloride (0.07 ml, 0.11 g, 0.84 mmol) in dichloromethane (3 ml) at -60°C. After stirring for 2 min, a solution of the alcohol (273) (0.3 g, 0.76 mmol) in the same solvent (1 ml) was added. The reaction mixture was then allowed to stir at -60°C for 20 min. Triethylamine (0.53 ml, 0.38 g, 3.81 mol) was then added and the reaction mixture allowed to come to room temperature. Water (20 ml) and dichloromethane (10 ml) were added and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were washed with brine (20 ml) and dried (MgSO₄). The solvent was removed by evaporation. The residue was dissolved in THF (10 ml) and added dropwise to a suspension of sodium hydride (80%, 0.03 g, 1.14 mmol) in THF (60 ml) at 0°C. After stirring at room temperature for 2 h, water (60 ml) and ether (60 ml) were added. The aqueous layer was extracted with ether (3 x 40 ml) and the combined organic extracts washed with brine (80 ml) and then dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the title compound (0.044 mg, 24%). (Found M⁺NH₄⁺, 256.1010. C₁₂H₁₄O₃S⁺NH₄ requires 256.1007); νmax (film)/ cm⁻¹ 2933, 1323, 1311, 1261, 1158, 1109, 1077, 1049 and 1024; δH (250 MHz; CDCl₃) 1.54-1.63 (2 H, m, 5-CH₂), 1.80-1.89 (2 H, m, 6-CH₂), 2.29-2.36 (2 H, m, 4-CH₂), 3.77 (2 H, t, J 5.0, 7-CH₂), 6.58 (1 H, t, J 6.3, 3-CH) and 7.50-7.95 (5 H, m, C₆H₅); δC (62.9 MHz; CDCl₃) 24.49 (5-CH₂), 26.25 (6-CH₂).
31.42 (4-CH₂), 74.99 (7-CH₂), 120.11 (3-CH), 128.50 (C₆H₅), 128.97 (C₆H₅), 133.46 (C₆H₅), 138.63 (C₆H₅) and 156.99 (2-C); m/z (Cl⁺) 256 (M⁺NH₄⁺, 100%), 239 (MH⁺, 34), 125 (12), 114 (11), 97 (11) and 55 (39).

Diethyl 1-(5-t-butyldimethylsiloxy)pentyloxy-1-diethyl phosphonomethane-phosphonate (276)

A mixture of diethyl phosphono-diethyl phosphono-diazomethane (186) (2.0 g, 6.36 mmol), 1-(t-butyldimethylsiloxy)-pentan-5-ol (4.16 g, 19.1 mmol) and rhodium (II) trifluoroacetamide (42 mg, 0.064 mmol) was refluxed for 2 h in dry toluene (60 ml). The solvent was removed by evaporation and the residue chromatographed on silica (dichloromethane-methanol) to yield the title compound (2.38 g, 74%), (Found M⁺H⁺, 505.2515. C₂₀H₄₆O₈P₂Si+H requires 505.2515); νmax (film)/ cm⁻¹ 2980, 1253, 1107, 1050, 1025, 968, 769 and 696; δH (250 MHz; CDCl₃) 0.037 (6 H, s, SiMe₂), 0.89 (9 H, s, t-BuSi), 1.36 (12 H, t, J 7.1, OCH₂Me), 1.36-1.66 (6 H, m, (CH₂)₃), 3.60 (2 H, t, J 6.4, OCH₂), 3.754 (2 H, t, J 6.6, OCH₂), 3.908 (1 H, t, J 17.6, OCHP) and 4.175-4.291 (8 H, m, OCH₂Me); δC (62.9 MHz; CDCl₃) -5.29 (SiMe₂), 16.15-16.50 (4 C, m, OCH₂Me), 18.31 (C-Si), 22.26 (CH₂), 25.95 (t-BuSi), 29.58 (CH₂), 32.54 (CH₂), 62.97 (CH₂OSi), 63.11-63.34 (4 C, m, OCH₂Me), 73.55 (1 C, t, J 157.0, OCHP) and 75.06-75.21 (1 C, m, OCH₂); m/z (Cl⁺) 505 (MH⁺, 100%), 447 (M⁺-t-Bu, 6), 419 (3), 347 (11), 315 (44), 289 (41), 139 (23) and 44 (54).
Diethyl 1-diethyl phosphono-1-(5-hydroxy)pentyloxymethane-phosphonate (277)

The procedure used for the preparation of the ethyl ester derivative (241) was followed [Chromatographed on silica (dichloromethane-methanol)], (0.63 g, 82%), (Found M+H+, 391.1650. C_{14}H_{32}O_{8}P_{2}+H requires 391.1651); \(\nu_{\text{max}}\) (film)/ cm\(^{-1}\) 3437, 2984, 2936, 1253, 1165, 1098, 1047, 1027 and 976; \(\delta_{H}\) (250 MHz; CDCl\(_3\)) 1.36 (12 H, t, J 7.1, OCH\(_2\)Me), 1.41-1.70 (6 H, m, (CH\(_2\))\(_3\)), 2.81 (1 H, br s, OH), 3.62 (2 H, t, J 6.3, OCH\(_2\)), 3.78 (2 H, t, J 6.2, OCH\(_2\)), 3.91 (1 H, t, J 17.7, OCHP) and 4.16-4.29 (8 H, m, OCH\(_2\)Me); \(\delta_{C}\) (250 MHz; CDCl\(_3\)) 16.23-16.32 (4 C, m, OCH\(_2\)Me), 21.77 (CH\(_2\)), 29.03 (CH\(_2\)), 31.99 (CH\(_2\)), 62.00 (CH\(_2\)OH), 63.09-63.25 (1 C, m, OCH\(_2\)), 73.22 (1 C, t, J 157.9, OCHP) and 74.78-74.93 (4 C, m, OCH\(_2\)Me); m/z (Cl\(^+\)) 391 (MH\(^+\), 100%), 331 (6), 289 (15), 261 (6), 167 (7), 139 (15), 91 (11) and 44 (14).

\[
\begin{align*}
&\text{EtO}^\circ\text{P} - \text{H} - \text{O} - \text{C} - \text{OEt} \\
&\text{EtO}^\circ\text{P} - \text{O} - \text{OEt} \\
&\text{(277)}
\end{align*}
\]

\[
\begin{align*}
&\text{EtO}^\circ\text{P} - \text{O} - \text{OEt} \\
&\text{OH} \\
&\text{2-Diethyl phosphono-4,5,6,7-tetrahydro-oxepin (279)}
\end{align*}
\]

The procedure used for the preparation of the benzenesulphonyl derivative (275) was followed [Chromatographed on silica (dichloromethane-methanol)], (0.085 g, 28%), (Found M+H+, 235.1100. C\(_{10}\)H\(_{19}\)O\(_4\)P+H requires 235.1099); \(\nu_{\text{max}}\) (film)/ cm\(^{-1}\) 2933, 1640, 1252, 1130, 1051, 1027, 980, 969 and 732; \(\delta_{H}\) (250 MHz; CDCl\(_3\)) 1.35 (6 H, t, J 7.0, OCH\(_2\)Me), 1.62-1.66 (2 H, m, 5-CH\(_2\)), 1.85-1.92 (2 H, m, 6-CH\(_2\)), 2.26-2.31 (2 H, m, 4-CH\(_2\)), 3.96 (2 H, t, J 5.2, 7-CH\(_2\)), 4.06-4.19 (4 H, m, OCH\(_2\)Me) and 6.13-6.23 (1 H, m, 3-CH); \(\delta_{C}\) (62.9 MHz; CDCl\(_3\)) 16.35 (OCH\(_2\)Me), 16.45 (OCH\(_2\)Me), 25.04 (5-CH\(_2\)), 27.31 (1 C, d, J 16.5, 4-CH\(_2\)), 31.69 (6-CH\(_2\)), 62.28 (OCH\(_2\)Me), 62.37 (OCH\(_2\)Me), 73.81 (1 C, d, J 6.8, 7-CH\(_2\)), 126.91 (1 C, d, J 30.9, 3-CH) and 150.32 (1 C, d, J 227.4, 2-C); m/z (Cl\(^+\)) 235 (MH\(^+\), 100%), 139 (1), 102 (3), 97 (6), 55 (4) and 44 (1).

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Experimental for Chapter Four

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\text{Diethyl (1-diazo-6-hydroxy-3-oxododecyl)phosphonate (205)}^{67,154,159}
\]

n-Butyllithium (1.6 M, 27.1 ml, 43 mmol) was added dropwise to a solution of diethyl methyl phosphonate (6.0 g, 39.5 mmol) in THF at -78°C. After stirring the solution for 30 min, undecanoic acid δ-lactone (7.26 g, 39.5 mmol) in THF (5 ml) was added over 5 min. The solution was allowed to warm to room temperature and left to stir for 2 h after which it was recooled to -78°C. A solution of LDA (prepared from diisopropylamine (6.08 ml, 4.39 g, 43 mmol) and n-butyllithium (1.6 M, 27.1 ml, 43 mmol) in THF (20 ml)) was then added dropwise. After a further 30 min at -78°C, chlorotrimethylsilane (9.96 ml, 8.53 g, 79 mmol) was added and the solution allowed to warm to room temperature overnight. Saturated aqueous ammonium chloride solution (100 ml) was added and the solution extracted with ether (3 x 100 ml). The combined organic extracts were washed with brine (100 ml) and dried (MgSO₄). Evaporation of the solvent yielded crude diethyl (2-oxo-6-trimethylsilyloxy-dodecyl)phosphonate \((v_{\text{max}} \text{ (film)}/ \text{cm}^{-1} 1719)\). The phosphonate was then dissolved in dichloromethane (60 ml) and triethylamine (5.5 ml, 3.99 g, 39.5 mmol) and mesyl azide (4.78 g, 39.5 mmol) added. After stirring the mixture at room temperature for 48 h, water (60 ml) was added and the aqueous phase extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed with brine (75 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (diethyl ether) to yield diethyl (1-diazo-2-oxo-6-trimethylsilyloxy-dodecyl)phosphonate (9.44 g, 55%) as a yellow oil \((v_{\text{max}} \text{ (film)/ cm}^{-1} 2121 \text{ and } 1661)\). To a solution of this diazo compound in THF (100 ml) was added hydrochloric acid (0.5 M, 40 ml). After stirring for 0.5 h at room temperature, dichloromethane (100 ml) and water (100 ml) were added. The aqueous phase was extracted with dichloromethane (2 x 50 ml)
and the combined organic extracts washed with brine (100 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the title compound as a pale yellow oil (5.64 g, 56%); ν_max (film)/ cm⁻¹ 3487, 2121, 1658, 1369, 1262, 1018 and 975; δ_H(250 MHz; CDCl₃) 0.88 (3 H, t, J 6.7, Me), 1.19-1.76 (18 H, m, 4-CH₂ and 5-CH₂, Me(CH₂)₅ and OCH₂Me), 1.95 (1 H, br s, OH), 2.46-2.72 (2 H, m, 3-CH₂), 3.57 (1 H, m, CH₃OH) and 4.10-4.31 (4 H, m, OCH₂Me). Rest of data reported in reference 67.

Diethyl (1-diazo-6-hydroxy-2-oxohexyl)phosphonate

n-Butyllithium (1.6 M, 27.1 ml, 43 mmol) was added dropwise to a solution of diethyl methyl phosphonate (6.0 g, 39.5 mmol) in THF at -78°C. After stirring the solution for 30 min, δ-valerolactone (7.26 g, 39.5 mmol) in THF (5 ml) was added. The solution was allowed to warm to room temperature and left to stir for 3 h after which it was recooled to -78°C. A solution of LDA [prepared as above (43 mmol) in THF (20 ml)] was then added dropwise. After a further 30 min at -78°C, chlorotrimethylsilane (9.96 ml, 8.53 g, 79 mmol) was added and the solution allowed to warm to room temperature overnight. Work up as previously gave crude diethyl (2-oxo-6-trimethylsilyloxyhexyl)phosphonate which was dissolved in dichloromethane (60 ml). Triethylamine (5.5 ml, 3.99 g, 39.5 mmol) and mesyl azide (4.78 g, 39.5 mmol) were then added and the reaction mixture stirred for 48 h at room temperature after which dichloromethane (60 ml) and water (50 ml) were added. The organic phase was washed again with water (50 ml) and brine (50 ml) and dried (MgSO₄). The solvents were removed by evaporation and the residue chromatographed on silica (ether) to give diethyl (1-diazo-2-oxo-6-trimethylsilyloxy-hexyl)phosphonate (9.0 g, 65%). This oil was dissolved in THF (100 ml) and hydrochloric acid (0.5 M; 40 ml) added. After stirring for 0.5 h at room temperature, dichloromethane (100 ml) and water (100 ml) were added. The aqueous phase was extracted with dichloromethane (2 x 50 ml) and the combined
organic extracts washed with brine (100 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the title compound as a pale yellow oil (5.4 g, 76%); ν$_{\text{max}}$ (film)/ cm$^{-1}$ 3412, 2938, 2122, 1657, 1020 and 799; δ$_{\text{H}}$(250 MHz; CDCl$_3$) 1.35 (6 H, t, J 10.0, OCH$_2$Me), 1.50-1.62 (2 H, m, 4-CH$_2$ or 5-CH$_2$), 1.68-1.80 (2 H, m, 4-CH$_2$ or 5-CH$_2$), 1.97 (1 H, br s, OH), 2.60 (2 H, t, J 10.0, 3-CH$_2$), 3.58-3.67 (2 H, m, 6-CH$_2$) and 4.12-4.28 (4 H, m, OCH$_2$Me). Rest of data reported in reference 67.

**General Procedure for the Rh(II) Catalysed Cyclisation of α-Diazo-Phosphonates** $^{67,154,159}$

![Chemical structure](attachment:structure.png)

A solution of the diazo alcohol (16.6 mmol) in benzene (CAUTION) (200 ml) was added dropwise over 20 min. to a solution of rhodium (II) acetate (0.15 g, 0.33 mmol) in hot benzene (CAUTION) (60-70°C) (400 ml). An additional amount of rhodium (II) acetate (0.15 g, 0.33 mmol) was then added. The reaction mixture was brought to full reflux and heating continued for a further 60 min. The solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the respective 2-phosphono substituted 3-oxooxepane as a colourless oil.

**Diethyl 7-hexyl-3-oxooxepane-2-phosphonate** (208) (51%); ν$_{\text{max}}$ (film)/ cm$^{-1}$ 3473, 1715, 1632, 1259, 1118, 1055 and 1025; δ$_{\text{H}}$(250 MHz; CDCl$_3$) 0.85 (3 H, t, J 6.7, Me(CH$_2$)$_5$), 1.18-1.84 (18 H, m, 5-CH$_2$, OCH$_2$Me and (CH$_2$)$_5$), 1.89-2.04 (2 H, m, 6-CH$_2$), 2.44 (1 H, dd, J 6.2, 15.0, 4-CHH), 3.02-3.20 (2 H, m, 4-CHH and 7-CH) and 4.09-4.28 (5 H, m, 2-CH and OCH$_2$Me). Rest of data reported in reference 67.

**Diethyl 3-oxooxepane-2-phosphonate** (290) (54%); ν$_{\text{max}}$ (film)/ cm$^{-1}$ 2938, 1714, 1259, 1024 and 961; δ$_{\text{H}}$(250 MHz; CDCl$_3$) 1.28-1.38 (6 H, m, OCH$_2$Me),
2.05-2.36 (6 H, m, 5-CH₂, 6-CH₂ and 7-CH₂), 3.04-3.14 (1 H, ddd, J 5.0, 13.5, 16.0, 4-CHH), 3.25-3.36 (1 H, dddd, 3.0, 13.5, 16.0, 4-CHH), 4.15-4.27 (4 H, m, OCH₂Me) and 4.35-4.44 (1 H, m, 2-CH). Rest of data reported in reference 67.

**General Procedure for the Preparation of Dimethylthexylsiloxy-alkanols**

![Diagram of the reaction](image)

Dimethylthexylsilylchloride (11.0 ml, 10.0 g, 56 mmol) was added dropwise over 30 min to a solution of the diol (0.22 mol) and imidazole (5.71 g, 84 mmol) in DMF (120 ml). After stirring the reaction for 48 h at room temperature, ether (120 ml) and water (120 ml) were added. The aqueous phase was extracted with ether (3 x 75 ml) and the combined ethereal extracts washed successively with water (150 ml) and brine (150 ml) and then dried (MgSO₄). Evaporation of the solvent followed by Kugelrohr distillation of the residue yielded the pure mono-protected diol.

<table>
<thead>
<tr>
<th>mono-protected TDS diol</th>
<th>yield</th>
<th>boiling point (approx.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO(CH₂)₃OTDS</td>
<td>89%</td>
<td>130°C/3 mmHg</td>
</tr>
<tr>
<td>HO(CH₂)₄OTDS</td>
<td>80%</td>
<td>150°C/2 mmHg</td>
</tr>
<tr>
<td>HO(CH₂)₅OTDS</td>
<td>89%</td>
<td>130°C/1 mmHg</td>
</tr>
</tbody>
</table>

**General Procedure for the Preparation of Dimethylthexylsiloxy-alkyl-aldehydes**

![Diagram of the reaction](image)

The procedure used to prepare the analogous t-butyldimethylsilyl protected derivatives described earlier was followed.
General Procedure for the Preparation of 2-Alkylidene Substituted Oxepanones

Sodium hydride (80%, 0.23 g, 7.78 mmol) was added to a solution of the oxepane phosphonate [(208) or (290)] (5.99 mmol) in THF (80 ml) at 0°C. After stirring for 30 min, the appropriate dimethylhexylsilox-alkylaldehyde (0.01 mol) was added and the solution allowed to come room temperature overnight. Ether (80 ml) and water (80 ml) were added and the aqueous phase extracted with ether (3 x 50 ml). The combined ethereal extracts were washed with brine (80 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the respective 2-alkylidene substituted 3-oxooxepane as a colourless oil.

\[
\text{2-((3-Dimethylhexylsilox-1-propylidene)-7-hexyl-oxepan-3-one} \quad (283, \ n=1) \ (63%), \ \text{(Found: } M^+H^+, \ 397.3138. \ \text{C}_{23}H_{44}O_3Si+H \text{ requires 397.3138)}; \nu_{\text{max}} (\text{film})/ \text{cm}^{-1} \ 2952, \ 2860, \ 1694, \ 1630, \ 1326, \ 1252, \ 1098, \ 1058, \ 832 \text{ and } 778; \ \delta_H (250 \text{ MHz; } \text{CDCl}_3) \ 0.08 \ (6 \text{ H, s, SiMe}_2), \ 0.82-0.89 \ (16 \text{ H, m, Si-}
\text{thex and Me}), \ 1.26 \ (8 \text{ H, br s, Me(CH}_2)_4), \ 1.26-1.84 \ (6 \text{ H, m, 5-CH}_2, \ 6-\text{CH}_2 \text{ and (CH}_2)_4\text{CH}_2), \ 2.39-2.48 \ (3 \text{ H, m, CHCH}_2 \text{ and 4-CHH}), \ 2.78 \ (1 \text{ H, dt, } J \ 2.9, \ 12.2, \ 4-\text{CHH}), \ 3.40-3.55 \ (1 \text{ H, m, 7-CH}), \ 3.65 \ (2 \text{ H, dt, } J \ 1.7, \ 6.7, \ \text{CH}_2\text{OSi}) \text{ and } 6.01 \ (1 \text{ H, t, } J \ 7.5, \ C=\text{CHCH}_2); \ m/z (\text{Cl}^+) \ 413 \ (M^+\text{NH}_4^+, \ 29%), \ 397 \ (MH^+, \ 100), \ 311 \ (9), \ 273 \ (9), \ 261 \ (19), \ 241 \ (24), \ 202 \ (26), \ 185 \ (18) \text{ and } 92 \ (19).
2-(3-t-Butyldimethylsiloxy-1-propylidene)-7-hexyl-oxepan-3-one (56%), (Found: \( M^+H^+ \), 369.2825. \( C_{21}H_{40}O_3Si+H \) requires 369.2825); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2930, 2859, 1697, 1629, 1472, 1326, 1255, 1102, 836, 776 and 666; \( \delta_H \) (250 MHz; CDCl\(_3\)) 0.05 (6 H, s, SiMe\(_2\)), 0.89 (9 H, m, t-Bu), 0.89 (3 H, m, Me), 1.29 (8 H, br s, Me(CH\(_2\))\(_4\)), 1.29-1.95 (6 H, m, 5-CH\(_2\), 6-CH\(_2\) and \( (CH_2)_4CH_2 \)), 2.40-2.54 (3 H, m, CHCH\(_2\) and 4-CH\(_2\)), 2.78 (1 H, dt, J 2.9, 12.3, 4-CH\(_2\)), 3.46-3.49 (1 H, m, 7-CH), 3.64-3.70 (2 H, m, CH\(_2\)O\(_2\)Si) and 6.01 (1 H, t, J 7.5, C=CH\(_2\)); \( m/z \) (CI\(^+\)) 369 (MH\(^+\), 19%), 253 (17), 237 (24), 219 (18), 202 (22), 185 (100), 91 (33) and 74 (46).

2-(4-Dimethylthexylsiloxy-1-butyldiene)-7-hexyl-oxepan-3-one (283, n=2) (76%), (Found: \( M^+H^+ \), 411.3294. \( C_{24}H_{46}O_3Si+H \) requires 411.3294); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2952, 1694, 1626, 1464, 1326, 1250, 1098, 828, 776 and 656; \( \delta_H \) (250 MHz; CDCl\(_3\)) 0.08 (6 H, s, SiMe\(_2\)), 0.84-0.91 (16 H, m, Me and Si-thex), 1.29 (8 H, br s, Me(CH\(_2\))\(_4\)), 1.29-1.64 (8 H, m, CHCH\(_2\)CH\(_2\), \( (CH_2)_4CH_2 \), 5-CH\(_2\) and 6-CH\(_2\)), 2.20-2.39 (2 H, m, CHCH\(_2\)), 2.42-2.58 (1 H, m, 4-CH\(_2\)), 2.78 (1 H, dt, J 2.6, 12.6, 4-CH\(_2\)), 3.36-3.47 (1 H, m, 7-CH), 3.61 (2 H, t, J 6.3, CH\(_2\)OSi) and 6.00 (1 H, t, J 7.6, C=CH\(_2\)); \( m/z \) (Cl\(^+\)) 411 (MH\(^+\), 5%), 327 (3), 247 (41), 233 (100), 185 (34), 88 (26) and 71 (31).

\[
\begin{align*}
\text{o-C}_6\text{H}_3 & \quad \text{OTDS} \\
(283, \text{n}=3) \\
\end{align*}
\]

\[
\begin{align*}
\text{o-C}_6\text{H}_3 & \quad \text{OTDS} \\
(291, \text{n}=2) \\
\end{align*}
\]

*2-(5-Dimethylthexylsiloxy-1-pentylidene)-7-hexyl-oxepan-3-one (283, n=3) (47%); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2932, 2860, 1694, 1626, 1464, 1326, 1250, 1174, 1098, 830 and 776; \( \delta_H \) (250 MHz; CDCl\(_3\)) 0.08 (6 H, s, SiMe\(_2\)), 0.84-0.91 (16 H, m, Me and Si-thex), 1.29 (8 H, br s, Me(CH\(_2\))\(_4\)), 1.29-1.64 (10 H, m, CHCH\(_2\)CH\(_2\), \( (CH_2)_4CH_2 \), 5-CH\(_2\) and 6-CH\(_2\)), 2.20-2.39 (2 H, m, CHCH\(_2\)), 2.42-2.58 (1 H, m, 4-CH\(_2\)), 2.78 (1 H, dt, J 2.6, 12.6, 4-CH\(_2\)), 3.36-3.47 (1 H, m, 7-CH), 3.61 (2 H, t, J 6.3, CH\(_2\)OSi) and 6.00 (1 H, t, J 7.6, C=CH\(_2\)).
2-(5-t-Butyldimethylsiloxyl-1-pentylidene)-7-hexyl-oxepan-3-one (50%,
(Found: M+H+, 397.3140. C_{23}H_{44}O_3Si+H, requires 397.3138); v_max (film)/
cm\(^{-1}\) 2932, 2860, 1727, 1624, 1326, 1250, 1174, 1098, 830 and 776;
\(\delta_H\) (250 MHz; CDCl\(_3\)) 0.04 (6 H, s, SiMe\(_2\)), 0.89 (9 H, s, t-Bu), 0.89 (3 H, m,
Me), 1.29 (8 H, br s, Me(CH\(_2\))\(_4\)), 1.29-1.84 (10 H, m, 5-CH\(_2\), 6-CH\(_2\),
(CH\(_2\))\(_4\)CH\(_2\) and (CH\(_2\))\(_2\)), 2.22-2.27 (2 H, m, CHCH\(_2\)), 2.40-2.46 (1 H, m, 4-
CHH), 2.74 (1 H, dt, J 2.8, 12.2, 4-CHH), 3.40-3.41 (1 H, m, 7-CH), 3.61 (2
H, t, J 6.1, CH\(_2\)OSi) and 6.00 (1 H, t, J 7.6, C=CH); \(\delta_C\) (250 MHz; CDCl\(_3\)) -5.29
(SiMe\(_2\)), 14.09 (Me), 18.35 (C-Si), 22.62 (CH\(_2\)), 23.31 (CH\(_2\)), 25.15 (2 x
CH\(_2\)), 25.84 (CH\(_2\)), 25.98 (t-Bu), 29.25 (CH\(_2\)), 31.80 (CH\(_2\)), 32.64 (CH\(_2\)),
35.95 (CH\(_2\)), 36.91 (CH\(_2\)), 42.12 (CH\(_2\)), 62.89 (CH\(_2\)OSi), 85.14 (7-CH),
123.40 (C=CH), 153.64 (C=CH) and 201.173 (C=O); m/z (Cl\(^+\)) 413 (100%),
395 (60), 265 (38), 217 (67), 185 (71), 171 (38), 85 (56) and 74 (40).

2-(4-Dimethylthexylsiloxy-1-butylidene)-oxepan-3-one (291, n=2) (51%)
(Found: M+H+, 327.2355. C\(_{18}\)H\(_{34}\)O\(_3\)Si+H requires 327.2355); v_max (film)/
cm\(^{-1}\) 2952, 2864, 1694, 1628, 1324, 1250, 1150, 1056, 830 and 776; \(\delta_H\)
(250 MHz; CDCl\(_3\)) 0.08 (6 H, m, SiMe\(_2\)), 0.84-0.97 (13 H, m, Si-thex), 1.56-
1.92 (6 H, m, 5-CH\(_2\), 6-CH\(_2\) and CHCH\(_2\)CH\(_2\)), 2.20-2.29 (2 H, m, CHCH\(_2\)),
2.64-2.69 (2 H, m, 4-CH\(_2\)), 3.60 (2 H, t, J 6.3, CH\(_2\)OSi), 4.11-4.14 (2 H, m,
7-CH\(_2\)) and 6.08 (1 H, t, J 7.7, C=CHCH\(_2\)); m/z (Cl\(^+\)) 327 (MH\(^+\), 66%), 243
(100), 167 (25), 151 (25), 91 (18), 74 (21) and 55 (13).

\[
\text{OTDS} \quad \text{(283, n=2)} \quad \rightarrow \quad \text{OH} \quad \text{(282, n=2)}
\]

7-Hexyl-2-(4-hydroxy-1-butylidene)-oxepan-3-one (282, n=2)
The oxepanone (283, n=2) (0.30 g, 0.73 mmol) was stirred in a 5% HCl/ethanol
mixture (10 ml) for 40 min at room temperature. Ether (20 ml) and water (20
ml) were added and the aqueous phase extracted with ether (3 x 20 ml). The
combined organic extracts were washed successively with water (30 ml) and brine
(30 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the title compound as a colourless oil (0.11 g, 56%). (Found: M⁺, 268.2038. C₁₆H₂₈O₃ requires 268.2038); ν_max (film)/ cm⁻¹ 3452, 2928, 2856, 1690, 1624, 1452, 1326 and 1058; δ_H (250 MHz; CDCl₃) 0.89 (3 H, t, J 6.9, Me), 1.29 (8 H, br s, Me(CH₂)₄), 1.29-1.85 (4 H, m, 5-CH₂ and 6-CH₂), 2.07-2.45 (2 H, m, CHCH₂), 2.49-2.59 (1 H, m, 4-CHH), 2.79 (1 H, dt, J 2.8, 12.2, 4-CHH), 3.45-3.49 (1 H, m, 7-CH), 3.64 (2 H, t, J 5.7, CH₂OH) and 6.00 (1 H, t, J 7.6, C=CHCH₂); m/z (El⁺) 268 (M⁺, 26%), 251 (18), 111 (22), 97 (29), 83 (48), 71 (39), 55 (100) and 71 (31).

**General Procedure for the Hydrogenation of Enol Ethers**

A mixture of the enol ether (2.44 mmol) and palladium on charcoal (10%, 0.1 g) was hydrogenated at atmospheric pressure for 1 h in ethyl acetate (20 ml). After removing the catalyst by filtration, the solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the oxepanone as a mixture of diastereomers in approximately quantitative yield. Epimerisation of the mixture (if necessary) was carried out by dissolving the mixture of diastereomers in dry methanol (10 ml) and adding a small amount of sodium (ca. 10 mg) and stirring for 48 h. Ether (30 ml) and water (30 ml) were then added and the aqueous phase extracted with ether (3 x 30 ml). The combined ethereal extracts were washed with brine (60 ml) and then dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the oxepanone as the single cis-diastereomer.
2-(3-Dimethylthexylsiloxy-1-propyl)-7-hexyl-oxepan-3-one (285, n=1) (66%), (Found: M+H+, 399.3294. C_{23}H_{46}O_{3}Si+H requires 399.3294); ν_{max} (film)/ cm⁻¹ 2952, 2928, 2860, 1712, 1250, 1098 and 830; δ_{H} (250 MHz; CDCl₃) 0.08 (6 H, s, SiMe₂), 0.83-0.93 (16 H, m, Me and Si-thex), 1.28 (8 H, br s, Me(CH₂)₄), 1.28-1.75 (9 H, m, 5-CH₂, 6-CHH, (CH₂)₄CH₂ and (CH₂)₂CH₂O), 1.93-1.98 (1 H, m, 6-CHH), 2.28-2.35 (1 H, m, 4-CHH), 2.91 (1 H, _dt, J 2.5, 11.6, 4-CHH) and 3.15 (1 H, m, 7-CH), 3.58-3.71 (3 H, m, 2-CH and CH₂OSi); m/z (Cl⁺) 399 (MH⁺, 100%), 313 (12), 258 (19), 239 (22), 221 (10), 145 (6), 127 (7) and 92 (6).

2-(4-Dimethylthexylsiloxy-1-butyl)-7-hexyl-oxepan-3-one (285, n=2) (76%), (Found: M+H+, 413.3451. C_{24}H_{48}O_{3}Si+H, requires 413.3451); ν_{max} (film)/ cm⁻¹ 2940, 2856, 1712, 1462, 1378, 1250, 1114, 1108, 876, 830 and 776; δ_{H} (250 MHz; CDCl₃) 0.07 (6 H, s, SiMe₂), 0.84-0.89 (16 H, m, Me and Si-thex), 1.28 (8 H, br s, Me(CH₂)₄), 1.28-1.80 (12 H, m, 5-CH₂, 6-CH₂, (CH₂)₄CH₂ and (CH₂)₃CH₂O), 2.28-2.35 (1 H, m, 4-CHH), 2.91 (1 H, dt, J 3.0, 14.0, 4-CHH), 3.07-3.16 (1 H, m, 7-CH), 3.58-3.75 (3 H, m, 2-CH and CH₂OSi); m/z (Cl⁺) 413 (MH⁺, 100%), 327 (25), 235 (12), 159 (12), 92 (10) and 74 (10).

2-(5-Dimethylthexylsiloxy-1-pentyl)-7-hexyl-oxepan-3-one (285, n=3) (75%), (Found: M+H+, 427.3607. C_{25}H_{50}O_{3}Si+H, requires 427.3607); ν_{max} (film)/ cm⁻¹ 2930, 2860, 1710, 1465, 1250, 1100, 830 and 775; δ_{H} (250 MHz; CDCl₃) 0.07 (6 H, s, SiMe₂), 0.83-1.00 (16 H, m, Me and Si-thex), 1.28 (8 H, br s, Me(CH₂)₄), 1.28-1.90 (12 H, m, 5-CH₂, 6-CH₂, (CH₂)₄CH₂ and (CH₂)₃CH₂O), 2.28-2.35 (1 H, m, 4-CHH), 2.91 (1 H, dt, J 3.0, 14.0, 4-CHH), 3.07-3.16 (1 H, m, 7-CH), 3.58-3.75 (3 H, m, 2-CH and CH₂OSi); m/z (Cl⁺) 427 (MH⁺, 100%), 339 (25), 245 (12), 159 (12), 92 (10) and 74 (10).
MHz; CDCl\textsubscript{3}) 0.07 (6 H, s, SiMe\textsubscript{2}), 0.82-0.89 (16 H, m, Me and Si-thex), 1.21 (8 H, br s, Me(CH\textsubscript{2})\textsubscript{4}), 1.21-1.75 (13 H, m, 5-CH\textsubscript{2}, 6-CHH, (CH\textsubscript{2})\textsubscript{4}CH\textsubscript{2} and (CH\textsubscript{2})\textsubscript{4}CH\textsubscript{2}OSi), 1.80-2.00 (1 H, m, 6-CHH), 2.28-2.33 (1 H, m, 4-CHH), 2.90 (1 H, ~dt, 4-CHH), 3.07-3.16 (1 H, m, 7-CH), 3.57 (2 H, t, J 6.3, CH\textsubscript{2}OSi), 3.66-3.71 (1 H, m, 2-CH); m/z (Cl\textsuperscript{+}) 427 (MH\textsuperscript{+}, 100%), 275 (54), 247 (39), 201 (25), 185 (51), 115 (25), 102 (39) and 85 (55).

2-(4-Dimethylthexylsiloxy-1-butyl)-oxepan-3-one (292, n=2) (98%), (Found: M\textsuperscript{+}, 328.2434. C\textsubscript{18}H\textsubscript{36}O\textsubscript{3}Si requires 328.2434); \(\nu\)\textsubscript{max} (film)/ cm\textsuperscript{-1} 2952, 2860, 1710, 1462, 1252, 1100, 832 and 776; \(\delta\) (250 MHz; CDCl\textsubscript{3}) 0.07 (6 H, s, SiMe\textsubscript{2}), 0.83-0.89 (13 H, m, Me and Si-thex), 1.42-1.91 (10 H, m, 5-CH\textsubscript{2}, 6-CH\textsubscript{2}, and CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}OSi), 2.37-2.40 (1 H, m, 4-CHH), 2.84 (1 H, ~dt, J 2.8, 11.5, 4-CHH), 3.27 (1 H, ~dt, 7-CHH), 3.57 (2 H, t, J 5.9, CH\textsubscript{2}OSi), 3.70 (1 H, m, 7-CHH) and 4.19-4.25 (1 H, m, 2-CH); m/z (El\textsuperscript{+}): 243 (23%), 151 (17), 105 (13), 81 (28), 75 (100), 55 (28), 41 (42) and 27 (14).

**General Procedure for the Preparation of Hydroxy-Alkyl Oxepanones**

![Diagram](image)

The dimethylthexylsilyloxy-alkyloxepanone (0.63 mmol) was stirred in a 5% hydrochloric acid/ ethanol mixture (10 ml) until all of the starting material had been consumed (by TLC) (ca. 1 h). Ether (20 ml) and water (20 ml) were then added and the aqueous layer extracted with ether (3 x 20 ml). The combined ethereal extracts were washed successively with saturated sodium bicarbonate solution (40 ml) and brine (40 ml) and dried (MgSO\textsubscript{4}). The solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the respective hydroxy-alkyl oxepanone as a colourless oil.
7-Hexyl-2-(3-hydroxy-1-propyl)-oxepan-3-one (281, n=1) (58%), (Found: M⁺, 256.2038. C₁₅H₂₈O₃ requires 256.2038); νmax (film)/ cm⁻¹ 3436, 2924, 2856, 1708, 1452, 1320 and 1120; δH (250 MHz; CDCl₃) 0.89 (3 H, t, J 6.8, Me), 1.28 (8 H, br s, Me(CH₂)₄, 1.28-2.39 (10 H, m, 5-CH₂, 6-CH₂, (CH₂)₄CH₂ and CH₂CH₂), 2.31-2.39 (1 H, m, 4-CHH), 2.87-2.93 (1 H, m, 4-CHH), 3.20-3.90 (4 H, m, 5-CH₂, 6-CH₂, (CH₂)₄CH₂ and CH₂OH). OH not observed; m/z (Cl⁺) 274 (M+NH₄⁺, 16%), 257 (MH⁺, 67), 239 (M⁺-OH, 100), 221 (7), 171 (3), 143 (6), 71 (7) and 58 (3).

7-Hexyl-2-(4-hydroxy-1-butyl)-oxepan-3-one (281, n=2) (71%), (Found: M⁺, 270.2182. C₁₆H₃₀O₃ requires 270.2195); νmax (film)/ cm⁻¹ 3420, 2932, 2856, 1710, 1454, 1434, 1376, 1322, 1120 and 870; δH (250 MHz; CDCl₃) 0.89 (3 H, t, J 6.2, Me), 1.28 (8 H, br s, Me(CH₂)₄, 1.28-1.82 (11 H, m, 5-CH₂, 6-CHH, (CH₂)₄CH₂ and (CH₂)₃), 1.92-2.00 (1 H, m, 6-CHH), 2.30-2.37 (1 H, m, 4-CHH), 2.90 (1 H, dt, J 2.6, 12.6, 4-CHH), 3.16 (1 H, ~t, J 7.1, 7-CH), 3.63-3.73 (3 H, m, 2-CH and CH₂OH). OH not observed; m/z (Cl⁺) 288 (M+NH₄⁺, 44%), 271 (M+H⁺, 77), 253 (100), 235 (12), 157 (25), 139 (12), 16 (8) and 85 (25).

7-Hexyl-2-(5-hydroxy-1-pentyl)-oxepan-3-one (281, n=3) (70%), (Found: M⁺, 284.2350. C₁₇H₃₂O₃ requires 284.2351); νmax (film)/ cm⁻¹ 3420, 2930, 2860, 1710, 1455, 1320, 1120 and 1055; δH (250 MHz; CDCl₃) 0.89 (3 H, t, J 6.4, Me), 1.24 (8 H, br s, Me(CH₂)₄, 1.24-1.85 (13 H, m, 5-CH₂, 6-
CH₂, (CH₂)₄CH₂ and (CH₂)₄), 1.89-2.04 (1 H, m, 6-CH₂), 2.27-2.38 (1 H, m, 4-CH₂), 2.91 (1 H, dt, J 2.6, 12.6, 4-CH₂), 3.15 (1 H, ~t, 7-CH), 3.61 (2 H, t, J 6.6, CH₂OH) and 3.64-3.71 (1 H, m, 2-CH). OH not observed; m/z (El⁺) 284 (M⁺, 30%), 256 (1), 213 (1), 198 (9), 187 (4) and 169 (100).

2-(4-hydroxy-1-butyl)-oxepan-3-one (293, n=2) (72%), (Found: M⁺, 186.1256. C₁₀H₁₈O₃ requires 186.1256); v max (film)/ cm⁻¹ 3420, 3404, 2936, 2860, 1708, 1320, 1140, 1120, 1086 and 1074; δH (250 MHz; CDCl₃) 3.34-1.95 (10 H, m, 5-CH₂, 6-CH₂ and (CH₂)₃), 2.39-2.41 (1 H, m, 4-CH₂), 2.90 (1 H, dt, J 2.8, 12.8, 4-CH₂), 3.28 (1 H, dt, J 2.3, 10.6, 7-CH), 3.64 (2 H, t, J 6.3, CH₂OH), 3.70-3.75 (1 H, m, 7-CH) and 4.20-4.26 (1 H, m, 2-CH). OH not observed; m/z (El⁺) 186 (M⁺, 9%), 111 (3), 85 (100), 67 (9), 56 (30), 41 (55), 31 (22) and 27 (26).

**General Procedure for Cyclisation of Hydroxy-Alkyl Oxepanones**

A mixture of the hydroxy-alkyl oxepanone (0.30 mmol) and triethylsilane (0.47 ml, 0.34 g, 2.96 mmol) in dichloromethane (5 ml) at 0°C was treated dropwise with trimethylsilyl triflate (0.057 ml, 66 mg, 0.30 mmol). The reaction was stirred for 1 h at 0°C and then allowed to come to room temperature. Dichloromethane (20 ml) and water (20 ml) were added and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were washed with brine (20 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the respective 7-n-fused bicyclic ether derivative.
6-Hexyl-3,4,4a,6,7,8,9,9a-octahydro-pyrano[3,2-b]oxepin (287) (78%), (Found: M+H+, 241.2168. C_{15}H_{28}O_{2}+H requires 241.2168); \nu_{\text{max}} (film)/\text{cm}^{-1} 2924, 2852, 1454, 1144, 1094 and 1036; (mixture of cis/trans-isomers) \delta_H (250 MHz; CDCl_3) 0.88 (3 H, t, J 6.8, Me), 1.27 (8 H, br s, Me(CH_2)_4), 1.27-2.03 (12 H, m, 3-CH_2, 4-CH_2, 7-CH_2, 8-CH_2, 9-CH_2 and (CH_2)_4CH_2), 3.00-3.04 (1 H, m, 4a-CH), 3.30-3.56 (3 H, m, 2-CHH, 6-CH and 9a-CH) and 3.84-3.90 (1 H, m, 2-CHH); \delta_C (62.9 MHz; CDCl_3) 14.03, 19.60, 20.33, 21.25, 22.56, 25.81, 26.16, 26.29, 29.18, 29.67, 31.34, 31.80, 32.70, 33.88, 34.46, 36.75, 37.03, 37.87, 67.62, 76.19, 77.49, 78.25, 79.85, 79.90, 82.28 and 83.22; \textit{m/z} (Cl^+) 258 (M+NH_4^+, 71%), 241 (M+H^+, 100), 223 (12), 155 (65), 98 (15) and 71 (29).

7-Hexyl-2,3,4,5,5a,7,8,9,10,10a-decahydro-oxepino[3,2-b]oxepin (286) (51%), (Found: C, 75.71; H, 12.00. C_{16}H_{30}O_2 requires C, 75.54; H, 11.89%), (Found: M+H+, 255.2324. C_{16}H_{30}O_{2}+H requires 255.2324); \nu_{\text{max}} (film)/\text{cm}^{-1} 2928, 2856, 1452, 1378, 1118, 1098, 1022 and 882; (trans isomer) \delta_H (400 MHz; CDCl_3) 0.86 (3 H, t, J 7.0, Me), 1.26 (8 H, br s, Me(CH_2)_4), 1.26-1.77 (12 H, m, 3-CH_2, 4-CH_2, 5-CHH, 8-CH_2, 9-CH_2, 10-CHH and (CH_2)_4CH_2), 1.89-1.96 (1 H, m, 10-CHH), 2.00-2.06 (1 H, m, 5-CHH), 3.22-3.28 (1 H, m, 5a-CH), 3.31-3.36 (1 H, m, 10a-CH), 3.41-3.46 (1 H, m, 7-CH), 3.62-3.76 (1 H, m, 2-CHH) and 3.77-3.82 (1 H, m, 2-CHH); \delta_C (125 MHz; CDCl_3) 13.99, 19.86, 20.90, 22.52, 26.15, 29.02, 29.13, 31.78, 34.39, 35.14, 35.87, 36.94, 69.22, 81.87, 82.29 and 84.60; \textit{m/z} (El^+) 255 (MH^+, 3%), 237 (2), 169 (15), 97 (10), 85 (100), 67 (23), 57 (16) and 41 (12).

2,3,4,5,5a,7,8,9,10,10a-Decahydro-oxepino[3,2-b]oxepin (289) (79%), (Found: M^+, 170.1307. C_{10}H_{18}O_2 requires 170.1307); \nu_{\text{max}} (film)/
cm⁻¹ 2928, 2856, 1450, 1124, 1104, 1084, 1032, 1014, 998 and 978; (mixture of cis/trans-isomers) δ_H (400 MHz; CDCl₃) 1.24-2.16 (12 H, m, 3-CH₂, 4-CH₂, 5-CH₂, 8-CH₂, 9-CH₂ and 10-CH₂), 3.28-3.34 (2 H, m, 10a-CH and 7-CHH), 3.56-3.67 (2 H, m, 5a-CH and 2-CHH), 3.84-3.90 (1 H, m, 2-CHH), 4.02-4.07 (1 H, m, 7-CHH); δ_C (125 MHz; CDCl₃) 20.99 (CH₂), 22.40 (CH₂), 29.77 (CH₂), 32.06 (CH₂), 32.78 (CH₂), 34.88 (CH₂), 70.31 (CH₂), 72.45 (CH₂), 83.43 (CH) and 84.85 (CH); m/z (EI⁺) 170 (M⁺, 28%), 85 (100), 69 (53), 57 (75), 41 (86) and 29 (55).

7-Hexyl-2-(1-propenyl)-oxepan-3-one (297)

A stirred mixture of the allyl oxepanone (296) (0.47 g, 1.39 mmol) and a few crystals of 4-toluene sulphonic acid was heated slowly to 150-160°C and maintained at this temperature for 10 min. After allowing to cool, ether (20 ml) and water (20 ml) were added and the aqueous phase extracted with ether (3 x 20 ml). The combined ethereal extracts were washed with brine (40 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound as a mixture of diastereomers. Epimerisation was carried out by adding a small amount of sodium (ca. 5 mg) to the mixture in dry methanol (3 ml) and stirring for 48 h. Another portion of sodium was then added and stirring continued for a further 48 h. Aqueous hydrochloric acid (0.5 M, 5 ml) was then added and the methanol removed by evaporation. The aqueous mixture was extracted with ether (3 x 10 ml) and the combined ethereal extracts washed with brine (20 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound as the single cis-diastereomer (by NOE studies) (0.19 g, 59 %). (Found: C, 75.11; H, 11.20. C₁₅H₂₆O₂ requires C, 75.58; H, 11.20%), (Found: M+H⁺, 239.2011. C₁₅H₂₆O₂⁺ requires 239.2011); \( \nu_{max} \) (film)/
cm⁻¹ 2928, 2856, 1710, 1638, 1432, 1378, 1316, 1260, 1142, 1106, 996 and 914; δH (400 MHz; CDCl₃) 0.87 (3 H, t, J 7.0, Me), 1.26 (8 H, br s, Me(CH₂)₄), 1.26-1.61 (4 H, m, CH₂ and 5-CH₂), 1.76-1.79 (1 H, m, 6-CHH), 1.93-1.97 (1 H, m, 6-CHH), 2.31-2.42 (3 H, m, CH₂CH=CH₂ and 4-CHH), 2.86 (1 H, dt, J 2.4, 12.2, 4-CHH), 3.16-3.17 (1 H, m, 7-CHH), 3.74-3.77 (1 H, m, 2-CH), 5.06 (1 H, dd, J₆₇ 1.5, J₇₈ 9.2, CH=CHH), 5.10 (1 H, dd, J₆₇ 1.5, Jtrans 15.8, CH=CHH) and 5.80-5.90 (1 H, m, CH=CH₂); δC (125 MHz; CDCl₃) 14.11 (Me), 22.61 (CH₂), 23.78 (CH₂), 25.64 (CH₂), 29.16 (CH₂), 31.82 (CH₂), 36.29 (CH₂), 37.17 (CH₂), 37.55 (CH₂), 41.51 (CH₂), 83.71 (7-CH), 86.49 (2-CH), 117.50 (CH=CH₂), 133.94 (CH=CH₂) and 216.690 C=O; m/z (Cl⁺) 239 (MH⁺, 100%), 221 (18), 198 (32), 169 (21), 151 (18), 125 (9), 95 (8) and 84 (8).

![Ethylene ketal of 7-hexyl-2-(1-propenyl)-oxepan-3-one (298)](image)

Ethylene ketal of 7-hexyl-2-(1-propenyl)-oxepan-3-one (298)

A mixture of the allyl oxepanone (297) (0.50 g, 2.1 mmol), ethane-1,2-diol (0.13 ml, 0.14 g, 2.31 mmol) and 4-toluenesulphonic acid (4.0 mg, 0.021 mmol) in toluene (30 ml) was refluxed for 45 min in a flask fitted with a Dean-Stark trap. After allowing to cool, water (30 ml) was added and the aqueous phase extracted with ether (3 x 20 ml). The combined ethereal extracts were washed with brine (40 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound as a colourless oil (0.26 g, 63 %), (Found M⁺, 282.2195. C₁₇H₃₀O₃ requires 282.2195); νmax (film)/cm⁻¹ 2924, 1452, 1438, 1178, 1158, 1140, 1104, 1064, 1040, 948 and 912; δH (400 MHz; CDCl₃) 0.86 (3 H, t, J 7.0, Me), 1.26 (8 H, br s, Me(CH₂)₄), 1.26-1.83 (8 H, m, 4-CH₂, 5-CH₂, 6-CH₂ and CH₂), 2.19-2.32 (2 H, m, CH₂CH=CH₂), 3.33-3.39 (1 H, m, 7-CH), 3.48-3.51 (1 H, dd, J 3.0, 10.0, 2-CH), 3.80-4.02 (4 H, m, OCH₂CH₂O), 5.01 (1 H, dd, Jcis 10.0 Hz, CH=CHH), 5.09 (1 H, dd, J₆₇ 1.8, Jtrans 17.2 Hz, CH=CHH) and
5.85-5.96 (1 H, m, CH=CH2); δC (125 MHz; CDCl3) 14.00 (Me), 20.49 (CH2), 22.53 (CH2), 26.06 (CH2), 29.16 (CH2), 31.75 (CH2), 34.06 (CH2), 37.12 (CH2), 37.17 (CH2), 37.41 (CH2), 63.71 (OCH2), 65.51 (OCH2), 83.81 (7-CH), 84.66 (2-CH), 112.92 (3-C), 116.07 (CH=CH2) and 136.363 (kH = CH2);
m/z (Cl+) 283 (M+H+, 43%), 265 (7), 227 (28), 141 (11), 99 (100), 86 (9) and 73 (8).

Ethylene ketal of 7-hexyl-2-(3-hydroxy-1-propyl)-oxepan-3-one (299)

A solution of the allyl oxepane (298) (0.16 g, 0.57 mmol) in THF (2 ml) was added dropwise to a solution of borane-tetrahydrofuran complex (1 M, 0.62 ml, 0.62 mmol) at 0°C. After stirring for 2 h at room temperature, the reaction mixture was recooled to 0°C and aqueous sodium hydroxide (3 M, 0.19 ml, 0.57 mmol) added dropwise. This was followed by the dropwise addition of hydrogen peroxide solution (30%, 0.23 ml, 1.99 mmol). The mixture was then stirred for 1.5 h at room temperature. Ether (20 ml) was added and the organic phase washed successively with water (4 x 10 ml) and brine (10 ml). After drying (MgSO4), the solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the title compound as a colourless oil (0.10 g, 61 %), (Found: M+H+, 301.2379). C17H32O4+H requires 301.2379; νmax (film)/ cm⁻¹ 3428, 2928, 2856, 1452, 1176, 1156, 1106, 1020, 950 and 926; δH (400 MHz; CDCl3) 0.86 (3 H, t, J 7.0, Me), 1.28 (8 H, br s, Me(CH2)4), 1.28-1.89 (12 H, m, (CH2)2CH2OH, 4-CH2, 5-CH2, 6-CH2 and (CH2)4CH2), 3.37-3.41 (1 H, m, 7-CH), 3.43-3.46 (1 H, m, 2-CH), 3.63-3.66 (2 H, m, CH2OH), 3.82-3.91 (2 H, m, OCH2CH2O) and 3.93-3.99 (2 H, m, OCH2CH2O). OH not observed; δC (125 MHz; CDCl3) 13.98 (Me), 20.38 (CH2), 22.53 (CH2), 25.63 (CH2), 26.05 (CH2), 29.23 (CH2), 29.36 (CH2), 31.71 (CH2), 36.88 (CH2), 37.05 (CH2), 37.13 (CH2), 63.05 (CH2OH), 63.78 (OCH2), 83.67 (7-CH), 84.63 (2-CH) and
112.91 (3-C); m/z (Cl⁺) 301 (M+H⁺, 13%), 239 (100), 210 (19), 141 (9), 113 (16), 99 (96), 86 (15) and 71 (11).

7-Hexyl-2-(3-hydroxy-1-propyl)-oxepan-3-one (281, n=1)
The hydroxy alkyl-oxepane (299) (0.07 g, 0.23 mmol) was stirred in a mixture of 5 % HCl/THF (5 ml) for 4 h at room temperature. Ether (20 ml) and water (10 ml) were then added and the aqueous phase extracted with ether (3 x 10 ml). The combined ethereal extracts were washed with brine (20 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound as a colourless oil (0.044 g, 74 %). This displayed identical spectral properties to the same compound prepared previously. See above for data (page 232).

7-Hexyl-2-(1-propenyl)-oxepan-3-ol (300)
A solution of the allyl oxepanone (297) (0.40 g, 1.68 mmol) in methanol (5 ml) was treated successively with cerium chloride heptahydrate (0.69 g, 1.85 mmol) and sodium borohydride (70 mg, 1.85 mmol). After stirring for 10 min, the suspension was acidified to pH 2 using 0.5 M hydrochloric acid. Ether (20 ml) and water (20 ml) were added and the aqueous phase extracted with ether (3 x 20 ml). The combined ethereal extracts were washed with brine (40 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound as a mixture of cis- and trans-diastereoisomers (0.38 g, 94 %, E:Z ratio ca. 1:1), (Found: C, 74.72; H,
C_{15}H_{28}O_{2} requires C, 74.95; H, 11.74\%. (Found: M+H\+, 241.2168. C_{15}H_{28}O_{2}+H requires 241.2168); [Analysis carried out on cis-isomer (by NOE)]: \nu_{\text{max}} \text{ (film)/ cm}^{-1} 3456, 2924, 2856, 1638, 1452, 1376, 1338, 1132, 1088, 996 and 912; \delta_{\text{H}} (400 MHz; CDCl_{3}) 0.87 (3 H, t, J 6.7, Me), 1.26 (8 H, br s, Me(CH_{2})_{4}), 1.26-1.86 (8 H, m, 4-CH_{2}, 5-CH_{2}, 6-CH_{2} and CH_{2}), 2.20-2.24 (1 H, m, CHHCH=CH_{2}), 2.29 (1 H, d, J 9.9, OH), 2.39-2.47 (1 H, m, CHHCH=CH_{2}), 3.39-3.43 (1 H, m, 2-CH), 3.52-3.55 (1 H, m, 7-CH), 3.70-3.75 (1 H, m, 3-CH), 5.01-5.14 (2 H, m, CH=CH_{2}) and 5.79-5.96 (1 H, m, CH=CH_{2}); \delta_{\text{C}} (125 MHz; CDCl_{3}) 13.99 (Me), 17.66 (CH_{2}), 22.54 (CH_{2}), 26.07 (CH_{2}), 29.14 (CH_{2}), 31.77 (CH_{2}), 35.15 (CH_{2}), 36.39 (CH_{2}), 36.56 (CH_{2}), 37.48 (CH_{2}), 71.30 (2-CH), 79.15 (7-CH), 79.90 (3-CH), 116.51 (CH=CH_{2}) and 135.60 (CH=CH_{2}); m/z (Cl\textsuperscript{+}) 241 (M+H\+, 100\%), 223 (39), 199 (10), 169 (9), 152 (10), 109 (9), 95 (11) and 81 (12).

\[
\begin{array}{c}
\text{n-C}_{6}\text{H}_{13} \quad \text{OH} \\
\text{(300)} \quad \rightarrow \quad \text{n-C}_{6}\text{H}_{13} \quad \text{OH} \\
\text{(301)}
\end{array}
\]

7-Hexyl-2-(3-hydroxy-1-propyl)-oxepan-3-ol (301)

A solution of the allyl oxepanol (300) (0.60 g, 2.5 mmol) in THF (4 ml) was added dropwise to a solution of borane-tetrahydrofuran complex (1 M, 2.75 ml, 2.75 mmol) at 0°C. The reaction mixture was stirred for 2 h at room temperature after which it was recooled to 0°C and sodium hydroxide solution (3 M, 0.83 ml, 2.5 mmol) added dropwise. This was followed by the dropwise addition of hydrogen peroxide solution (30\%, 1.0 ml, 8.75 mmol). The mixture was then stirred for 1.5 h at room temperature. Ether (30 ml) and water (20 ml) were added and the organic phase washed successively with water (3 x 20 ml) and brine (10 ml). After drying (MgSO\textsubscript{4}), the solvent was removed by evaporation and the residue chromatographed on silica (ether-ethyl acetate) to yield the title compound as a colourless oil (0.45 g, 70\%). (Found: M\textsuperscript{+}, 258.2195. C_{15}H_{30}O_{3} requires 258.2195); [Analysis carried out on cis-isomer (by NOE)]: \nu_{\text{max}} \text{ (film)/ cm}^{-1} 3384, 2920, 1452, 1376, 1338, 1132 and 1062; \delta_{\text{H}} (400 MHz; CDCl_{3}) 0.86 (3 H, t, J 7.0, Me),
1.25 (8 H, br s, Me(CH$_2$)$_4$), 1.25-1.85 (12 H, m, 4-CH$_2$, 5-CH$_2$, 6-CH$_2$, CH$_2$CH$_2$ and (CH$_2$)$_4$CH$_2$), 2.05 (1 H, br s, OH), 2.46 (1 H, br s, OH), 3.39-3.41 (1 H, m, 2-CH), 3.52-3.58 (1 H, m, 7-CH), 3.64 (2 H, t, J 6.0, CH$_2$OH) and 3.68-3.71 (1 H, m, 3-CH); δ$_C$ (125 MHz; CDCl$_3$) 13.95 (Me), 17.64 (CH$_2$), 22.50 (CH$_2$), 26.05 (CH$_2$), 29.16 (2 x CH$_2$), 29.33 (CH$_2$), 31.70 (CH$_2$), 34.99 (CH$_2$), 36.32 (CH$_2$), 36.51 (CH$_2$), 62.67 (2-CH), 72.02 (7-CH), 79.37 (CH$_2$OH) and 79.96 (3-CH); m/z (EI$^+$) 259 (MH$^+$, 86%), 241 (32), 223 (14), 95 (11), 89 (26), 82 (15), 71 (100) and 43 (23).

$$\text{OTBS}$$

A solution of t-butyldimethylsiloxyl chloride (0.23 g, 1.55 mmol) in dichloromethane (5 ml) was added dropwise over 30 min to a mixture of the hydroxy alkyl-oxepanol (301) (0.40 g, 1.55 mmol), triethylamine (0.24 ml, 0.17 g, 1.71 mmol) and 4-dimethylaminopyridine (76 mg, 0.06 mmol) in dichloromethane (20 ml) at 0°C. The reaction was left to stir for 24 h at room temperature after which water (20 ml) was added. The aqueous phase was extracted with dichloromethane (3 x 20 ml) and the combined organic extracts washed with brine (40 ml) and dried (MgSO$_4$). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound as a colourless oil (0.33 g, 57%), (Found: C, 67.30; H, 11.88. C$_{21}$H$_{44}$O$_3$Si requires C, 67.68; H, 11.90%), (Found: M+H$^+$, 373.3138, C$_{21}$H$_{44}$O$_3$Si+H requires 373.3138); ν$_{max}$ (film)/cm$^{-1}$ 3448, 2928, 2856, 1460, 1254, 1100, 836, 814 and 776; cis isomer: δ$_H$ (400 MHz; CDCl$_3$) 0.04 (6 H, s, SiMe$_2$), 0.88 (9 H, s, t-BuSi), 0.88 (3 H, m, Me), 1.25 (8 H, br s, Me(CH$_2$)$_4$), 1.25-1.85 (12 H, m, 4-CH$_2$, 5-CH$_2$, 6-CH$_2$, CH$_2$CH$_2$ and (CH$_2$)$_4$CH$_2$), 2.30 (1 H, d, J 9.8, OH), 3.37-3.40 (1 H, m, 2-CH) and 3.51-3.71 (4 H, m, 3-CH, 7-CH and CH$_2$OSi); trans isomer: δ$_H$ (400 MHz; CDCl$_3$) 0.04 (6 H, s, SiMe$_2$), 0.88 (9 H, s, t-BuSi), 0.88 (3 H, m, Me), 1.25 (8 H, br s, Me(CH$_2$)$_4$), 1.25-1.97 (12 H, m, 4-CH$_2$, 5-CH$_2$, 6-CH$_2$, CH$_2$CH$_2$ and 240
(CH₂)₄CH₂), 3.12-3.17 (1 H, ßdt, J 2.6, 8.7, 2-CH), 3.37-3.42 (1 H, m, 7-CH) and 3.56-3.70 (3 H, m, 3-CH and CH₂OSi); m/z (Cl⁺) 373 (MH⁺, 100%), 297 (15), 241 (87), 203 (21), 145 (21), 121 (12) and 92 (12).

OTBS OTBS

2-(3-t-Butyldimethylsiloxy-1-propyl)-7-hexyl-oxepan-3-one (303)
A solution of the oxepanol (302) (0.16 g, 0.43 mmol) in dichloromethane (2 ml) was added to a suspension of pyridinium dichromate (PDC) (0.24 g, 0.65 mmol) in the same solvent (5 ml). The reaction was allowed to stir for 48 h at room temperature after which it was filtered through a short pad of silica under suction. The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound as a colourless oil (0.14 g, 88 %), (Found: M⁺, 370.2903. C₂₁H₄₂O₃Si requires 370.2903); νmax (film)/cm⁻¹ 2928, 2856, 1710, 1462, 1320, 1256 and 1100; δH (400 MHz; CDCl₃)

0.04 (6 H, s, SiMe₂), 0.87 (9 H, s, t-Bu), 0.87 (3 H, m, Me), 1.26 (8 H, br s, Me(CH₂)₄), 1.26-1.78 (9 H, m, 5-CH₂, 6-CHH, CH₂CH₂ and (CH₂)₄CH₂), 1.92-1.98 (1 H, m, 6-CHH), 2.29-2.33 (1 H, m, 4-CHH), 2.86-2.93 (1 H, ßdt, J 2.7, 12.2, 4-CHH), 3.11-3.17 (1 H, m, 7-CH), 3.59-3.64 (2 H, m, CH₂OSi) and 3.67-3.70 (1 H, m, 2-CH); m/z (Cl⁺) 371 (MH⁺, 100%), 313 (35), 239 (48), 203 (10), 145 (27) and 92 (12).

7-Hexyl-2-(3-hydroxy-1-propyl)-oxepan-3-one (281, n=1)
A mixture of the oxepanone (303) (0.09 g, 0.24 mmol), THF (1 ml), water (1 ml) and glacial acetic acid (3 ml) was heated at 40-50°C for 30 min. Ether (20 ml)
and water (20 ml) were then added and the aqueous phase extracted with ether (2 x 20 ml). The combined organic extracts were washed successively with saturated sodium bicarbonate solution (3 x 20 ml) and brine (40 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the title compound as a colourless oil (0.05 g, 82%). This displayed identical spectral properties to the same compound prepared previously. See above for data (page 232).
(E)-Diethyl 3,10-dioxo-dodec-6-enedioate (312)

A solution of ethyl acetoacetate (8.33 g, 64.1 mmol) in THF (10 ml) was added dropwise to a suspension of sodium hydride (80%, 2.02 g, 67.2 mmol) in THF (150 ml) at 0°C. After stirring for 15 min, a solution of n-butyllithium (1.6 M, 42 ml, 67.2 mmol) was added dropwise. The reaction mixture was stirred for a further 15 min at 0°C and a solution of trans-1,4-dichlorobut-2-ene (Aldrich) (2.0 g, 16 mmol) in THF (10 ml) was then added. After stirring for 2 h at 0°C, the reaction was quenched by the dropwise addition of water. The reaction was then made slightly acidic by the addition of 0.5 M hydrochloric acid. Ether (100 ml) and water (100 ml) were added and the aqueous phase extracted with ether (3 x 75 ml). The combined organic extracts were washed with brine (150 ml) and dried (MgSO4). The solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the title compound as a yellow oil (3.53 g, 41%), (Found: M+NH4+, 330.1917. C16H24O6+NH4 requires 330.1917; νmax (film)/ cm⁻¹: 2980, 1742, 1712, 1410, 1368, 1316, 1246, 1184, 1096, 1034 and 734; δH (250 MHz; CDCl₃) 1.28 (6 H, t, J 7.1, OCH₂Me), 2.24-2.30 (4 H, m, CHCH₂), 2.60 (4 H, t, J 7.1, CH₂CH₂CO), 3.42 (4 H, s, CH₂CO₂Et), 4.19 (4 H, q, J 7.1, OCH₂Me), 5.43-5.45 (2 H, m, CH=CH) and 12.09 (enol proton); m/z (CI⁺) 330 (M+NH4⁺, 100%), 313 (MH⁺, 23), 284 (16), 267 (26), 221 (6), 213 (3), 200 (2) and 183 (23).
(E)-Diethyl 2,11-bis-diazo-3,10-dioxo-dodec-6-enedioate (313)

A mixture of the di-ester (312) (0.15 g, 0.48 mmol) and tosyl azide (0.21 g, 1.06 mmol) in acetonitrile (10 ml) at 0°C was treated dropwise with triethylamine (0.15 ml, 0.11 g, 1.06 mmol). After stirring for 6 h, water (20 ml) and ether (20 ml) were added and the aqueous phase extracted with ether (3 x 20 ml). The combined organic extracts were washed with brine (40 ml) and dried (MgSO4). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound as a yellow solid (mpt. 45-47°C) (0.11 g, 65%), (Found: C 53.00; H 5.50; N 15.57. C16H20O6N4 requires C 52.75; H 5.49; N 15.38%), (Found: M+H+, 365.1461. C16H20O6N4+H requires 365.1461); v_max (CHCl3)/ cm⁻¹ 2136, 1708, 1646, 1392, 1374, 1304, 1230, 1174, 1130, 1094, 1054 and 972; δ_H (360 MHz; CDCl3) 1.33 (6 H, t, J 7.1, OCH2Me), 2.29-2.35 (4 H, m, CHCH2), 2.90 (4 H, t, J 7.2, CH2CO), 4.30 (4 H, q, J 7.1, OCH2Me) and 5.49-5.51 (2 H, m, CH=CH); δ_C (62.9 MHz; CDCl3) 14.37 (Me), 27.13 (OCH2Me), 39.98 (C=CH2), 61.41 (CH2CO), 129.53 (C=C), 161.37 (CO2Et) and 191.92 (C=O); m/z (Cl⁺) 382 (M+NH4⁺, 100%), 354 (11) and 337 (8).

(E)-Diethyl 2,11-bis-diazo-6,7-dihydroxy-3,10-dioxo-dodecandoic acid (315)

A solution of 3-chloroperbenzoic acid (50-60%, 0.57 g, 3.30 mmol) in dichloromethane (5 ml) was added dropwise to a suspension of the diazo di-ester (313) (0.80 g, 2.20 mmol) and sodium hydrogencarbonate (0.24 g) in dichloromethane (20 ml) at 0°C. After stirring at 0°C for 2 h, sodium sulphite solution (10%, 20 ml) was added. The aqueous phase was extracted with dichloromethane (3 x 10 ml) and the combined organic extracts washed with brine (20 ml). After drying (MgSO4), the solvent was removed by evaporation and the residue dissolved in a mixture of THF (24 ml) and water (6 ml). This solution was
treated with 4 drops of perchloric acid (60%) and left to stir for 3 h. Ether (20 ml) and water (20 ml) were then added and the aqueous phase extracted with ether (3 x 20 ml). The combined organic extracts were washed with brine (30 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether-ethyl acetate) to yield the title compound as a yellow solid (m.p. 105-107°C), (0.40 g, 45%), (Found: 343.1393. C₁₆H₂₂O₈+H (MH⁺-2N₂) requires 343.1393; ν_max (CDCl₃)/ cm⁻¹ 3508, 2136, 1710, 1644, 1394, 1374, 1308, 1176, 1134, 1020 and 910; δ_H (360 MHz; CDCl₃) 1.34 (6 H, t, J 7.1, OCH₂Me), 1.75-1.96 (4 H, m, CH₂CHOH), 2.83-2.84 (2 H, br s, OH), 3.05 (4 H, t, J 6.9, CH₂CO), 3.56-3.57 (2 H, m, CH₂OH) and 4.31 (4 H, q, J 7.1, OCH₂Me); m/z (CI⁺) 416 (M+NH₄⁺, 20%), 399 (MH⁺, 23), 388 (M+NH₄⁺-2N₂, 26), 381 (100), 302 (59), 276 (73), 258 (41), 190 (95), 188 (58) and 121 (34).

(E)-Diethyl 2-diazo-3,10-dioxo-dodec-6-enedioate (316)

A solution of tosyl azide (0.32 g, 1.62 mmol) in acetonitrile (30 ml) was added dropwise over 1 h to a mixture of the di-ester (312) (0.50 g, 1.60 mmol) and triethylamine (0.22 ml, 0.16 g, 1.60 mmol) in acetonitrile (100 ml). After stirring for 2 h at room temperature, most of the solvent was removed by evaporation. Ether (30 ml) and water (30 ml) were then added and the aqueous phase extracted with ether (3 x 20 ml). The combined organic extracts were washed with brine (30 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the title compound as a yellow oil (0.27 g, 50%), (Found: M+H⁺, 339.1556. C₁₆H₂₂O₆N₂+H requires 339.1556; ν_max (film)/ cm⁻¹ 2136, 1740, 1712, 1654, 1370, 1304, 1236 and 1210; δ_H (360 MHz; CDCl₃) 1.28 (3 H, t, J 7.1, CH₂CO₂CH₂Me), 1.33 (3 H, t, J 7.1, CN₂CO₂CH₂Me), 2.21-2.34 (4 H, m, CHCH₂), 2.59 (2 H, t, J 7.2, CH₂COCH₂), 2.90 (2 H, t, J 7.3, CN₂COCH₂), 3.42 (2 H, s, CH₂CO₂Et), 4.19 (2 H, q, J 7.1, CH₂CO₂CH₂Me), 4.30 (2 H, q, J 7.2, 245
CN$_2$CO$_2$CH$_2$Me), 5.45-5.49 (2 H, m, CH=CH) and 12.08 (enol proton); m/z (Cl$^-$) 337 (M-H$^+$, 15%), 309 (9), 267 (7), 266 (43), 181 (43), 137 (100), 127 (17) and 110 (10).

**General Procedure for the Alkylation of the Dianion of Diethyl 2-Oxopropylphosphonate**

![Chemical structure](image)

A solution of diethyl 2-oxopropylphosphonate (318) (1.50 g, 7.73 mmol) in THF (10 ml) was added dropwise to a suspension of sodium hydride (80%, 0.28 g, 9.28 mmol) in THF (60 ml) at 0°C. After stirring for 1.5 h at room temperature, the reaction mixture was cooled to -10°C and a solution of n-butyllithium in hexanes (1.6 M, 5.8 ml, 9.28 mmol) was added dropwise. After stirring for 20 min at 0°C, the alkyl halide (ethyl iodide or allyl bromide) (7.73 mmol) was added. The reaction mixture was then stirred for 1 h at 0°C and then carefully quenched by the addition of water (60 ml). Ether (60 ml) was added and the aqueous phase extracted with ether (3 x 40 ml). The combined ethereal extracts were washed with brine (80 ml) and dried (MgSO$_4$). The solvent was removed by evaporation and the residue chromatographed on silica to yield the respective diethyl (2-oxoalkyl)-phosphonate.

![Chemical structure](image)

**Diethyl 2-oxopentylphosphonate** (328) (38%), (Found: $M^+$, 222.1015. C$_9$H$_{19}$O$_4$P requires 222.1021); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 2964, 2932, 1712, 1258, 1024, 970; $\delta_H$ (250 MHz; CDCl$_3$) 0.91 (3 H, t, $J$ 6.0, Me), 1.33 (6 H, m, OCH$_2$Me), 1.55-1.74 (2 H, m, MeCH$_2$), 2.61 (2 H, t, $J$ 7.2, CH$_2$CO), 3.07 (2 H, d, $J$ 22.8, CH$_2$P) and 4.09-4.21 (4 H, m, OCH$_2$Me); m/z (Cl$^+$) 222 ($M^+$, 35%), 207 (38), 179 (100), 152 (65), 125 (76), 109 (72), 97 (49), 43
Diethyl 2-oxo-(5-hexenyl)phosphonate (329) (41%), (Found: $M^+$, 234.1024. $C_{10}H_{19}O_4P$ requires 234.1021); $\nu_{\max}$ (film)/cm$^{-1}$ 2980, 2928, 1714, 1442, 1394, 1368, 1258, 1190, 1164, 1098, 1052 and 966; $\delta_H$ (250 MHz; CDCl$_3$) 1.34 (6 H, m, OCH$_2$Me), 2.30-2.39 (2 H, m, CH$_2$CH=CH$_2$), 2.74 (2 H, t, J 7.2, COCH$_2$), 3.08 (2 H, d, J 22.8, CH$_2$P), 4.09-4.21 (4 H, m, OCH$_2$Me), 4.96-5.08 (2 H, m, CH=CH$_2$) and 5.70-5.90 (1 H, m, CH=CH$_2$); $m/z$ (Cl$^+$) 234 ($M^+$, 57%), 179 (75), 151 (59), 123 (100), 109 (73), 97 (63), 55 (33) and 29 (67).

**General Procedure for the Preparation of DiazO Derivatives**

Piperidine (0.17 g, 2.05 mmol) was added dropwise to a mixture of the phosphonate [(328) or (329)] (1.82 mmol) and mesyl azide (0.25 g, 2.05 mmol) in dichloromethane (20 ml) at 0°C. After stirring for 48 h at room temperature, dichloromethane (10 ml) and water (20 ml) were added. The aqueous phase was extracted with dichloromethane (2 x 20 ml) and the combined organic extracts washed with brine (40 ml) and dried (MgSO$_4$). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the respective pure diazo substrates as pale yellow oils.

$\text{O} \quad \text{O} \quad \text{O} \quad \text{Me}$

$\text{OCH}_2\text{Me}$

(330)

$\text{O} \quad \text{O} \quad \text{O} \quad \text{P}$

$\text{OCH}_2\text{Me}$

(331)

Diethyl 1-diazo-2-oxopentylphosphonate (330) (47%); $\nu_{\max}$ (film)/cm$^{-1}$ 2968, 2936, 2112, 1658, 1368, 1266, 1202, 1164, 1096, 1044 and 978; $\delta_H$
Diethyl 1-diazo-2-oxo-(5-hexenyl)phosphonate (331) (67%), (Found: $M^+$, 261.1004. C$_{10}$H$_{17}$O$_4$PN$_2$ requires 261.1004); $\nu$$_{\text{max}}$ (film)/ cm$^{-1}$ 2980, 2120, 1656, 1266, 1204, 1164, 1098, 1046, 1018 and 976; $\delta$$_H$ (250 MHz; CDCl$_3$) 1.36-1.42 (6 H, m, OCH$_2$Me), 2.36-2.44 (2 H, m, C=CH$_2$), 2.66 (2 H, t, J 7.2, COCH$_2$), 4.13-4.25 (4 H, m, OCH$_2$Me), 4.98-5.10 (2 H, m, CH=CH$_2$) and 5.77-5.84 (1 H, m, CH=CH$_2$); $m/z$ (Cl$^+$) 261 (MH$^+$, 52%), 233 (MH$^+$-N$_2$, 100), 191 (50), 135 (64), 81 (37), 65 (39), 39 (42) and 29 (44).

*Diethyl 1-isopropyloxy-2-oxopentylphosphonate (332) (46%); $\nu$$_{\text{max}}$ (film)/ cm$^{-1}$ 2972, 2932, 1716, 1258, 1114, 1052, 1026 and 974; $\delta$$_H$ (250 MHz;
CDCl$_3$ 0.93 (3 H, t, J 7.4, Me), 1.18-1.25 (6 H, m, CHMe$_2$), 1.32-1.38 (6 H, m, OCH$_2$Me), 1.55-1.70 (2 H, m, MeCH$_2$), 2.67 (2 H, t, J 7.2, CH$_2$CO), 3.69 (1 H, h, J 6.1, CHMe$_2$), 4.13-4.25 (4 H, m, OCH$_2$Me) and 4.28 (1 H, d, J 20.7, OCHP); m/z (El$^+$) 280 (M$^+$, 1%), 210 (36), 167 (100), 139 (29), 111 (35), 65 (19), 43 (34) and 27 (18).

Diethyl 1-isopropoxy-2-oxo-(1-hexenyl)phosphonate (333) (42%); $v_{\text{max}}$ (film)/ cm$^{-1}$ 2976, 1720, 1258, 1166, 1134, 1098, 1052, 1022 and 972; $\delta_H$ (250 MHz; CDCl$_3$) 1.19-1.23 (6 H, m, CHMe$_2$), 1.31-1.37 (6 H, m, OCH$_2$Me), 2.30-2.39 (2 H, m, CH$_2$CH=CH$_2$), 2.73-2.80 (2 H, m, COCH$_2$), 3.70 (1 H, h, J 6.1, CHMe$_2$), 4.13-4.25 (4 H, m, OCH$_2$Me), 4.29 (1 H, d, J 20.6, OCHP), 4.96-5.09 (2 H, m, CH=CH$_2$) and 5.70-5.90 (1 H, m, CH=CH$_2$); m/z (El$^+$) 292 (M$^+$, 1%), 210 (45), 167 (100), 139 (30), 111 (36), 83 (12), 65 (20) and 43 (20).

**General Procedure for the Alkylation of the Dianion of Phenyl 2-Oxopropylsulphoxide**

![Diagram]

A solution of phenyl (2-oxopropyl)sulphoxide (325) (2.0 g, 0.011 mol) in THF (10 ml) was added dropwise to a suspension of sodium hydride (80%, 0.40 g, 0.013 mol) in THF (40 ml) at 0°C. After stirring for 30 min at room temperature, the reaction mixture was cooled to -10°C and a solution of n-butyllithium in hexanes (1.6 M, 8.29 ml, 0.013 mol) was added dropwise. After stirring for 20 min at 0°C, the alkyl halide (ethyl iodide or allyl bromide) (0.011 mol) was added. The reaction mixture was then stirred for 1 h at 0°C and then carefully quenched by the addition of water (50 ml). Ether (50 ml) was added and the aqueous phase extracted with ether (3 x 40 ml). The combined ethereal extracts were washed with brine (80 ml) and dried (MgSO$_4$). The solvent was removed by evaporation and the residue chromatographed on silica to yield the respective pure phenyl (2-oxoalkyl)sulphoxide as a white crystalline solid.
Phenyl 2-oxopentylsulphoxide (334) (58%); δ_H (250 MHz; CDCl_3) 0.88 (3 H, t, J 7.4, Me), 1.50-1.64 (2 H, m, CH_2Me), 2.38-2.55 (2 H, m, COCH_2), 3.76 (1 H, d, J 13.6, SOCH(H)), 3.89 (1 H, d, J 13.6, SOCH(H)) and 7.51-7.66 (5 H, m, C_6H_5); m/z (CI+) 228 (M+NH_4^+, 100%), 212 (93), 211 (MH^+, 21), 194 (7) and 104 (6).

Phenyl 2-oxo-(5-hexenyl)sulphoxide (335) (55%); δ_H (250 MHz; CDCl_3) 1.78-2.34 (2 H, m, CH_2CH=CH_2), 2.55-2.65 (2 H, m, COCH_2), 3.78 (1 H, d, J 13.6, SOCH(H)), 3.89 (1 H, d, J 13.6, SOCH(H)), 4.94-5.05 (2 H, m, CH=CH_2), 5.66-5.82 (1 H, m, CH=CH_2) and 7.53-7.65 (5 H, m, C_6H_5).

**General Procedure for the Preparation of Sulphone Derivatives**

A solution of Oxone (1.32 g, 2.14 mmol) in water (10 ml) was added dropwise to a solution of the sulphoxide [(334) or (335)] (1.43 mmol) in methanol (10 ml) at -10°C. After stirring at room temperature for 4 h, water (20 ml) and dichloromethane (20 ml) were added. The aqueous phase was extracted with dichloromethane (3 x 20 ml) and the combined organic extracts washed with brine (60 ml) and dried (MgSO_4). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the respective phenyl (2-oxoalkyl)sulphone derivative as a colourless, viscous oil.
Phenyl 2-oxopentylsulphone (336) (50%), (Found: M+, 226.0664. C_{11}H_{14}O_{3}S requires 226.0664); υ_{max} (film)/ cm\(^{-1}\) 2964, 2932, 1716, 1446, 1322, 1156, 1084, 1038, 750, 738 and 688; δ\(_{H}\) (250 MHz; CDCl\(_3\)) 0.91 (3 H, t, J 7.4, Me), 1.52-1.67 (2 H, m, CH\(_2\)Me), 2.69 (2 H, t, J 7.1, COCH\(_2\)), 4.15 (2 H, s, SCH\(_2\)) and 7.55-8.03 (5 H, m, C\(_6\)H\(_5\)); δ\(_{C}\) (62.9 MHz; CDCl\(_3\)) 13.37 (Me), 16.60 (CH\(_2\)), 46.27 (COCH\(_2\)), 66.82 (SCH\(_2\)), 128.29 (C\(_6\)H\(_5\)), 129.34 (C\(_6\)H\(_5\)), 134.28 (C\(_6\)H\(_5\)), 138.73 (C\(_6\)H\(_5\)) and 198.12 (C=O); m/z (EI\(^{+}\)) 226 (M\(^{+}\), 6%), 141 (43), 125 (11), 77 (82), 71 (100), 51 (28), 43 (59) and 27 (16).

Phenyl 2-oxo-(5-hexenyl)sulphone (337) (100%); υ_{max} (film)/ cm\(^{-1}\) 1720, 1446, 1396, 1322, 1152, 1084, 1068, 1000, 920, 762, 738 and 688; δ\(_{H}\) (250 MHz; CDCl\(_3\)) 2.28-2.36 (2 H, m, CH\(_2\)CH=CH\(_2\)), 2.83 (2 H, t, J 7.2, COCH\(_2\)), 4.16 (2 H, s, SCH\(_2\)), 4.98-5.08 (2 H, m, CH=CH\(_2\)), 5.69-5.85 (1 H, m, CH=CH\(_2\)) and 7.56-7.90 (5 H, m, C\(_6\)H\(_5\)); δ\(_{C}\) (62.9 MHz; CDCl\(_3\)) 27.04 (CH\(_2\)CH=CH\(_2\)), 43.39 (COCH\(_2\)), 66.72 (SCH\(_2\)), 115.79 (CH=CH\(_2\)), 128.23 (C\(_6\)H\(_5\)), 129.35 (C\(_6\)H\(_5\)), 134.29 (C\(_6\)H\(_5\)), 136.16 (CH=CH\(_2\)), 138.71 (C\(_6\)H\(_5\)) and 197.41 (C=O); m/z (Cl\(^{+}\)) 256 (M+NH\(_4\)^{+}, 100%), 113 (7) and 96 (10).

**General Procedure for the Preparation of Diazo Derivatives**

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R\(\text{\textsuperscript{1}}\)-C=\(\text{\textsuperscript{2}}\)C\(=\text{\textsuperscript{3}}\)SO\(_2\)Ph \rightarrow R\(\text{\textsuperscript{1}}\)-C=\(\text{\textsuperscript{2}}\)C\(=\text{\textsuperscript{3}}\)SO\(_2\)Ph
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Triethylamine (0.32 ml, 0.23 g, 2.31 mmol) was added dropwise to a mixture of the sulphone [(336) or (337)] (2.10 mmol) and mesyl azide (0.28 g, 2.31 mmol) in dichloromethane (20 ml). After stirring for 24 h at room temperature, dichloromethane (20 ml) and water (40 ml) were added. The aqueous phase was extracted with dichloromethane (2 x 20 ml) and the combined organic extracts washed with brine (40 ml) and dried (MgSO\(_4\)). The solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the respective phenyl 1-diazo-(2-oxoalkyl)sulphone derivative as a pale

251
yellow oil.

\[
\begin{align*}
\text{MeCO} & \quad \text{SO}_2\text{Ph} \\
\text{N}_2 \\
(338) \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2=\text{CHCO} & \quad \text{SO}_2\text{Ph} \\
\text{N}_2 \\
(339) \\
\end{align*}
\]

*Phenyl 1-diazo-2-oxopentylsulphone (338) (42%); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2964, 2116, 1662, 1446, 1334, 1310, 1238, 1204, 1178, 1156, 1086, 724 and 686; \( \delta_H \) (250 MHz; CDCl\(_3\)) 0.88 (3 H, t, J 7.4, Me), 1.55-1.66 (2 H, m, CH\(_2\)Me), 2.53 (2 H, t, J 7.2, COCH\(_2\)) and 7.56-8.01 (5 H, m, C\(_6\)H\(_5\)); \( m/z \) (El\(^+\)) 224 (M\(^+\)-N\(_2\), 9%), 195 (9), 141 (22), 103 (31), 91 (31), 77 (100), 51 (53), 43 (44) and 27 (41).

Phenyl 1-diazo-2-oxo-(5-hexenyl)sulphone (339) (47%); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2108, 1662, 1446, 1334, 1312, 1230, 1208, 1178, 1154, 1084, 726 and 686; \( \delta_H \) (250 MHz; CDCl\(_3\)) 2.27-2.35 (2 H, m, CH\(_2\)CH=CH\(_2\)), 2.66 (2 H, t, J 7.1, COCH\(_2\)), 4.93-5.01 (2 H, m, CH=CH\(_2\)), 5.67-5.74 (1 H, m, CH=CH\(_2\)) and 7.59-8.01 (5 H, m, C\(_6\)H\(_5\)); \( m/z \) (Cl\(^+\)) 254 (M+NH\(_4\)+-N\(_2\), 100%), 222 (11), 114 (7) and 98 (3).

**General Procedure for the Preparation of Diethyl (n-t-butyl-dimethylsiloxy-2-oxo)-alkylphosphonates**

The procedure used for the preparation of the phosphonates (328) and (329) was followed. [Chromatographed on silica (light petroleum ether)].
Diethyl (5-t-butyldimethylsiloxy-2-oxo)-pentylphosphonate (340, n=1) (49%), (Found: M+H+, 353.1910. C₁₅H₃₃O₅PSi+H requires 353.1913); νₓₐₓₑₙ (film)/ cm⁻¹ 2956, 2930, 2858, 1716, 1257, 1098, 1056, 1027, 966, 836 and 777; δₜ (360 MHz; CDCl₃) 0.04 (6 H, s, SiMe₂), 0.88 (9 H, s, t-BuSi), 1.34 (6 H, t, J 7.1, OCH₂Me), 1.77-1.84 (2 H, m, CH₂), 2.70 (2 H, t, J 7.2, COCH₂), 3.09 (2 H, d, J 22.7, PCH₂CO), 3.62 (2 H, t, J 6.1, CH₂OSi) and 4.10-4.19 (4 H, m, OCH₂Me); δ_C (62.9 MHz) -5.38 (SiMe₂), 18.28 (C-Si), 25.93 (t-Bu), 26.72 (CH₂CH₂O), 40.55 (COCH₂), 42.44 (1 C, d, J 127.15, CH₂P), 61.98 (CH₂O), 62.40 (OCH₂Me), 62.45 (OCH₂Me) and 201.85 (1 C, d, J 6.0, C=O); m/z (EI⁺) 353 (MH⁺, 14%), 295 (M⁺-t-Bu, 100), 267 (M⁺-OTBS, 42), 221 (73), 179 (29), 155 (17), 123 (12) and 75 (27).

Diethyl (6-t-butyldimethylsiloxy-2-oxo)-hexylphosphonate (340, n=2) (63%), (Found: M+H+, 367.2070. C₁₆H₃₅O₅PSi+H requires 367.2070); νₓₐₓₑₙ (film)/ cm⁻¹ 2952, 2928, 2856, 1716, 1257, 1096, 1028, 970, 838 and 777; δₜ (360 MHz; CDCl₃) 0.04 (6 H, s, SiMe₂), 0.89 (9 H, s, t-BuSi), 1.34 (6 H, t, J 7.0, OCH₂Me), 1.47-1.55 (2 H, m, COCH₂CH₂), 1.60-1.66 (2 H, m, CH₂CH₂O), 2.65 (2 H, t, J 7.0, COCH₂), 3.07 (2 H, d, J 22.7, PCH₂CO), 3.61 (2 H, t, J 6.3, CH₂OSi) and 4.08-4.19 (4 H, m, OCH₂Me); m/z (EI⁺) 384 (M⁺NH₄⁺, 100%), 367 (MH⁺, 80), 325 (8) and (M⁺-t-Bu, 11).

\[
\text{TBSO} \quad \text{O} \quad \text{OEt} \quad \text{P} \quad \text{OEt}
\]

(340, n=3)

Diethyl (7-t-butyldimethylsiloxy-2-oxo)-heptylphosphonate (340, n=3) (48%), (Found: M+H+, 381.2230. C₁₇H₃₇O₅PSi+H requires 381.2228); νₓₐₓₑₙ (film)/ cm⁻¹ 2956, 2930, 2858, 1716, 1257, 1098, 1056, 1027, 966, 836 and 777; δₜ (360 MHz; CDCl₃) 0.04 (6 H, s, SiMe₂), 0.89 (9 H, s, t-BuSi), 1.34 (6 H, t, J 7.0, OCH₂Me), 1.48-1.64 (6 H, m, CH₂CH₂CH₂), 2.63 (2 H, t, J 7.3, COCH₂), 3.07 (2 H, d, J 22.8, PCH₂CO), 3.59 (2 H, t, J 6.5, CH₂OSi) and 4.10-
4.19 (4 H, m, OCH₂Me); δ_C (62.9 MHz; CDCl₃) -5.32 (SiMe₂), 16.28 (OCH₂Me), 16.37 (OCH₂Me), 18.30 (C-Si), 19.90 (COCH₂CH₂), 25.95 (t-Bu), 32.01 (CH₂CH₂OSi), 42.34 (1 C, d, J 127.6, CH₂P), 43.74 (COCH₂), 62.41 (OCH₂Me), 62.51 (OCH₂Me), 62.72 (CH₂OSi), and 201.83 (1 C, d, J 6.1, C=O); m/z (Cl+) 398 (M+NH₄⁺, 40%), 381 (MH⁺, 100), 323 (M⁺-t-Bu, 9) and 52 (31).

**General Procedure for the Preparation of Diazo Derivatives**

A solution of the phosphonate (340, n=1-3) (6.58 mmol) in THF (10 ml) was added dropwise to a suspension of sodium hydride (80%, 0.22 g, 7.24 mmol) in THF (50 ml) at 0°C. After stirring for 45 min, tosyl azide (1.43 g, 7.24 mmol) was added dropwise. The reaction mixture then allowed to stir at 0°C for 2 h. Ether (60 ml) and water (60 ml) were added and the aqueous phase extracted with ether (3 x 40 ml). The combined organic extracts were washed with brine (60 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether-hexane) to yield the respective diazo derivative as a pale yellow oil.

**Diethyl (5-t-butyldimethylsiloxy-1-diazo-2-oxo)-pentylphosphonate** (341, n=1) (62%), (Found: M+H⁺, 379.1820. C₁₅H₃₁O₅N₂PSi+H requires 379.1818); ν_max (film)/ cm⁻¹ 2956, 2929, 2124, 1660, 1266, 1102, 1048, 1020 and 837; δ_H (360 MHz; CDCl₃) 0.04 (6 H, s, SiMe₂), 0.89 (9 H, s, t-Bu), 1.38 (6 H, t, J 7.1, OCH₂Me), 1.81-1.89 (2 H, m, CH₂), 2.65 (2 H, t, J 7.3,
COCH₂), 3.64 (2 H, t, J 6.0, CH₂OSi) and 4.14-4.26 (4 H, m, OCH₂Me); δC (62.9 MHz; CDCl₃) -5.37 (SiMe₂), 16.12 (OCH₂Me), 16.23 (OCH₂Me), 18.29 (C-Si), 25.90 (t-Bu), 27.13 (CH₂), 35.96 (COCH₂), 62.03 (CH₂OSi), 63.39 (OCH₂Me), 63.48 (OCH₂Me), 128.00 (1 C, d, J 201.0, C=N₂) and 192.75 (1 C, d, J 12.8, C=O); m/z (Cl⁺) 396 (M+NH₄⁺, 15%), 379 (MH⁺, 53), 370 (49), 353 (100), 236 (34) and 156 (34).

Diethyl (6-t-butyldimethylsiloxy-1-diazo-2-oxo)-hexylphosphonate (341, n=2) (69%), (Found: M+H⁺, 393.1980. C₁₆H₃₃O₅N₂PSi+H requires 393.1975); ν max (film)/ cm⁻¹ 2931, 2121, 1659, 1257, 1164, 1101, 1048, 1019, 975, 837 and 777; δH (360 MHz; CDCl₃) 0.04 (6 H, s, SiMe₂), 0.89 (9 H, t, t-Bu), 1.38 (6 H, t, J 7.0, OCH₂Me), 1.50-1.58 (2 H, m, COCH₂), 1.66-1.74 (2 H, m, CH₂CH₂O), 2.58 (2 H, t, J 7.2, COCH₂), 3.61 (2 H, t, J 6.3, CH₂OSi) and 4.12-4.26 (4 H, m, OCH₂Me); δC (62.9 MHz; CDCl₃) -5.31 (SiMe₂), 16.13 (OCH₂Me), 16.23 (OCH₂Me), 18.33 (C-Si), 20.79 (COCH₂CH₂), 25.95 (t-Bu), 32.24 (CH₂CH₂OSi), 39.20 (COCH₂), 62.74 (CH₂OSi), 63.42 (OCH₂Me), 63.51 (OCH₂Me) and 192.82 (1 C, d, J 13.0, C=O); m/z (Cl⁺) 393 (MH⁺, 25%), 365 (MH⁺-N₂, 100), 337 (6), 307 (MH⁺-N₂-t-Bu, 31), 279 (12), 233 (13), 189 (29) and 108 (6).

\[ \text{TBSO} \quad \begin{array}{c} \text{O} \\ \text{P} \\ \text{OEt} \\ \text{N₂} \\ \text{OEt} \end{array} \quad \text{(341, n=3)} \]

Diethyl (7-t-butyldimethylsiloxy-1-diazo-2-oxo)-heptylphosphonate (341, n=3) (72%), (Found: C 49.97; H 8.39; N 7.02. C₁₇H₃₅O₅N₂PSi requires C 50.25; H 8.02; N 6.90%); ν max (film)/ cm⁻¹ 2953, 2931, 2122, 1659, 1264, 1048, 1020, 836 and 776; δH (360 MHz; CDCl₃) 0.03 (6 H, s, SiMe₂), 0.89 (9 H, s, t-Bu), 1.33-1.39 (2 H, m, CH₂CH₂CH₂OSi), 1.37 (6 H, t, J 7.1, OCH₂Me), 1.48-1.69 (4 H, m, CH₂CH₂CH₂CH₂OSi), 2.55 (2 H, t, J 7.3, COCH₂), 3.59 (2 H, d, J 6.4, CH₂OSi) and 4.13-4.26 (4 H, m, OCH₂Me); δC (62.9 MHz; CDCl₃) -5.29 (SiMe₂), 16.12 (OCH₂Me), 16.23 (OCH₂Me), 18.33 (C-Si), 24.10
General Procedure for the Preparation of Hydroxy Derivatives

The procedure used for the preparation of the hydroxy-alkyl phosphonates (240, n=1-4) was followed. [Chromatographed on silica (ether-ethyl acetate)].

Dieethyl (1-diazo-5-hydroxy-2-oxo)-pentylphosphonate (342, n=1) (57%), (Found: M+NH4+, 282.1220. C9H17O5N2P+NH4+ requires 282.1219); vmax (film)/ cm⁻¹ 3450, 3442, 3437, 2122, 1658, 1260, 1203, 1164, 1045, 1020 and 977; δH (360 MHz; CDCl3) 1.39 (6 H, t, J 7.1, OCH2Me), 1.77 (1 H, br s, OH), 1.92 (2 H, m, CH2), 2.72 (2 H, t, J 6.8, COCH2), 3.66 (2 H, t, J 5.9, CH2OH) and 4.14-4.29 (4 H, m, OCH2Me); m/z (CI+) 282 (M+NH4+, 68%), 265 (MH+, 25), 254 (M+NH4+-N2, 46), 238 (71), 221 (55), 170 (69), 104 (85) and 52 (100).

Dieethyl (1-diazo-6-hydroxy-2-oxo)-hexylphosphonate (342, n=2) (68%), (Found: M+H+, 279.1110. C10H19O5N2P+H+ requires 279.1110); vmax (film)/ cm⁻¹ 3450, 3443, 3438, 2939, 2119, 1657, 1260, 1206, 1163,
1048, 1020 and 977; \( \delta_H \) (360 MHz; CDCl3) 1.34-1.39 (6 H, m, OCH2Me), 1.56-1.64 (2 H, m, COCH2CH2), 1.72-1.80 (3 H, m, CH2CH2OH), 2.62 (2 H, t, J 7.1, COCH2), 3.65 (2 H, t, J 6.2, CH2OH) and 4.10-4.29 (4 H, m, OCH2Me); \( \delta_C \) (62.9 MHz; CDCl3) 16.12 (OCH2Me), 16.22 (OCH2Me), 20.52 (COCH2CH2), 31.89 (CH2CH2OH), 38.99 (COCH2), 61.77 (CH2OH), 63.55 (OCH2Me), 63.64 (OCH2Me) and 193.16 (1 C, d, J 13.9, C=O); m/z (EI+) 279 (MH+, 8%), 251 (MH+-N2, 100), 233 (M+H-N2-OH, 17), 205 (12), 177 (13) and 109 (15).

![Diethyl (1-diazo-7-hydroxy-2-oxo)-heptylphosphonate](image)

Diethyl (1-diazo-7-hydroxy-2-oxo)-heptylphosphonate (342, n=3) (81%), (Found: M+NH4+, 310.1532. C11H21O5N2P+NH4+ requires 310.1540); \( \nu_{\text{max}} \) (film)/ cm\(^{-1}\) 3450, 2121, 1658, 1263, 1206, 1047, 1019 and 977; \( \delta_H \) (360 MHz; CDCl3) 1.39 (6 H, t, J 7.1, OCH2Me), 1.55-1.73 (7 H, m, CH2CH2CH2 and OH), 2.58 (2 H, t, J 7.2, COCH2), 3.65 (2 H, t, J 6.5, CH2OH) and 4.12-4.29 (4 H, m, OCH2Me); \( \delta_C \) (62.9 MHz; CDCl3) 16.12 (OCH2Me), 16.23 (OCH2Me), 23.96 (COCH2CH2CH2), 25.31 (COCH2CH2), 32.33 (CH2CH2OH), 39.36 (COCH2), 62.36 (CH2OH), 63.50 (OCH2Me), 63.58 (OCH2Me) and 193.04 (1 C, d, J 13.2, C=O); m/z (Cl+) 310 (M+NH4+, 100%), 293 (MH+, 22), 284 (65), 282 (M+NH4+-N2, 26), 265 (MH+-N2, 24), 249 (23), 156 (25) and 132 (14).

**General Procedure for the Preparation of Phenyl 2-oxo-(6-siloxy)-hexyl sulfoxides**

The procedure used for the preparation of the sulfoxides (334) and (335) was followed. [Chromatographed on silica (light petroleum-ether)].
Phenyl (6-t-butyldimethylsiloxy-2-oxo)-hexylsulphoxide (347) (46%), (Found: C 60.69; H 8.15; N 9.41. C_{18}H_{30}O_3Si requires C 61.02; H 8.47; N 9.04%), (Found: M+H+, 355.1760. C_{18}H_{30}O_3Si requires 355.1763); ν_max (film)/cm⁻¹ 1705, 1252, 1109, 1098, 1088, 1025, 1021, 834, 772 and 744; δ_H (360 MHz; CDCl₃) 0.03 (6 H, s, SiMe₂), 0.88 (9 H, s, t-BuSi), 1.42-1.49 (2 H, m, COCH₂CH₂), 1.56-1.64 (2 H, m, CH₂CH₂O), 2.42-2.58 (2 H, m, COCH₂), 3.57 (2 H, t, J 6.2, CH₂OSi), 3.76 (1 H, d, J 13.6, SCH₂), 3.88 (1 H, d, J 13.6, SCH₂) and 7.53-7.67 (5 H, m, C₆H₅SO); δ_C (62.9 MHz) -5.32 (SiMe₂), 18.29 (C-Si), 19.61 (COCH₂CH₂), 25.94 (t-BuSi), 31.88 (CH₂CH₂OSi), 44.71 (COCH₂), 62.61 (CH₂OSi), 68.08 (SCH₂), 124.03 (C₆H₅), 129.43 (C₆H₅), 131.57 (C₆H₅), 143.09 (C₆H₅) and 201.52 (C=O); m/z (Cl⁺) 355 (MH⁺, 100%), 297 (M⁺-t-Bu, 23), 223 (M⁺-OTBS, 25), 171 (25), 125 (7), 99 (11) and 74 (8).

Phenyl (2-oxo-6-triisopropylsiloxo)-hexylsulphoxide (349) (51%); ν_max (film)/cm⁻¹ 2943, 2866, 1713, 1104, 1090, 1056 and 689; δ_H (360 MHz; CDCl₃) 1.05 (21 H, m, Si(i-Pr)₃), 1.44-1.52 (2 H, m, COCH₂CH₂), 1.58-1.67 (2 H, m, CH₂CH₂O), 2.43-2.58 (2 H, m, COCH₂), 3.65 (2 H, t, J 6.2, CH₂OSi), 3.76 (1 H, d, J 13.6, SCH₂), 3.88 (1 H, d, J 13.6, SCH₂) and 7.52-7.67 (5 H, m, C₆H₅SO); δ_C (62.9 MHz) 11.94 (SiCHMe₂), 18.02 (SiCHMe₂), 19.69 (COCH₂CH₂), 32.07 (CH₂CH₂OSi), 44.81 (COCH₂), 62.87 (CH₂OSi), 68.12 (SCH₂), 123.96 (C₆H₅), 124.06 (C₆H₅), 129.45 (C₆H₅), 131.60 (C₆H₅) and 201.61 (C=O); m/z (Cl⁺) 397 (MH⁺, 100%), 353 (M⁺-i-Pr, 23) and 223 (12).
A solution of 3-chloroperbenzoic acid (m-CPBA) (50-60%, 1.85 g, 5.88 mmol) in dichloromethane (10 ml) was added dropwise to a suspension of the sulphoxide [(347) or (349)] (5.88 mmol) and sodium hydrogen carbonate (0.65 g) in dichloromethane (60 ml) at 0°C. After stirring at 0°C for 2 h, sodium sulphite solution (10%, 80 ml) was added. The aqueous phase was extracted with dichloromethane (3 x 50 ml) and the combined organic extracts washed with brine (80 ml). After drying (MgSO4), the solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the respective phenyl 2-oxo-(6-siloxy)alkyl sulphone derivative as a colourless, viscous oil.

Phenyl (6-t-butyldimethylsiloxy-2-oxo)-hexylsulphone (348) (87%) (Found: M+NH4+, 388.1980. C18H30O4SSi+NH4+ requires 388.1978); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2930, 1721, 1324, 1312, 1156, 1097, 1087 and 837; \( \delta_H \) (360 MHz; CDCl\(_3\)) 0.04 (6 H, s, SiMe\(_2\)), 0.89 (9 H, s, t-BuSi), 1.45-1.53 (2 H, m, COCH\(_2\)CH\(_2\)), 1.57-1.67 (2 H, m, CH\(_2\)CH\(_2\)O), 2.74 (2 H, t, J 7.0, COCH\(_2\)), 3.60 (2 H, t, J 6.2, CH\(_2\)OSi), 4.14 (2 H, s, CH\(_2\)S) and 7.56-7.90 (5 H, m, C\(_6\)H\(_5\)SO\(_2\); \( \delta_C \) (62.9 MHz) -5.32 (SiMe\(_2\)), 18.31 (C-Si), 19.67 (COCH\(_2\)CH\(_2\)), 25.95 (t-BuSi), 31.78 (CH\(_2\)CH\(_2\)OSi), 44.17 (COCH\(_2\)), 62.59 (CH\(_2\)OSi), 66.80 (SCH\(_2\)), 128.28 (C\(_6\)H\(_5\)), 129.34 (C\(_6\)H\(_5\)), 134.28 (C\(_6\)H\(_5\)), 143.09 (C\(_6\)H\(_5\)) and 198.06 (C=O); m/z (Cl\(^+\)) 388 (M+NH\(_4\)+, 100%), 371 (MH\(^+\)), 313 (8), 231 (3) and 171 (5).

*Phenyl (2-oxo-6-triisopropylsiloxy)-hexylsulphone (350) (100%); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2943, 2866, 1721, 1324, 1311, 1155, 1106, 1086 and 687; \( \delta_H \) (360 MHz; CDCl\(_3\)) 1.05-1.07 (21 H, m, Si(i-Pr)\(_3\)), 1.48-1.70 (4 H, m, COCH\(_2\)CH\(_2\)CH\(_2\)), 2.74 (2 H, t, J 7.1, COCH\(_2\)), 3.67 (2 H, t, J 6.2, CH\(_2\)OSi), 4.14 (2 H, s, SCH\(_2\)) and 7.56-7.90 (5 H, m, C\(_6\)H\(_5\)SO\(_2\)); m/z (Cl\(^+\)) 397
(M+H+, 100%), 353 (M+-i-Pr, 23) and 223 (12).

Phenyl (1-diazo-2-oxo-6-triisopropylsiloxy)-hexyl sulphone (351)

The procedure used for the preparation of the α-diazo sulphones (338) and (339) was followed. [Chromatographed on silica (light petroleum-ether)] (0.52 g, 50%), (Found: M+H+, 439.2090. C_{21}H_{34}O_{4}SSi+H+ requires 439.2087); ν\text{max} (film)/cm\(^{-1}\) 2943, 2866, 2121, 1669, 1344, 1156, 1107, 686 and 608; δ\text{H} (360 MHz; CDCl\(_3\)) 1.03-1.04 (21 H, m, Si(i-Pr)\(_3\)), 1.45-1.69 (4 H, m, COCH\(_2\)CH\(_2\)CH\(_2\)), 2.59 (2 H, t, J 7.2, COCH\(_2\)), 3.63 (2 H, t, J 6.2, CH\(_2\)OSi) and 7.56-8.00 (5 H, m, C\(_6\)H\(_5\)SO\(_2\)); m/z (Cl\(^+\)) 456 (M+NH\(_4\)^+, 6%), 439 (MH\(^+\), 17), 274 (8), 273 (39), 218 (8), 100 (16) and 63 (13).
7.6 Experimental for Chapter Six

(Z)-1-Benzzyloxy-4-triisopropylsiloxy-but-2-ene (371)

Triisopropylsilyle chloride (10.7 g, 0.056 mol) was added dropwise to a mixture of 1-benzyloxy-4-hydroxy-but-2-ene (370) (9.0 g, 0.051 mol) and imidazole (8.61 g, 0.13 mol) in DMF (60 ml). After stirring for 24 h at room temperature, ether (60 ml) and water (60 ml) were added. The aqueous layer was extracted with ether (3 x 60 ml) and the combined organic extracts washed with brine and dried (MgSO4). The solvent was removed by evaporation and the residue chromatographed on silica [ether-petrol (60-80)] to yield the title compound as a colourless oil (17.4 g, 100%). (Found: M+H+, 335.2406. C20H34O2Si+H requires 335.2406); \( \nu_{\text{max}} \) (film)/ cm\(^{-1}\) 2943, 2891, 2866, 1463, 1455, 1092, 1069, 882, 686, 658 and 643; \( \delta_H \) (360 MHz; CDCl3) 1.02-1.26 (21 H, m, Si(i-Pr)3), 4.08 (2 H, d, J 6.1, CH20), 4.29 (2 H, d, J 5.5, OCH2), 4.50 (2 H, s, PhCH2O), 5.60-5.77 (2 H, m, CHCH) and 7.25-7.37 (5 H, m, C6H5); \( \delta_C \) (62.9 MHz; CDCl3) 11.95 (3 x C-Si), 17.98 (3 x CHMe2), 59.83 (CH2O), 65.90 (OCH2), 77.02 (OCH2Ph), 126.40 (CHCH2O), 127.63 (C6H5), 127.79 (C6H5), 128.38 (C6H5), 133.23 (CHCH2O) and 138.21 (C6H5); \( m/z \) (Cl+) 352 (M+NH4+, 100%), 335 (MH+, 74), 206 (MH+-3 x iPr, 5), 180 (13), 161 (6) and 108 (8).

(±)-(2R,3S)-1-Benzzyloxy-2,3-dihydroxy-4-triisopropylsiloxybutane (372)

A solution of osmium tetroxide in t-butanol (2.5%) (1.5 ml) was added dropwise to a mixture of the olefin (16.0 g, 0.048 mol) (371) and N-methylmorpholine-N-
oxide (60%, 11.7 g, 0.06 mol) in t-butanol (240 ml). The solution was then heated to 60°C and held at this temperature for 24 h. After cooling and quenching with sodium metabisulphite (5%, 60 ml), most of the t-butanol was removed by evaporation. Water (150 ml) and dichloromethane (150 ml) were added and the aqueous layer extracted with dichloromethane (3 x 100 ml). The combined organic extracts were washed with brine (150 ml) and dried (MgSO4). The solvent was removed by evaporation and the residue chromatographed on silica [ether-petrol 60-80)] to yield the title compound as a colourless oil (13.6 g, 77%), (Found: M+H+, 369.2461. C20H36O4Si+H requires 369.2461); νmax (film)/ cm⁻¹ 3451, 2943, 2890, 2867, 1103, 1069, 883, 695 and 683; δH (360 MHz; CDCl3) 1.07-1.10 (21 H, m, Si(i-Pr)3), 2.78 (2 H, br m, OH), 3.63-3.87 (6 H, m, CH2O, CH2OSi and CHCH), 4.57 (2 H, s, OCH2Ph) and 7.28-7.37 (5 H, m, C6H5); δC (62.9 MHz; CDCl3) 11.82 (3 x C-Si), 17.92 (3 x CHMe2), 64.57 (CH2OSi), 71.07 (OCH), 71.75 (OCH2), 71.95 (OCH), 73.54 (OCH2Ph), 127.81 (C6H5), 128.45 (C6H5), 128.38 (C6H5) and 138.21 (C6H5); m/z (Cl⁺) 386 (M+NH4⁺, 100%), 369 (MH⁺, 61), 262 (33), 174 (20), 148 (40), 125 (49), 108 (61) and 63(58).

(±)-(4R,5S)-5-Benzylxymethyl-2,2-dimethyl-4-triisopropylsiloxymethyl-1,3-dioxolane (373)

A solution of the diol (372) (12.5 g, 0.034 mol) and 2,2-dimethoxypropane (17.7 g, 0.17 mol) in dichloromethane (120 ml) was treated with a catalytic amount of p-toluenesulphonic acid (0.30 g, 3.4 mmol) and stirred at room temperature overnight. Water (80 ml) was then added and the aqueous layer extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed with brine (100 ml) and dried (MgSO4). The solvent was removed by evaporation and the residue chromatographed on silica [ether-petrol (60-80)] to yield the title compound as a colourless oil (10.5 g, 76%), (Found: M+H+, 409.2774.
C\textsubscript{23}H\textsubscript{40}O\textsubscript{4}Si+H requires 409.2774; \nu\textsubscript{max} (film)/ cm\textsuperscript{-1} 2942, 2891, 2867, 1097, 1056, 882, 696 and 682; \delta\textsubscript{H} (360 MHz; CDCl\textsubscript{3}) 1.01-1.03 (21 H, m, Si(i-Pr\textsubscript{3})), 1.37 (3 H, s, Me), 1.44 (3 H, s, Me), 3.54-3.81 (4 H, m, OCH\textsubscript{2} and CH\textsubscript{2}OSi), 4.13-4.18 (1 H, m, CHCH), 4.39-4.44 (1 H, m, CHCH), 4.52 (1 H, d, J 12.3, OCHHPh), 4.67 (1 H, d, J 12.3, OCHHPh) and 7.25-7.35 (5 H, m, C\textsubscript{6}H\textsubscript{5}); m/z (Cl\textsuperscript{+}) 426 (M+NH\textsubscript{4}\textsuperscript{+}, 36\%), 409 (MH\textsuperscript{+}, 97), 137 (40), 100 (40) and 63 (100).

(±)-(4\textit{R},5\textit{S})-5-Benzylxoxymethyl-2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane (374)

A solution of the acetonide (373) (8.0 g, 0.02 mol) in THF (320 ml) was cooled to 0°C and treated dropwise with a solution of tetrabutylammonium fluoride (1 M, 20.6 ml, 0.021 mol). After stirring for 1 h, most of the THF was removed by evaporation. Water (100 ml) and dichloromethane (100 ml) were then added and the aqueous layer extracted with dichloromethane (3 x 60 ml). The combined organic extracts were washed with brine (100 ml) and dried (MgSO\textsubscript{4}). The solvent was removed by evaporation and the residue chromatographed on silica [ether-petrol (60-80)] to yield the title compound as a colourless oil (4.24 g, 86\%), (Found: M+H\textsuperscript{+}, 253.1440. C\textsubscript{14}H\textsubscript{20}O\textsubscript{4}+H requires 253.1440); \nu\textsubscript{max} (film)/ cm\textsuperscript{-1} 3488, 2986, 2896, 1380, 1371, 1248, 1217, 1077, 1054 and 699; \delta\textsubscript{H} (360 MHz; CDCl\textsubscript{3}) 1.36 (3 H, s, Me), 1.43 (3 H, s, Me), 2.60 (1 H, br s, OH), 3.54-3.68 (2 H, m, OCH\textsubscript{2}), 3.71-3.73 (2 H, m, OCH\textsubscript{2}Ph), 4.28-4.41 (2 H, m, CHCH), 4.55 (1 H, d, J 11.8, OCH2Ph), 4.59 (1 H, d, J 11.8, OCHHPh) and 7.28-7.38 (5 H, m, C\textsubscript{6}H\textsubscript{5}); \delta\textsubscript{C} (62.9 MHz; CDCl\textsubscript{3}) 25.17 (Me), 27.74 (Me), 60.74 (OCH\textsubscript{2}), 68.37 (OCH\textsubscript{2}), 73.61 (OCH\textsubscript{2}Ph), 75.39 (OCH), 77.33 (OCH), 108.45 (CMe\textsubscript{2}), 127.84 (C\textsubscript{6}H\textsubscript{5}), 127.89 (C\textsubscript{6}H\textsubscript{5}), 128.45 (C\textsubscript{6}H\textsubscript{5}) and 137.38 (C\textsubscript{6}H\textsubscript{5}); m/z (Cl\textsuperscript{+}) 270 (M+NH\textsubscript{4}\textsuperscript{+}, 100\%), 253 (MH\textsuperscript{+}, 13), 237 (7), 195 (10), 176 (7) and 108 (7).
(±)-(4R,5S)-5-Benzylxoyethyl-2,2-dimethyl-4-(4-toluenesulphonyloxy)-methyl-1,3-dioxolane (375)

A solution of the alcohol (374) (1.8 g, 0.0071 mol) and 4-toluenesulphonyl chloride (1.50 g, 7.9 mmol) in dichloromethane (30 ml) was treated sequentially with pyridine (1.13 g, 0.014 mol) and a catalytic amount of 4-dimethylaminopyridine (0.087 g, 0.71 mmol). After stirring for 24 h, dichloromethane (60 ml) and saturated copper sulphate solution (60 ml) were added. The organic phase was washed again with copper sulphate solution (60 ml) and also with brine (60 ml). After drying (MgSO₄), the solvent was removed by evaporation and the residue chromatographed on silica [ether-petrol (60-80)] to yield the title compound as a colourless oil (2.1 g, 72%), \( \nu_{\text{max}} \) (film)/ cm⁻¹ 1366, 1218, 1189, 1177, 1096, 976, 815 and 665; \( \delta_H \) (360 MHz; CDCl₃) 1.31 (3 H, s, Me), 1.35 (3 H, s, Me), 2.43 (3 H, s, MeC₆H₄), 3.51-3.53 (2 H, m, CH₂OTs), 3.98-4.03 (1 H, m, CH), 4.18-4.22 (1 H, m, CH), 4.29-4.36 (2 H, m, CH₂OBn), 4.46 (1 H, d, J 11.9, OCH₂Ph), 4.52 (1 H, d, J 11.9, OCH₂Ph) and 7.26-7.76 (9 H, m, C₆H₅ and C₆H₄). Satisfactory analytical data could not be obtained.

(±)-(4R,5R)-5-Benzylxoy-2,2-dimethyl-4-formyl-1,3-dioxolane (377)

A solution of oxalyl chloride (0.38 ml, 0.55 g, 4.37 mmol) in dry dichloromethane (10 ml) was cooled to -60°C and treated dropwise with a solution of dimethyl sulphoxide (0.62 ml, 0.68 g, 8.73 mmol) in dichloromethane (2 ml). After stirring for 2 min, a solution of the alcohol (374) (1.0 g, 3.97 mmol) in the same
solvent (4 ml) was added dropwise maintaining the temperature at below -60°C. The reaction mixture was stirred for 20 min after which triethylamine (2.76 ml, 2.0 g, 0.02 mol) was added dropwise. After a further 5 min at -60°C, the reaction mixture was allowed to warm to room temperature. Dichloromethane (30 ml) was added and the organic phase washed with water (2 x 30 ml). The aqueous extracts were re-extracted with dichloromethane (3 x 20 ml) and the combined organic extracts washed with brine (50 ml) and dried (MgSO4). The solvent was removed by evaporation and the residue used without further purification [\(v_{\text{max}}\) (film)/ cm\(^{-1}\) 1730; \(\delta_H\) (360 MHz; CDCl3) 9.66 (CHO)]

![Chemical Structure](377)

\[
\text{(377)} \quad \xrightarrow{\text{Wittig Method}} \quad \text{BnO} \quad \text{H} \quad \text{O} \\
\text{O} \quad \text{O} \\
\text{(378)}
\]

\((\pm)-(4R,5S)-\text{Methyl 3-[5-benzyloxyethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-prop-2-enoate (378)}\)

**Wittig Method**

A mixture of the aldehyde (377) (theoretical 3.97 mmol) and methyl (triphenylphosphoranylidene)acetate (Aldrich) (1.59 g, 4.76 mmol) in toluene (35 ml) was heated at reflux for 2 h. The solvent was removed by evaporation and the residue chromatographed on silica [ether-petrol (60-80)] to yield the **title compound** as a mixture of cis- and trans-isomers in a colourless oil (1.18 g, 97%).

**Wadsworth-Emmons Method**

A solution of trimethyl phosphonoacetate (0.72 g, 3.97 mmol) in THF (5 ml) was added dropwise to a suspension of sodium hydride (80%, 0.13 g, 4.37 mmol) in THF (20 ml) at 0°C. After stirring for 30 min, a solution of the aldehyde (377) (theoretical 3.97 mmol) in the same solvent (5 ml) was added dropwise. The reaction mixture was then stirred for 2 h at room temperature. Ether (50 ml) and water (50 ml) were added and the aqueous phase extracted with ether (3 x 50 ml).
The combined organic extracts were washed with brine (75 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica [ether-petrol (60-80)] to yield the title compound as predominantly the trans-isomer in a colourless oil (0.80 g, 66%), (Found: M+NH₄⁺, 324.1811. C₁₇H₂₂O₅+NH₄ requires 324.1810; νₘₐₓ (film)/ cm⁻¹ 1724, 1380, 1308, 1258, 1216, 1196, 1166, 1090, 1030 and 700; δₜ (360 MHz; CDCl₃) 1.39 (3 H, s, Me), 1.50 (3 H, s, Me), 3.37-3.50 (2 H, m, OCH₂), 3.75 (3 H, s, OMe), 4.42-4.60 (4 H, m, OCH₂Bn and CHCH), 6.13 (1 H, dd, J 1.6, 15.6, MeO₂C₇H₇), 6.93 (1 H, d, J 5.4, 15.6, MeO₂CH₇) and 7.26-7.36 (5 H, m, C₆H₅); δₜ (62.9 MHz; CDCl₃) 25.23 (Me), 27.66 (Me), 51.65 (OMe), 68.99 (CH₂O), 73.56 (OCH₂Ph), 76.25 (CH), 76.71 (CH), 109.53 (CMₑ₂), 122.15 (CHCH=CH), 127.81 (C₆H₅), 127.91 (C₆H₅), 128.43 (C₆H₅), 37.64 (C₆H₅), 143.07 (MeO₂C₇H₇=CH) and 166.41 (C=O); m/z (Cl⁺) 324 (M+NH₄⁺, 100%), 307 (MH⁺, 10), 266 (13), 249 (8), 108 (16) and 98 (8).

(±)-(4R,5S)-Methyl 3-[5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-propanoate (379)

A solution of the olefin (378) (0.30 g, 0.98 mmol) in ethyl acetate (20 ml) was hydrogenated over platinum (IV) oxide (0.011 g, 0.049 mmol) for 12 h. The catalyst was filtered off and the solvent removed by evaporation. The residue was chromatographed on silica [ether-petrol (60-80)] to yield the title compound as a colourless oil (0.25 g, 81%), (Found: M+H⁺, 309.1700. C₁₇H₂₄O₅+H requires 309.1702; νₘₐₓ (film)/ cm⁻¹ 1736, 1372, 1370, 1248, 1218, 1168, 1098 and 1078; δₜ (360 MHz; CDCl₃) 1.36 (3 H, s, Me), 1.42 (3 H, s, Me), 1.72-1.88 (2 H, m, CHCH₂), 2.36-2.57 (2 H, m, CH₂CO₂Me), 3.46-3.57 (2 H, m, OCH₂), 3.67 (3 H, s, OMe), 4.11-4.16 (1 H, m, CHCH), 4.27-4.32 (1 H, m, CHCH), 4.52 (1 H, d, J 12.0, OCH₇H₇), 4.59 (1 H, d, J 12.0, OCH₇H₇) and 7.26-7.37 (5 H, m, C₆H₅); δₜ (62.9 MHz; CDCl₃) 24.97 (CHCH₂), 25.57 (Me), 28.16 (Me), 266 (13), 249 (8), 108 (16) and 98 (8).
30.79 (COCH₂), 51.54 (OMe), 68.70 (CH₂O), 73.52 (OCH₂Ph), 76.18 (CHCH), 108.30 (CMe₂), 127.68 (C₆H₅), 127.74 (C₆H₅), 128.41 (C₆H₅), 137.85 (C₆H₅) and 173.70 (C=O); m/z (Cl⁺) 326 (M⁺NH₄⁺, 100%), 309 (MH⁺, 47), 251 (57), 129 (21), 108 (18) and 91 (7).

\[
\begin{array}{c}
\text{BnO} \\
\text{H} \\
\text{O} \\
\text{O}
\end{array}
\rightarrow
\begin{array}{c}
\text{BnO} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\]

(±)-(4R,5S)-Methyl 5-[5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-3-oxo-pent-4-enolate (380)

Sodium hydride (80%, 0.24 g, 7.94 mmol) was added to a stirred solution of (3-methoxycarbonyl-2-oxopropylidene)-triphenylphosphorane¹⁷⁰,¹⁷¹ (1.49 g, 3.97 mmol) in THF (30 ml). This was then followed by the addition of the acetonide-aldehyde (377) (theoretical 3.97 mmol) and two drops of water. After heating the reaction mixture at 40°C for 1 h, water (30 ml) and ether (30 ml) were added. The aqueous phase was extracted with ether (3 x 20 ml) and the combined organic extracts washed with brine (50 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica [ether-petrol (60-80)] to yield the title compound as a mixture of cis- and trans-isomers in a colourless oil (0.48 g, 35%), (Found: M⁺NH₄⁺, 366.1917. C₁₉H₂₄O₆⁺NH₄ requires 366.1917); νₘₐₓ (film)/cm⁻¹ 1747, 1599, 1448, 1244, 1216, 1165, 1150, 1096 and 1076; δ_H (360 MHz; CDCl₃) 1.38-1.50 (6 H, m, Me₂C), 3.26-3.53 (4 H, m, CH₂CO₂Me and CHCH₂O), 3.71-3.76 (3 H, m, CO₂Me), 4.42-6.87 (6 H, m, OCH₂Ph, CHCH and HC=CH) and 7.25-7.36 (5 H, m, C₆H₅); m/z (Cl⁺) 348 (M⁺, 16%), 290 (14), 170 (18), 169 (100), 127 (11) and 81 (17).
(±)-(4R,5S)-Methyl 5-[5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-3-oxo-pentanoate (381)

A solution of the olefin (380) (2.31 g, 6.64 mmol) in ethyl acetate (150 ml) was hydrogenated over platinum (IV) oxide (0.075 g, 0.33 mmol) for 12 h. The catalyst was filtered off and the solvent removed by evaporation. The residue was chromatographed on silica [ether-petrol (60-80)] to yield the title compound as a colourless oil (1.35 g, 58%). (Found: M+NH4+, 368.2073. C19H26O6+NH4 requires 368.2073; ν max (film)/ cm−1 1749, 1718, 1248, 1219, 1102 and 1076; (NOE shows ring protons cis) δH (360 MHz; CDCl3) 1.32 (3 H, s, Me), 1.423 (3 H, s, Me), 1.68-1.88 (2 H, m, CH2), 2.59-2.79 (2 H, m, CH2), 3.44 (2 H, s, CH2CO2Me), 3.49-3.56 (2 H, m, OCH2), 3.73 (3 H, s, OMe), 4.08-4.13 (1 H, m, CHCH), 4.26-4.31 (1 H, m, CHC!), 4.51 (1 H, d, J 12.0, OCHPh), 4.58 (1 H, d, J 12.0, OCHPh), 7.26-7.37 (5 H, m, C6H5) and 12.02 (enol proton); δC (62.9 MHz; CDCl3) 23.32 (CH2), 25.42 (Me), 27.98 (Me), 39.59 (CH2), 48.95 (CH2CO2Me), 52.21 (2 x OCH), 68.57 (OCH2), 73.42 (OCH2Ph), 76.02 (Me), 108.15 (CMe2), 127.60 (C6H5), 128.31 (C6H5), 128.31 (C6H5), 137.66 (C6H5), 167.15 (CO2Me) and 202.05 (C=O); m/z (Cl−) 350 (M+, 17%), 349 (82), 259 (18), 184 (52), 153 (7), 127 (66) and 79 (100).

(±)-(4R,5S)-Methyl 5-[5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-2-diazo-3-oxo-pentanoate (382)

Triethylamine (0.77 ml, 0.56 g, 5.54 mmol) was added dropwise to a mixture of the ester (381) (1.14 g, 3.26 mmol) and tosyl azide (0.71 g, 3.58 mmol) in acetonitrile (45 ml) at 0°C. After stirring for 6 h at room temperature, ether (45 ml) and water (45 ml) were added. The aqueous phase was extracted with ether (3 x 30 ml) and the combined organic extracts washed with brine (60 ml) and dried (MgSO4). The solvent was removed by evaporation and the residue chromatographed on silica [ether-petrol (60-80)] to yield the title compound as a pale yellow oil (1.14 g, 93%), (Found: M+NH4+, 394.1978. C19H24O6N2+NH4 requires
394.1978); \( v_{\text{max}} \) (film)/ cm\(^{-1}\) 2133, 1725, 1657, 1372, 1312, 1244, 1215, 1191, 1170, 1102 and 1083; \( \delta_H \) (360 MHz; CDCl\(_3\)) 1.33 (3 H, s, Me), 1.42 (3 H, s, Me), 1.76-1.90 (2 H, m, CH\(_2\)), 2.91-3.09 (2 H, m, CH\(_2\)), 3.49-3.59 (2 H, m, OCH\(_2\)), 3.82 (3 H, s, Me), 4.15-4.20 (1 H, m, CHCH), 4.28-4.33 (1 H, m, CHCH), 4.52 (1 H, d, J 12.0, OCH\(_2\)Ph), 4.59 (1 H, d, J 12.0, OCH\(_2\)Ph) and 7.25-7.37 (5 H, m, C\(_6\)H\(_5\)); \( \delta_C \) (92.6 MHz; CDCl\(_3\)) 24.01 (CH\(_2\)), 25.59 (Me), 28.16 (Me), 37.06 (CH\(_2\)), 52.16 (OME), 68.82 (OCH\(_2\)), 73.49 (OCH\(_2\)Ph), 76.26 (CHCH), 108.25 (CMe\(_2\)), 127.67 (C\(_6\)H\(_5\)), 127.82 (C\(_6\)H\(_5\)), 128.36 (C\(_6\)H\(_5\)), 137.89 (C\(_6\)H\(_5\)), 161.72 (COOMe) and 192.06 (C=O); \( m/z \) (Cl\(^{+}\)) 394 (M+NH\(_4\)^{+}, 100%), 368 (85), 366 (16), 263 (11), 235 (7), 218 (13), 106 (7) and 69 (28).

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\begin{align*}
&\quad \text{BnO} \quad \text{N}_2 \\
&\quad \text{O} \quad \\text{O} \\
&\quad \text{HO} \quad \text{OMe} \\
&\quad \text{N}_2 \\
&\quad \text{O} \quad \text{OMe} \\
&\quad \text{N}_2 \\
&\quad \text{O} \quad \text{OMe}
\end{align*}
\]

(382) \quad \rightarrow \quad \text{BnO} \quad \text{H} \quad \text{OH} \quad \text{O} \quad \text{OH} \quad \text{O} \quad \text{OMe}

(383)

\((4R,5S)\)-Methyl 8-benzyloxy-2-diazo-6,7-dihydroxy-3-oxo-octanoate (383)

A mixture of the diazo acetonide (382) (0.69 g, 1.84 mmol), THF (3 ml), water (3 ml) and glacial acetic acid (9 ml) was stirred at room temperature for 24 h. Ether (20 ml) and water were then added (20 ml) and the aqueous phase extracted with ether (3 x 20 ml). The combined organic extracts were washed successively with sodium bicarbonate (3 x 20 ml) and brine (40 ml) and dried (MgSO\(_4\)). The solvent was removed by evaporation and the residue chromatographed on silica (ether) to yield the title compound as a pale yellow oil (0.21 g, 34%); \( v_{\text{max}} \) (film)/ cm\(^{-1}\) 2927, 2144, 1724, 1655, 1438, 1314, 1210, 1134, 1094 and 1075; \( \delta_H \) (360 MHz; CDCl\(_3\)) 1.76-1.98 (2 H, m, CH\(_2\)), 2.84 (1 H, br s, OH), 2.88 (1 H, br s, OH), 3.02-3.08 (2 H, m, CH\(_2\)), 3.57-3.69 (4 H, m, CHCH and OCH\(_2\)), 3.83 (3 H, s, OMe), 4.55 (2 H, s, OCH\(_2\)Ph) and 7.25-7.37 (5 H, m, C\(_6\)H\(_5\)); \( \delta_C \) (92.6 MHz; CDCl\(_3\)) 27.12 (CH\(_2\)), 36.67 (CH\(_2\)), 52.30 (Me), 71.44 (OCH\(_2\)), 72.46 (CH), 72.48 (CH), 73.66 (OCH\(_2\)Ph), 127.82 (C\(_6\)H\(_5\)), 127.91 (C\(_6\)H\(_5\)), 128.52 (C\(_6\)H\(_5\)), 137.71 (C\(_6\)H\(_5\)), 161.75 (COOMe) and 193.34 (C=O). CN\(_2\) not observed. Satisfactory analytical data could not be obtained.
2-(3-Benzyloxy-1-propylidene)-7-hexyl-oxepan-3-one (364)

The procedure used to prepare the corresponding dimethylthexylsiloxy derivative (283, n=1) was used. The requisite aldehyde, 3-(phenylmethoxy)-propanal, is a literature compound;172,173 (29%); ν\text{max} (film)/ cm\(^{-1}\) 2953, 2931, 2859, 1696, 1631, 1327, 1101, 1060, 736 and 698; δ\text{H} (250 MHz; CDCl\(_3\)) 0.88 (3 H, t, J 6.4, Me), 1.28 (8 H, br s, Me(CH\(_2\))\(_4\)), 1.28-1.83 (6 H, m, 5-CH\(_2\), 6-CH\(_2\) and (CH\(_2\))\(_4\)CH\(_2\)), 2.50-2.59 (3 H, m, CHCH\(_2\) and 4-CH\(_2\)), 2.78 (1 H, dt, J 2.9, 12.3, 4-CH\(_2\)), 3.49-3.78 (3 H, m, OCH\(_2\) and 7-CH), 4.52 (2 H, s, OCH\(_2\)Ph), 6.03 (1 H, t, J 7.5, C=CHCH\(_2\)) and 7.26-7.38 (5 H, m, C\(_6\)H\(_5\)); δ\text{C} (62.9 MHz; CDCl\(_3\)) 14.09 (Me), 22.61 (CH\(_2\)), 23.24 (CH\(_2\)), 25.78 (CH\(_2\)), 26.22 (CH\(_2\)), 29.23 (CH\(_2\)), 31.77 (CH\(_2\)), 35.79 (CH\(_2\)), 36.61 (CH\(_2\)), 42.07 (CH\(_2\)), 68.82 (OCH\(_2\)), 72.94 (OCH\(_2\)Ph), 85.10 (7-CH), 119.25 (C=CH), 127.56 (C\(_6\)H\(_5\)), 127.64 (C\(_6\)H\(_5\)), 128.35 (C\(_6\)H\(_5\)), 138.30 (C\(_6\)H\(_5\)), 154.55 (C=CH) and 200.89 (C=O); m/z (EI\(^{+}\)) 238 (MH\(^{+}\)-OCH\(_2\)Ph, 62%), 139 (7), 113 (18), 91 (100), 69 (15), 55 (45), 41 (30) and 29 (12).

2-(3-Benzyloxy-1-propyl)-7-hexyl-oxepan-3-one (385)

A mixture of the enol ether (364) (0.50 g, 1.45 mmol) and platinum (IV) oxide (0.05 g) in ethyl acetate (30 ml) was hydrogenated at atmospheric pressure for 30 min. After removing the catalyst by filtration, the solvent was removed by evaporation and the residue chromatographed on silica (light petroleum-ether) to yield the oxepanone as a mixture of diastereomers. Epimerisation and work-up was carried out as before (0.16 g, 32%), (Found: M\(^{+}\), 346.2510. C\(_{22}\)H\(_{34}\)O\(_3\) requires
346.2508); νmax (film)/ cm⁻¹ 2955, 2930, 2858, 1713, 1454, 1103, 735 and 697; δH (400 MHz; CDCl₃) 0.89 (3 H, t, J 6.7, Me), 1.27 (8 H, br s, Me(CH₂)$_4$), 1.27-1.88 (9 H, m, 5-CH₂, 6-CHH, CH₂CH₂ and (CH₂)$_4$CH₂), 1.90-1.99 (1 H, m, 6-CHH), 2.30-2.35 (1 H, m, 4-CHH), 2.87-2.94 (1 H, approx. dt, J 2.5, 12.3, 4-CHH), 3.12-3.17 (1 H, m, 7-CH), 3.49 (2 H, t, J 6.0, OCH₂), 3.69-3.72 (1 H, m, 2-CH), 4.50 (2 H, s, OCH₂Ph) and 7.27-7.37 (5 H, m, C₆H₅); δC (92.6 MHz; CDCl₃) 13.98 (Me), 22.51 (CH₂), 23.81 (CH₂), 25.54 (CH₂), 25.79 (CH₂), 29.09 (CH₂), 29.85 (CH₂), 31.68 (CH₂), 36.08 (CH₂), 37.10 (CH₂), 40.91 (CH₂), 69.74 (OCH₂), 72.76 (OCH₂Ph), 83.15 (7-CH), 86.34 (2-CH), 127.38 (C₆H₅), 127.50 (C₆H₅), 128.22 (C₆H₅), 138.41 (C₆H₅) and 217.13 (C=O); m/z (El⁺) 347 (MH⁺, 100%), 257 (11), 239 (55), 185 (14), 165 (10), 108 (15), 91 (39) and 71 (35).

![Chemical structure](image)

2-(3-Benzylxoy-1-propyl)-7-hexyl-oxepan-3-ol (386)

The procedure used to prepare the allyl oxepanol (300) was followed (82%), (Found: M+H⁺, 349.2740. C$_{22}$H$_{36}$O$_3$+H requires 349.2743); νmax (film)/ cm⁻¹ 3458, 2928, 2857, 1455, 1097, 734, 697 and 666; (cis isomer) δH (400 MHz; CDCl₃) 0.87 (3 H, t, J 6.7, Me), 1.26 (8 H, br s, Me(CH₂)$_4$), 1.26-1.85 (12 H, m, 4-CH₂, 5-CH₂, 6-CH₂, CH₂CH₂ and (CH₂)$_4$CH₂), 2.31 (1 H, d, J 9.8, OH), 3.35-3.70 (5 H, m, 2-CH, 3-CH, 7-CH and OCH₂), 4.49 (2 H, s, OCH₂Ph) and 7.27-7.34 (5 H, m, C₆H₅); δC (62.9 MHz; CDCl₃) 14.00 (Me), 17.56 (CH₂), 22.53 (CH₂), 26.11 (CH₂), 26.22 (CH₂), 29.20 (CH₂), 29.66 (CH₂), 31.74 (CH₂), 35.04 (CH₂), 36.47 (CH₂), 36.58 (CH₂), 70.23 (OCH₂), 71.91 (OCH₂Ph), 72.76 (2-CH or 7-CH), 79.07 (2-CH or 7-CH), 179.56 (3-CH), 127.38 (C₆H₅), 127.53 (C₆H₅), 128.22 (C₆H₅) and 138.46 (C₆H₅); (trans isomer) δH (400 MHz; CDCl₃) 0.87 (3 H, t, J 6.7, Me), 1.26 (8 H, br s, Me(CH₂)$_4$), 1.26-1.96 (12 H, m, 4-CH₂, 5-CH₂, 6-CH₂, CH₂CH₂ and (CH₂)$_4$CH₂), 3.11-3.16 (1 H, m, 2-CH or 7-CH), 3.36-3.40 (1 H, m, 2-CH or
7-CH), 3.47-3.53 (2 H, m OCH₂), 3.54-3.59 (1 H, m, 3-CH), 4.47-4.53 (2 H, m, OCH₂Ph) and 7.25-7.34 (5 H, m, C₆H₅); δC (62.9 MHz; CDCl₃) 13.99 (Me), 19.44 (CH₂), 22.53 (CH₂), 26.07 (CH₂), 26.11 (CH₂), 29.22 (CH₂), 31.33 (CH₂), 31.73 (CH₂), 35.33 (CH₂), 36.35 (CH₂), 37.24 (CH₂), 70.30 (OCH₂), 72.69 (OCH₂Ph), 75.90 (2-CH or 7-CH), 82.39 (2-CH or 7-CH), 84.95 (3-CH), 127.36 (C₆H₅), 127.53 (C₆H₅), 128.21 (C₆H₅) and 138.50 (C₆H₅); m/z (EI⁺) 349 (MH⁺, 100%), 331 (8), 259 (4), 241 (20), 223 (6), 108 (14), 91 (39) and 71 (49).

2-(3-Benzylloxy-1-propyl)-3-t-butyldimethylsiloxy-7-hexyl-oxepane (387)

A mixture of the alcohol (386) (0.072 g, 0.21 mmol) and 2,6-lutidine (0.048 ml, 0.044 g, 0.41 mmol) in dichloromethane (3 ml) at -20°C was treated dropwise with t-butyldimethylsilyl triflate (0.057 ml, 0.065 g, 0.25 mmol). After stirring for 2 h at 0°C, dichloromethane (10 ml) and water (10 ml) were added. The aqueous phase was extracted with dichloromethane (3 x 10 ml) and the combined organic extracts washed with brine (20 ml) and dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the title compound as a colourless oil (0.091 g, 97%), (Analysis performed on cis-isomer): (Found: M+H⁺, 463.3610. C₂₈H₅₀O₃Si+H requires 463.3607); νmax (film)/ cm⁻¹ 2954, 2929, 2856, 1253, 1098, 836, 774 and 667; δH (400 MHz; CDCl₃) 0.04 (6 H, s, SiMe₂), 0.89 (9 H, s, t-Bu), 0.89 (3 H, m, Me), 1.26 (8 H, br s, Me(CH₂)₄), 1.26-1.92 (12 H, m, 4-CH₂, 5-CH₂, 6-CH₂, CH₂CH₂ and (CH₂)₄CH₂), 3.22-3.32 (2 H, m, 2-CH and 7-CH), 3.46-3.56 (2 H, m, OCH₂), 3.76-3.80 (1 H, m, 3-CH), 4.52 (2 H, s, OCH₂Ph) and 7.23-7.39 (5 H, m, C₆H₅); δC (62.9 MHz; CDCl₃) -4.87 (SiMe), 14.01 (Me), 18.19 (C-Si), 19.52 (CH₂), 22.54 (CH₂), 25.91 (t-BuSi), 26.31 (CH₂), 26.69 (CH₂), 29.12 (CH₂), 29.23 (CH₂), 31.75 (CH₂), 34.37 (CH₂), 37.02 (CH₂), 37.24 (CH₂), 70.44 (OCH₂), 72.70 (OCH₂Ph), 74.50 (2-CH or 7-CH), 82.33
(2-CH or 7-CH), 84.72 (3-CH), 127.31 (C₆H₅), 127.47 (C₆H₅), 128.19 (C₆H₅) and 138.62 (C₆H₅); m/z (CI⁺) 463 (MH⁺, 41%), 332 (35), 313 (11), 297 (11), 223 (13), 108 (20), 91 (100) and 74 (18).

2-(3-Dimethylthexylsiloxy-1-propyl)-7-hexyl-oxepan-3-01 [(388)/(389)]

(a) Sodium Borohydride/ Cerium Chloride Method
The procedure used to prepare the allyl oxepanol (300) was followed although the reaction mixture was not treated with acid in this case (89%).

(b) Red-Al Method
A solution of the oxepanone (285) (0.05 g, 0.13 mmol) in ether (1 ml) was added dropwise to a solution of Red-Al (3.4 M in toluene, 0.06 ml, 0.2 mmol) in ether (2 ml) at 0°C. After stirring for 2 h at 0°C, water (15 ml) was added carefully. The mixture was extracted with ether (3 x 15 ml) and the combined organic extracts washed successively with water (15 ml) and brine. After drying (MgSO₄), the solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to afford the title compound as a mixture of diastereoisomers (0.039 g, 78%).

(c) L-Selectride Method
A solution of the oxepanone (285) (0.1 g, 0.25 mmol) in THF (2 ml) was added dropwise to a solution of L-Selectride (1.0 M in THF, 0.5 ml, 0.5 mmol) in THF (8 ml) at 0°C. After stirring for 2 h at 0°C, water (15 ml) was added carefully. The mixture was extracted with ether (3 x 15 ml) and the combined organic extracts washed successively with water (15 ml) and brine (15 ml). After drying (MgSO₄), the solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to afford the title compound as a single diastereoisomer (by TLC) (0.14 g, 100%), (Found: M+H⁺, 401.3450. C₂₃H₄₈O₃Si+H requires
401.3451); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 3480, 2955, 2929, 2863, 1251, 1096, 830 and 776; $\delta_H$ (250 MHz; CDCl$_3$) 0.08 (6 H, s, SiMe$_2$), 0.83-0.89 (16 H, m, Me and Si-thex), 1.27 (8 H, br s, Me(CH$_2$)$_4$), 1.27-1.71 (12 H, m, CH$_2$CH$_2$CH$_2$OSi, Me(CH$_2$)$_4$CH$_2$, 4-CH$_2$, 5-CH$_2$ and 6-CH$_2$), 2.30 (1 H, d, J 9.8, OH) and 3.53-3.72 (5 H, m, 2-CH, 3-CH, 7-CH and CH$_2$OSi); m/z (El$^+$) 401 (MH$^+$, 41%), 260 (18), 243 (100), 225 (75), 207 (10) and 161 (11).

2-(3-Dimethylthexylsiloxy-1-propyl)-3-acetoxy-7-hexyl-oxepane (390)

Acetic anhydride (0.035 ml, 0.04 g, 0.375 mmol) was added dropwise to a solution of the oxepanol [(388)/(389)] (0.1 g, 0.25 mmol) and 4-dimethylaminopyridine (1 crystal) in pyridine (2 ml). After stirring for 12 h at room temperature, water (10 ml) and ether (10 ml) were added. The aqueous phase was extracted with ether (3 x 10 ml) and the combined organic extracts washed successively with saturated copper sulphate solution (20 ml), water (20 ml) and brine (20 ml). After drying (MgSO$_4$), the solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the title compound as a colourless oil [0.076 g, 68% (81% based on recovered starting material)], (Found: M$+$H$^+$, 443.3560. C$_{25}$H$_{50}$O$_4$Si+H requires 443.3557); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 2956, 2931, 2863, 1739, 1248, 10948 and 830; $\delta_H$ (250 MHz; CDCl$_3$) (mixture of cis- and trans-isomers) 0.08 (6 H, s, SiMe$_2$), 0.83-0.89 (16 H, m, Si-thex and Me), 1.27 (8 H, br s, Me(CH$_2$)$_4$), 1.27-1.77 (12 H, m, 4-CH$_2$, 5-CH$_2$, 6-CH$_2$, CH$_2$CH$_2$CH$_2$OSi and (CH$_2$)$_4$CH$_2$), 2.03-2.07 (3 H, s, MeCO), 3.34-3.62 (4 H, m, 2-CH and 7-CH and CH$_2$OSi), 4.74-5.01 (1 H, m, 3-CH); m/z (Cl$^+$) 443 (MH$^+$, 100%), 383 (37), 297 (32), 283 (50), 223 (21), 205 (17), 145 (20) and 71 (21).
3-Benzylxy-2-(3-dimethylthexylsiloxy-1-propyl)-7-hexyl-oxepane (391)
A suspension of sodium hydride (80%, 0.009 g, 0.3 mmol) in DMF (4 ml) at 0°C was treated with a solution of the oxepanol [(388)/(389)] (0.1 g, 0.25 mmol) in the same solvent (1 ml). After stirring for 45 min at 0°C, benzyl bromide (0.03 ml, 0.043 g, 0.25 mmol) and tetrabutylammonium iodide (0.9 mg, 0.0025 mmol) were added. The reaction mixture was then stirred for 12 h at room temperature after which water (10 ml) and ether (10 ml) were added. The aqueous phase was extracted with ether (3 x 10 ml) and the combined organic extracts washed successively with water (20 ml) and brine (20 ml). After drying (MgSO₄), the solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the title compound as a colourless oil [0.096 g, 39% (88% based on recovered starting material)], (Found: M+H⁺, 491.3920. C₃₀H₅₄O₃Si+H requires 491.3920); νmax (film)/ cm⁻¹ 2955, 2929, 2862, 1455, 1251, 1097, 1029, 829 and 697; δH (250 MHz; CDCl₃) (mixture of cis- and trans-isomers) 0.08 (6 H, s, SiMe₂), 0.84-0.89 (16 H, m, Me and Si-thex), 1.26 (8 H, br s, Me(CH₂)₄), 1.26-1.86 (12 H, m, 4-CH₂, 5-CH₂, 6-CH₂, CH₂CH₂CH₂Osi and (CH₂)₄CH₂), 3.33-3.64 (5 H, m, 2-CH, 3-CH, 7-CH and CH₂Osi), 4.37-4.66 (2 H, m, OCH₂Ph) and 7.22-7.39 (5 H, m, C₆H₅); m/z (Cl⁺) 491 (MH⁺, 36%), 383 (18), 331 (27), 216 (34), 145 (18), 108 (41), 91 (100) and 71 (16).

2-(3-Dimethylthexylsiloxy-1-propyl)-3-t-butyldimethylsiloxy-7-hexyl-oxepane (392)
The procedure used to prepare the oxepane (387) was followed (0.15 g, 100%). [Chromatographed on silica (ether-light petroleum)], (Found: M+H+, 515.4320. C29H62O3Si2+H requires 515.4316); \( \gamma_{\text{max}} \) (film)/ cm\(^{-1} \) 2956, 2930, 2859, 1464, 1252, 1097, 836 and 777; \( \delta_H \) (250 MHz; CDCl\(_3\)) (mixture of cis- and trans-isomers) 0.0-0.09 (12 H, s, SiMe\(_2\)), 0.83-0.89 (25 H, m, t-BuSi, Si-thex and Me), 1.26 (8 H, br s, Me(CH\(_2\))\(_4\)), 1.26-1.83 (12 H, m, 4-CH\(_2\), 5-CH\(_2\), 6-CH\(_2\), CH\(_2\)CH\(_2\)CH\(_2\)OSi and (CH\(_2\))\(_4\)CH\(_2\)) and 3.17-3.78 (5 H, m, CH\(_2\)OSi, 2-CH, 3-CH and 7-CH); m/z (Cl\(^+\)) 515 (MH\(^+\), 100%), 383 (92), 355 (100), 297 (35), 223 (39), 92 (100), 74 (69) and 58 (48).

\[
\begin{align*}
\text{O} & \quad \text{OTDS} \\
\text{n-C}_6\text{H}_{13} & \quad \text{OH} \\
(388)/(389) & \quad \text{OTIPS} \\
\text{OTDS} & \quad \text{O} \\
(393) & \quad \text{n-C}_6\text{H}_{13}
\end{align*}
\]

2-(3-Dimethylthexylsiloxy-1-propyl)-7-hexyl-3-triisopropylsiloxy-oxepane (393)

A mixture of the alcohol [(388)/(389)] (0.20 g, 0.5 mmol) and 2,6-lutidine (0.12 ml, 0.11 g, 1.0 mmol) in dichloromethane (12 ml) at -20°C was treated dropwise with triisopropylsilyl triflate (0.16 ml, 0.18 g, 0.60 mmol). After stirring for 2 h at 0°C, dichloromethane (20 ml) and water (20 ml) were added. The aqueous phase was extracted with dichloromethane (3 x 15 ml) and the combined organic extracts washed with brine (20 ml). After drying (MgSO\(_4\)), the solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the title compound as a colourless oil (0.30 g, 100%), (Found: M+H+, 557.4785. C\(_{32}\)H\(_{68}\)O\(_3\)Si\(_2\)+H requires 557.4785); \( \gamma_{\text{max}} \) (film)/ cm\(^{-1} \) 2956, 2866, 1465, 1251, 1098, 1069, 829 and 679; \( \delta_H \) (250 MHz; CDCl\(_3\)) (mixture of cis- and trans-isomers) 0.08 (6 H, s, SiMe\(_2\)), 0.84-0.92 (16 H, m, Si-thex and Me), 1.03-1.07 (21 H, m, Si(i-Pr)\(_3\)), 1.26 (8 H, br s, Me(CH\(_2\))\(_4\)), 1.26-1.81 (12 H, m, 4-CH\(_2\), 5-CH\(_2\), 6-CH\(_2\), CH\(_2\)CH\(_2\)CH\(_2\)OSi and Me(CH\(_2\))\(_4\)CH\(_2\)) and 3.22-3.96 (5 H, m, 2-CH, 3-CH, 7-CH and CH\(_2\)OSi); m/z (Cl\(^+\)) 557 (MH\(^+\), 34%), 399 (27), 383 (100), 225 (30), 148 (39), 91 (35), 74 (28) and 58 (82).
7-Hexyl-2-(3-hydroxy-1-propyl)-3-trisopropylsiloxy-oxepane (394)

A mixture of the oxepane (393) (0.80 g, 1.44 mmol), glacial acetic acid (48 ml), THF (16 ml) and water (16 ml) was heated at 70-75°C for 2 h. After allowing to cool, water (60 ml) and dichloromethane (60 ml) were added. The organic phase was washed successively with water (40 ml), saturated sodium bicarbonate solution (5 x 40 ml) and brine (40 ml) and then dried (MgSO₄). The solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to afford the title compound as a colourless oil (0.54 g, 92%), (Analysis performed on cis-isomer): (Found: M+H+, 415.3610. C₂₄H₅₀O₃Si+H requires 415.3607); νmax (film)/ cm⁻¹ 3390, 2931, 2866, 1464, 1097, 1066, 996, 883 and 680; δH (250 MHz; CDCl₃) 0.85-1.07 (24 H, m, Me and Si(i-Pr)₃), 1.27 (8 H, br s, Me(CH₂)₄), 1.27-2.05 (12 H, m, 4-CH₂, 5-CH₂, 6-CH₂, CH₂CH₂CH₂OH and (CH₂)₄CH₂), 3.31-3.52 (2 H, m, 2-CH and 7-CH), 3.66 (2 H, m, CH₂OH) and 4.00-4.03 (1 H, m, 3-CH). OH not observed; 8C (62.9 MHz; CDCl₃) 12.71 (CHMe₂), 14.10 (Me), 18.22 (CHMe₂), 18.28 (CHMe₂), 22.21 (CH₂), 22.66 (CH₂), 26.13 (CH₂), 28.06 (CH₂), 29.36 (CH₂), 29.96 (CH₂), 31.87 (CH₂), 34.16 (CH₂), 36.67 (CH₂), 37.38 (CH₂), 63.20 (CH₂OH), 75.00 (2-CH or 7-CH), 80.52 (2-CH or 7-CH) and 83.08 (3-CH); m/z (Cl⁺) 415 (M⁺, 47%), 241 (86), 211 (17), 148 (15), 84 (39), 74 (31), 58 (100) and 45 (49).

*7-Hexyl-2-(3-hydroxy-1-propyl)-oxepan-3-ol (395)

A solution of the oxepane (393) (0.14 g, 0.25 mmol) in THF (5 ml) at 0°C was
treated dropwise with hydrogen fluoride-pyridine complex (CAUTION) (0.3 ml). After stirring for 30 min at 0°C and 1 h at room temperature, water (10 ml) and ether (15 ml) were added. The aqueous phase was extracted with ether (3 x 10 ml) and the combined organic extracts washed successively with saturated copper sulphate solution (20 ml) and brine (20 ml). After drying (MgSO₄), the solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the hydroxy-alkyl oxepane (394) (0.076 g, 73%). This compound was then dissolved in THF (3 ml) and again exposed to hydrogen fluoride-pyridine complex (0.3 ml) at 0°C. On stirring for 24 h at room temperature followed by work-up as before, evaporation of the solvent and chromatography on silica (ether) afforded the title compound as a colourless oil (0.024 g, 51%); νmax (film)/cm⁻¹ 3350, 2928, 2859 and 1062; δH (250 MHz; CDCl₃) (mixture of cis- and trans-isomers) 0.88 (3 H, t, J 7.0, Me), 1.28 (8 H, br s, Me(CH₂)₄), 1.28-2.06 (12 H, m, 4-CH₂, 5-CH₂, 6-CH₂, CH₂CH₂CH₂OH and (CH₂)₄CH₂), 3.43-3.73 (5 H, m, 2-CH, 3-CH, 7-CH and CH₂OH). OH not observed.

2-(2-formyl-ethyl)-7-hexyl-3-triisopropylsiloxy-oxepane (396)
A solution of dimethyl sulphoxide (0.19 ml, 0.21 g, 2.66 mmol) in dichloromethane (1.0 ml) was added dropwise to a solution of oxalyl chloride (0.12 ml, 0.17 g, 1.33 mmol) in dichloromethane (5 ml) at -60°C. After stirring for 2 min, a solution of the hydroxy-alkyl oxepane (394) (0.50 g, 1.21 mmol) in the same solvent (2.0 ml) was added. The reaction mixture was then allowed to stir at -60°C for 20 min. Triethylamine (0.84 ml, 0.61 g, 6.04 mmol) was added and the reaction mixture allowed to come to room temperature after stirring at -60°C for 5 min. Water (30 ml) and dichloromethane (30 ml) were added and the aqueous layer extracted with dichloromethane (3 x 30 ml). The combined organic extracts were washed with brine (30 ml) and dried (MgSO₄). The solvent was removed by evaporation and the
crude material used in the next step without further purification or characterisation.

2-(4-Diethyl phosphono-3-hydroxy)-1-butyl-7-hexyl-3-triisopropylsiloxy-oxepane (397)
n-Butyllithium (1.6 M, 0.83 ml, 1.33 mmol) was added dropwise to a solution of diethyl methylphosphonate (0.18 g, 1.21 mmol) in THF (20 ml) at -78°C. After stirring for 30 min at -78°C, a solution of the aldehyde (396) (theoretical 1.21 mmol) in THF (5 ml) was added dropwise. The reaction mixture was allowed to stir at 0°C for 2 h after which time water (20 ml) and ether (20 ml) were added. The aqueous phase was extracted with ether (3 x 20 ml) and the combined organic extracts washed with brine (50 ml). After drying (MgSO4), the solvent was removed by evaporation and the residue chromatographed on silica (ether-light petroleum) to yield the title compound as a colourless oil (0.32 g, 47%), (Found: M+H+, 565.4040±0.003. C29H61O6SiP+H requires 463.4053); νmax (film)/cm⁻¹ 3392, 2931, 2866, 1465, 1231, 1098, 1061, 1031 and 963; δH (250 MHz; CDCl₃) (mixture of cis- and trans-isomers) 0.88 (3 H, t, J 6.9, Me), 1.05-1.07 (21 H, s, Si(i-Pr)₃), 1.21-1.97 (28 H, CH₂PO(OEt)₂, (CH₂)₂, 4-CH₂, 5-CH₂, 6-CH₂ and Me(CH₂)₅) and 3.21-4.17 (8 H, m, 2-CH, 3-CH, 7-CH, CHOH and OCH₂Me). OH not observed; m/z (CI+) 565 (MH⁺, 100%), 521 (28), 391 (25), 221 (46) and 139 (21).
2-(4-Diethyl phosphono-3-oxo)-1-butyl-7-hexyl-3-triisopropylsiloxy-oxepane (398)

A solution of the oxepane (0.25 g, 0.44 mmol) (397) in dichloromethane (1 ml) was added to a suspension of pyridinium chlorochromate (PCC) (0.14 g, 0.66 mmol) in the same solvent (4 ml). After stirring the reaction mixture for 3 h at room temperature, light petroleum (5 ml) was added. The mixture was stirred for a further 15 min and then filtered through a short pad of silica. The silica was washed well with ether and the solvent then removed by evaporation. The residue was chromatographed on silica (ether) to furnish the title compound as a colourless oil [0.11 g, 45% (65% based on recovered starting material)], (Found: M+H+, 563.3900. C_{29}H_{59}O_{6}SiP+H requires 563.3897); ν_{max} (film)/ cm^{-1} 2931, 2868, 1717, 1258, 1098, 1028, 968 and 667; 8_{H} (250 MHz; CDCl_{3}) (mixture of cis- and trans-isomers) 0.88 (3 H, t, J 6.9, Me), 1.05-1.07 (21 H, s, Si(i-Pr)_{3}), 1.21-1.87 (26 H, 4-CH_{2}, 5-CH_{2}, 6-CH_{2}, Me(CH_{2})_{5}, (CH_{2})_{2} and OCH_{2}Me) and 2.73-4.09 (5 H, m, CH_{2}PO(OEt)_{2}, 2-CH, 3-CH and 7-CH) and 4.09-4.20 (4 H, m, OCH_{2}Me); m/z (Cl+) 563 (M+H+, 46%), 519 (100), 389 (60) and 324 (4).
Appendix A

**Compound Index for Experimental Section**

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Appendix B

Spectroscopic Data Additions

Benzenesulphonyl-ethoxy carbonyl-diazomethane (177), Mpt. 51-53°C, (Found: M+H+, 255.0440. C_{10}H_{10}O_{4}SN_{2}+H requires 255.0044); m/z (Cl+) 272 (M+NH_{4}+, 100%), 255 (MH+, 94), 246 (58), 163 (18), 125 (21) and 105 (15).

Ethyl 2-isopropoxy-3-phenyl-2-propenoate (225), (Found: M+H+, 235.1334. C_{14}H_{18}O_{3}+H requires 235.1334); m/z (Cl+) 252 (M+NH_{4}+, 7%), 235 (MH+, 100), 210 (13), 193 (32) and 118 (44).

2-(5-Dimethyloctylsiloxy-1-pentylidene)-7-hexyl-oxepan-3-one (283, n=3), (Found: M+H+, 425.3451. C_{25}H_{48}O_{3}Si+H requires 425.3451); m/z (Cl+) 425 (MH+, 25%), 407 (21), 341 (100), 265 (50), 241 (33), 169 (25), 145 (21) and 92 (19).

Diethyl 1-diazo-2-oxopentylphosphonate (330), (Found: M+H+, 249.1004. C_{9}H_{17}O_{4}PN_{2}+H requires 249.1004); m/z (Cl+) 249 (MH+, 100%), 223 (86), 179 (43) and 164 (60).

Diethyl 1-isopropoxy-2-oxopentylphosphonate (332), (Found: M+H+, 281.1518. C_{12}H_{25}O_{5}P+H requires 281.1518).

Phenyl 1-diazo-2-oxo-(5-hexenyl)sulphone (339), (Found: M+H+, 265.0647. C_{12}H_{12}O_{3}SN_{2} requires 265.0647).

Phenyl (2-oxo-6-triisopropylsiloxy)-hexylsulphoxide (349), (Found: M+H+, 397.2233. C_{21}H_{36}O_{3}SSi+H requires 397.2233).

Phenyl (2-oxo-6-triisopropylsiloxy)-hexylsulphone (350), (Found: M+H+, 413.2182. C_{21}H_{36}O_{4}SSi+H requires 413.2182).

7-Hexyl-2-(3-hydroxy-1-propyl)-oxepan-3-ol (395), (Found: M+H+, 259.2273. C_{15}H_{30}O_{3}+H requires 259.2273); m/z (Cl+) 259 (MH+, 100%), 241 (100), 223 (24) and 71 (57).
References

57. (a) A. Loose, J. Prakt. Chem., 1909, 79, 507; (b) L. Wolff, Annalen, 1912, 394, 23.
1982, 47, 1284.


96. The procedure used to prepare this compound was developed by K. J. Doyle, University of Loughborough.

97. In addition to the method described in the Experimental Section to prepare this compound, another procedure, involving the initial heating of the sodium salt of benzenesulphonic acid with ethyl bromoacetate followed by diazo transfer with p-acetamidobenzenesulphonyl azide or 1-ethyl-2-chloropyridinium tetrafluoroborate/sodium azide has been successfully developed (K. J. Doyle, University of Loughborough).


102. (a) M. Kennedy, M. A. McKervey, A. R. Maguire and G. H. P. Roos, *J. Chem. Soc., Chem. Commun.*, 1990, 361; (b) G. H. P. Roos and M. A. McKervey,

103. Many thanks to Professor M. A. McKervey (University of Belfast) for donating samples of these chiral rhodium catalysts for testing.


108. Prepared in an analogous fashion to the ethyl derivative (Experimental Section, Chapter 7)


155. (a) A. N. Pudovik and N. M. Lebedeva, *Chemical Abstracts*, 50, 3219e; (b) A. N. Pudovik, *Chemical Abstracts*, 50, 11230g.


180. Thanks to Dr. Oliver Howarth (SERC 400MHz NMR Service, University of Warwick) for helpful comments regarding NMR analysis.