TEMPLATE DIRECTED C-H INSERTION REACTIONS FOR STEREOCONTROLLED SYNTHESIS OF HETEROCYCLES

ERHUNMWUNSE, OROBOSA, MARVIS

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TEMPLATE DIRECTED C-H INSERTION REACTIONS FOR STEREOCONTROLLED SYNTHESIS OF HETEROCYCLES

Orobosa Marvis Erhunmwunse

Thesis submitted for the qualification Doctor of Philosophy

University of Durham

Department of Chemistry

2009
Abstract

Template Directed C-H Insertion Reactions for Stereocontrolled Synthesis of Heterocycles

Orobosa Marvis Erhunmwunse, PhD

Non aromatic heterocycles and their analogues are abundant in a large variety of bioactive natural products and continue to play crucial roles in modern day chemotherapy. The bioactivities of these heterocycles are highly dependent on the stereochemistry of the substituents and therefore the development of elegant new methodologies for the selective construction of heterocycles remains attractive to the synthetic chemist.

Described in this thesis, is a tandem methodology for the stereocontrolled synthesis of highly functionalised oxygen heterocycles. The strategy adopted resulted in the successful synthesis of 2,3,4,5-tetrasubstituted tetrahydrofurans and 2,3,4,5,6-pentasubstituted oxepanes. The key step involves catalytic C-H insertion of diazocarbonyl acetal templates. Diazocarbonyl substrates representing the three classes of carbenoids were synthesised. In the foremost route that led to the first class, the diazoacetoacetates were obtained from the oxidation of the diazoketols prepared by an aldol type condensation between the aldehyde acetics and ethyl diazoacetate. Good yields of the diazoketols and the required diazoacetoacetates were isolated. Importantly, the sequence led to the development of a general and efficient one-pot protocol for the synthesis of diazoacetoacetate derivatives. The synthesis of the vinyldiazoketones was equally achieved from the aldehyde acetals in 3 steps involving diazotransfer onto the vinylketones prepared by oxidation of the allylalcohols which resulted from treating the aldehyde acetals with allylmagnesium bromide. Good yields of products were achieved in all 3 steps. The aldehyde acetals were synthesised following a Swern oxidation protocol from the corresponding alcohols prepared from the ester acetals which were synthesised by ketalisation of 2-substitutedpropan-1,3-diols with pyruvate esters. Initial efforts in screening for catalyst suitable for the decomposition of the diazoacetoacetates resulted in the novel synthesis of the Barceloneic lactone derivatives in respectable yields. Further efforts led to the preparation of the achiral rhodium (II) heptafluorobutyramide which proved successful for the decomposition of the vinyldiazoketones to give the bicyclic acetals in moderate yields. An asymmetric synthesis of the bicyclic acetals was also achieved. Finally, the reductive cleavage of the bicyclic acetals in a regio- and stereoselective fashion resulted in the highly functionalised tetrahydrofurans and oxepanes.
Declaration:

The work in this thesis was carried out in the Department of Chemistry at the University of Durham between 1\textsuperscript{st} October 2006 and 15\textsuperscript{th} October 2009. It has not been submitted for any other degree and is the author’s own work, except where acknowledged by reference.

Copyright:

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Acknowledgements

I would foremost want to express my total submission to BABA GOD for his infinite mercies over the last three years. The completion of this work reaffirms that HE is the Beginning and the Ending.

I would now like to thank my supervisor, Dr. Patrick Steel for giving me the rare opportunity to study in his laboratory. The time spent in personally ‘moulding’ me into the chemist that I am aspiring to be has been invaluable and I am extremely grateful and indebted to him for his patience.

On a personal note, I would also want to thank my family especially my amiable wife Princess Mirhina and my lovely angels Ivie and Isiuwa for the love and understanding showed me. My parents, Pa. and Mrs. Pius Erhunmwunse for the undiluted love and steadfastness you continue to give me. My brothers, sisters and all my niece and nephews are also remembered at this time and I want to say thank you guys for everything, in particular the support and prayers. You guys are the best. Special thanks also go to my in-laws, especially my mother in-law for the love and support.

Over the years I have been fortunate to be taught by inspirational teachers, I would like to extend my thanks to Dr. Mrs Mary Edema for her mentoring and encouragement into the realms of organic chemistry. Prof. Felix Okieimen, Prof. Nosa Eghafona, Dr. Emma Ukpebor, Mrs Tina Ukpebor and all the staff members of Chemistry Department, University of Benin who I cannot name in person due to space constraints. I acknowledge and thank you all for believing in me.

I also want to specially thank Dr. Kathryn Knight and Dr. Liz Grayson for proof reading this thesis as well as for all the valuable comments.

My friends, my friends, my friends ‘una wan begin shout, nothing dey happen’. ‘Una turn don reach’. With as much owed respect, I want to thank all my friends for their trust and for keeping the faith. ‘Una know una selves’.

Also remembered are my lab mates over the past years fatboy Tom, Kathryn Knight, welsh Nick, big bear Pete, polish Michal, John D., John Mina, jackie chan Hazmi, Matt, John S., Willbo baggins and Harley for the fun shared in the lab.

Special thanks go to Dr. Alan Kenwright, Katherine and Ian for the NMR work. Drs. Mike Jones, Jackie Mosely, David Parker and Ms Lara (mass spectroscopy), Ms Jaroslava Dostal (elemental analysis).

Finally, I would like to thank the Commonwealth Scholarship Commission (CSC) for funding. I dedicate this thesis to GOD ALMIGHTY and my Family, THE ERHUNMWUNSE’S.
Abbreviations

$\alpha$ Observed optical rotation in degrees
[$\alpha$] Specific rotation
$\delta$ / ppm Chemical shift / Parts per million
ABSA Acetamidobenzenesulfonyl azide
Ac Acetyl
acac Acetylacetonate
acam Acetamide
Anal Elemental analysis
aq Aqueous
Ar Aryl
ATR Attenuated total reflection
Bn Benzyl
cap Caprolactam
cat. Catalyst
cm Centimetre
$\text{cm}^{-1}$ Wavenumbers
CM Complex mixture(s)
conc. Concentrated
COSY Correlation spectroscopy
d Doublet (spectral)
DOSP $4\text{-alkyl(C}_{11}\text{-C}_{13})\text{phenylsulfonyl-2R-pyrroldinecarboxylate}$
ds Diastereoselectivity
DBU $1,8\text{-Diazabicyclo[5.4.0]undec-7-ene}$
DCM Dichloromethane (CH$_2$Cl$_2$)
$\text{dd}$ Doublet of doublets
$\text{ddd}$ Doublet of doublet of doublets
DEAD Diethyl azodicarboxylate
DIBAL Diisobutylaluminium hydride
DMF N,N-Dimethylformamide
DMSO Dimethyl sulfoxide
EDA Ethyl diazoacetate
e.g For example
EI Electron impact
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<td>eq</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>Et₃N</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatography</td>
</tr>
<tr>
<td>GC / MS</td>
<td>Gas Chromatography / Mass Spectroscopy</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>hfacac</td>
<td>Hexafluoro acetylacetonate</td>
</tr>
<tr>
<td>hfb</td>
<td>Heptafluorobutyramide</td>
</tr>
<tr>
<td>HMDS</td>
<td>bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear shift correlations via multiple bond connectivities</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear single quantum correlation</td>
</tr>
<tr>
<td>IBX</td>
<td>Iodoxybenzoic acid</td>
</tr>
<tr>
<td>i.e</td>
<td>in extenso</td>
</tr>
<tr>
<td>IR</td>
<td>Infra red</td>
</tr>
<tr>
<td>J / Hz</td>
<td>Coupling constant / Hertz</td>
</tr>
<tr>
<td>L.A</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>Ln</td>
<td>n Ligands</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet (spectral)</td>
</tr>
<tr>
<td>M</td>
<td>mol/l</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MEPY</td>
<td>2-methyl-pyrrolidinecarboxylate</td>
</tr>
<tr>
<td>min</td>
<td>Minutes</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole(s)</td>
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<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
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<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>MsN₃</td>
<td>Mesylazole</td>
</tr>
<tr>
<td>MTPA</td>
<td>α-methoxy-α-(trifluoromethyl)phenylacetic acid</td>
</tr>
<tr>
<td>MTPA-Cl</td>
<td>α-methoxy-α-trifluoromethylphenylacetyl chloride</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-Butyl</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
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<tr>
<td>NOESY</td>
<td>Nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>Nu</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>OAc</td>
<td>Acetate</td>
</tr>
<tr>
<td>oct</td>
<td>Octanoate</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium dichromate</td>
</tr>
<tr>
<td>pfb</td>
<td>Perfluorobutrate</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>Pivaloyl (2,2-dimethylacetyl)</td>
</tr>
<tr>
<td>ppm</td>
<td>Part(s) per million</td>
</tr>
<tr>
<td>PTAD</td>
<td>1-adamantyl-N-phthalimidoacetate</td>
</tr>
<tr>
<td>PTTL</td>
<td>N-phthaloyl-tert-leucinate</td>
</tr>
<tr>
<td>q</td>
<td>Quartet (spectral)</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet (spectral)</td>
</tr>
<tr>
<td>sec-Bu</td>
<td>sec-Butyl</td>
</tr>
<tr>
<td>SM</td>
<td>Starting material</td>
</tr>
<tr>
<td>t</td>
<td>Triplet (spectral)</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMSOTf</td>
<td>tert-Butyldimethylsilyl trifluoromethanesulfonate</td>
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<tr>
<td>t-Bu</td>
<td>tert-Butyl</td>
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<tr>
<td>TBSP</td>
<td>1-(4-tert-butylphenyl)sulfonylpyrrolidinocarboxylate</td>
</tr>
<tr>
<td>Temp</td>
<td>Temperature</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate (trifluoromethanesulfonyl)</td>
</tr>
<tr>
<td>tfa</td>
<td>Trifluoroacetate</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
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<tr>
<td>TMEDA</td>
<td>$N',N',N',N'$-tetramethyl-1,2-ethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>tpa</td>
<td>Triphenylacetate</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetrapropyl ammonium perruthenate</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
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<tr>
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<tbody>
<tr>
<td>1D</td>
<td>Unidimensional</td>
</tr>
<tr>
<td>2D</td>
<td>Bidimensional</td>
</tr>
<tr>
<td>18-crown-6</td>
<td>1,4,7,10,13,16-Hexaoxacyclooctadecane</td>
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1.1 General Introduction

The unique biological activity of non-aromatic heterocycles and their derivatives play crucial roles in the modern day chemotherapy of a wide range of illnesses. This, when coupled with the range of intriguing structures for example \textbf{1}, \textbf{2} and \textbf{3} has provided a major synthetic goal for the organic chemist (Scheme 1.1).\textsuperscript{1} Such a challenge requires the development of new efficient methods of preparation.

\textbf{Scheme 1.1}

This project seeks to address this goal by developing efficient methodologies for the synthesis of highly substituted oxygen heterocycles in particular barceloneic lactones, tetrahydrofurans and oxepanes. The strategy adopted seeks to explore a sequence involving catalytic C-H insertion reactions of diazo acetals \textbf{4} followed by either high temperature or stereoselective reductive cleavage of the resultant bicyclic acetals \textbf{5} (Scheme 1.2)
Chapter I: Introduction

Although several methods for the construction of 2,5-disubstituted and 2,3,5-trisubstituted THFs have been extensively documented, fewer methods exist for the 2,3,4,5-tetrasubstituted THFs. Whilst, there is yet to be any reported synthesis for the barceloneic lactones and 2,3,4,5,6-pentasubstituted oxepanes.

The remainder of this chapter provides the background to the synthetic methodology adopted, focusing on carbene chemistry with a particular emphasis on carbenes derived from α-diazocarbonyl compounds. Chapter II will discuss the synthesis of the key aldehyde acetals while their elaboration to the diazoacetoacetates, which are known carbene precursors, will be described in Chapter III. The four subsequent chapters will discuss the synthesis of the barceloneic lactones, the enantioselective preparation of the bicyclic acetal core, and the reductive cleavage reactions that led to the synthesis of the THFs and oxepanes. Following a general conclusion, Chapter IX will provide comprehensive experimental procedures and both spectroscopic and analytical data of the compounds obtained in the course of this study.
1.2 C-H activation

The activation of unfunctionalised C-H bonds for the formation of carbon-carbon bonds has been extensively studied over the past two decades. However, C-H activation by metal-carbenoid induced C-H insertion is generally not included in reviews on C-H activation.

1.2.1 C-H activation by transition metals

Transition metals for example palladium and ruthenium have been widely developed to activate C-H bonds and subsequently form C-C bonds in a single preparative step. One of the generally accepted mechanisms for this process is oxidative addition, however efforts towards achieving a catalytic process have proved very challenging. A potential alternative with great promise, in terms of the catalytic process, is C-H activation by metal-carbenoids.

1.2.2 C-H activation by metal-carbenoids

The functionalisation of unactivated C-H bonds using metal-carbenoids is well documented. In this process, the metal atom is not thought to interact directly with the C-H bond as a metal-carbenoid undergoes the insertion. The attractive feature of metal-carbenoid induced C-H insertion is that it is catalytic (Scheme 1.3).

The cycle involves the decomposition of the diazo compound 6 by the metal complex 8 to generate molecular nitrogen and a high-energy carbenoid intermediate 7. Subsequent C-H insertion gives the functionalised product 9 and regenerates the active catalyst.

Scheme 1.3
Chapter I: Introduction

The subsequent sections will describe in more details the chemistry of metallocarbenes after a general summary of carbenes

1.3 Carbenes

1.3.1 Introduction

Carbenes can be defined as ‘divalent’ neutral carbon intermediates in which a carbon atom bears two covalent bonds to other groups and two non-bonding electrons. Carbenes exist in two spin states. A singlet carbene has two antiparallel spin electrons in an $sp^2$ orbital leaving a vacant $p$-orbital. While in the triplet carbene, both the $sp^2$ and $p$-orbitals contain one electron with parallel spins, and in many cases considered a diradical (Scheme 1.4).

![Singlet and Triplet States of Carbenes](image)

Scheme 1.4

The difference in energy between singlet and triplet states is small (≈32-42 kJ/mol for methylene carbene). The electronic properties of carbenes are affected by the nature of the substituents on the carbon atom. Substituents with $\pi$-donor character stabilise the singlet state by donating electron density into the vacant $p$-orbital on carbon. Thus, the carbene derived from dichloromethane (:\text{CCl}_2) is in a ground state singlet whereas methylene and phenylcarbene (:\text{CH}_2, \text{PhCH}_2) are in a ground state triplet.

Carbenes can be further classified into three distinct classes based on their chemistry:

- free carbenes,
- stable carbenes,
- reactive transition metal carbene complexes.

Free carbenes were the first to be investigated in some detail. They were long known to be capable of inserting into C-H bonds, but their high reactivity leads to low yields and selectivity, thereby limiting their use.
Consequently, in order to enhance the synthetic potential of carbenes, it was necessary to modulate their reactivity. This has been achieved in two ways by utilising steric and/or electronic factors. For example the distillate red oil phosphinosilyl carbene $10^8$, which is the only stable carbene with potential for C-H insertion$^9$ and 1,3-di-1-adamantylimidazol-2-yldene $11^{10}$, the first crystalline carbene, reported in 1991, which has found wide applications including complex formation (Scheme 1.5).

![Scheme 1.5](image)

In between these two extremes are transition metal carbene complexes referred to as carbenoids or metallocarbenes, which provide reagents with considerable synthetic potential. Unlike the previous two classes, these species acquire stabilization by interaction with the metal and through this interaction they become more selective in their behaviour. Metallocarbenes are conveniently generated by catalytic decomposition of diazocarbonyl compounds. The metal catalyst needs to have an accessible site for coordination with the diazo-compound. After coordination, molecular nitrogen is released and the carbenoid intermediate is generated (Scheme 1.3). The metal catalyst binds to the carbene through strong $\sigma$-acceptor interactions and weak $\pi$-back-donor interactions, which stabilise the carbene without affecting its electrophilic character. The degree of electrophilicity of the metallocarbenoids and their stability are governed by the nature of the metal catalyst, its ligands and the nature of the substituents adjacent to the carbene carbon. Much of this will be put into context in subsequent sections of this chapter.
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1.4 Metallocarbenes

1.4.1 Generation of metallocarbenes

Early investigations into diazo chemistry\textsuperscript{11} revealed that diazocarbonyl compounds can be catalytically decomposed by transition metals, thereby generating metallocarbenes. Earliest work in this regard employed the use of insoluble copper catalysts (Cu powder, Cu bronze, Cu$_2$O, CuO, CuSO$_4$, CuCl and CuBr).\textsuperscript{12} Although these catalysts are still being employed today, their use has significantly decreased with the intervening use of homogeneous copper catalyst (e.g Cu (I) triflate, Cu(acac)$_2$).\textsuperscript{13} In the late 1970s, Teyssie and co-workers\textsuperscript{14} discovered that rhodium carboxylates also facilitate nitrogen loss, and since then a wide range of transition metal complexes (e.g rhodium, palladium and cobalt based) have been studied extensively and used for the decomposition of $\alpha$-diazocarbonyl compounds.

1.5 Preparation of $\alpha$-diazocarbonyl compounds

As stated in the preceding section, diazocarbonyl compounds are metallocarbene precursors and do have a long history of useful applications in organic chemistry. They are easily prepared from readily accessible precursors and can be induced to undergo a large variety of applications. The first reported synthesis of any $\alpha$-diazocarbonyl compound was the diazotisation of glycine 12 (Scheme 1.6)\textsuperscript{15}.

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {H$_2$N\hspace{1mm}C\hspace{1mm}O\hspace{1mm}H} ;
  \node (B) at (3,0) {N$_2$\hspace{1mm}C\hspace{1mm}O\hspace{1mm}H} ;
  \node (C) at (6,0) {N$_2$\hspace{1mm}C\hspace{1mm}O\hspace{1mm}Et} ;
  \draw [->] (A) -- node {HNO$_2$} (B) ;
  \draw [->] (B) -- node {\hspace{2mm}Et} (C) ;
\end{tikzpicture}
\end{center}

Scheme 1.6

Since then, a large number of other methods have been described including acylation of diazomethane (the single most important route to acyclic terminal $\alpha$-diao ketones) and the more conventional diazo group transfer technique, which occupies an important place in diazocarbonyl methodology for access to both terminal and nonterminal systems. The subsequent sections will describe these more important methods of preparing diazocarbenols.
1.5.1 Acylation of diazoalkanes

Arndt and Eistert showed that acylation of diazomethane with an acyl chloride leads to diazocarbonyl compounds provided a sufficient excess of diazomethane is used in order to avoid the addition of hydrogen chloride to the diazoketone formed. Anhydrides are also suitable for acylating diazomethane. A convenient procedure involves treatment of the carboxylic acid 13 with dicyclohexylcarbodiimide 14 to form the activated acid 15 and then the corresponding anhydride 16 which is then allowed to react with ethereal diazomethane to give the diazocarbonyl 17 (Scheme 1.7).

\[
\begin{align*}
\text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{N}-\text{C}_6\text{H}_{11} + \text{RCOOH} & \rightleftharpoons \text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{N}-\text{C}_6\text{H}_{11} + \text{RCOO}^- \\
(14) & (13)
\end{align*}
\]

\[
\begin{align*}
\text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{N}\text{C}_6\text{H}_{11} + (\text{RCO})_2\text{O} & \rightarrow \text{RCOOH} \\
\text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{N}-\text{C}_6\text{H}_{11} + \text{RCOCHN}_2 & + \text{RCOOH} \\
(16) & (15) \\
\text{RCOCHN}_2 & + \text{RCOOH}
\end{align*}
\]

Scheme 1.7

However, a convenient in situ procedure to form mixed anhydrides is now more fashionable and contrary to the previous method, all the acid is converted into the corresponding diazoketone. The in situ method involves the formation of an anhydride between a carboxylic acid and a chloroformate, followed by treatment with diazomethane. This protocol has been applied in the synthesis of 3-(diazo-acetyl)-2,2-diphenyloxirane 19 from acid 18 and also for the production of homochiral \(\alpha\)-diazo ketones 20 and 21 from \(N\)-protected amino acids (proline and phenylalanine) (Scheme 1.8).
Although there is the possibility of acylating higher diazoalkanes using acyl chloride and anhydrides, this proceeds less efficiently compared with diazomethane. Furthermore, this method is not applicable to the preparation of cyclic α-diazo ketones.

1.5.2 Diazo-transfer reaction

Regitz, due to the limitation of acylating diazoalkanes, introduced the diazo-transfer technique which is now the standard route to cyclic and acyclic α-diazo ketones. In a broad sense, the technique involves the transfer of a complete diazo group from a donor (usually a sulfonyl azide) for example 22 to an acceptor 23 (Scheme 1.9).

R, R’= alkoxy; R, R’ = alkyl; R = alkyl, R’ = alkoxy

In the acceptor, the position for diazo transfer can be activated by a single carbonyl group or adjacent to two carbonyl groups. In the latter group comprising malonic esters, β-keto esters and β-diketones, simple treatment by the standard Regitz procedure involving exposure to tosyl azide in dry chloroform or ethanol using triethylamine as base is sufficient for the diazotransfer to occur to the acidic α-methylene position to give good yields of 2-diazo-1,3-dicarbonyl...
compounds. The diazotransfer to the reactive site of the former group activated by a single carbonyl generally results in a poor yield, however the efficiency can be improved by activation of the ketone precursor prior to diazotransfer. One generally accepted technique was developed by Danheiser,\(^{22}\) who observed that the efficiency of the diazo-transfer reaction could be improved, in some cases quite dramatically, by activating the ketone \(24\) to the corresponding \(\alpha\)-trifluoroacetyl derivative \(25\) prior to diazo transfer (Scheme 1.10).

\[
\begin{align*}
R_1 & \quad R_2 \quad R_1 \quad R_2 \quad R_1 \quad R_2 \\
& \quad \text{LiHMDS, THF} \quad \text{LiHMDS, THF} \quad \text{LiHMDS, THF} \quad \text{H}_2\text{O}/\text{CH}_3\text{CN} \\
& \quad \text{CF}_3\text{CO}_2\text{CH}_2\text{CF}_3 \quad \text{CF}_3\text{CO}_2\text{CH}_2\text{CF}_3 \quad \text{CF}_3\text{CO}_2\text{CH}_2\text{CF}_3 \\
& \quad \text{-78 °C, 10 min} \quad \text{25 °C, 2.5 hr} \quad \text{25 °C, 2.5 hr} \\
\end{align*}
\]

Scheme 1.10

Doyle\(^{23}\) applied the strategy to achieve diazo transfer into a base sensitive N-acyloxazolidinone derivative \(26\) (Scheme 1.11).

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_3 \quad \text{Ph} \quad \text{CH}_3 \quad \text{Ph} \quad \text{CH}_3 \\
& \quad \text{LDA, -78 °C} \quad \text{CF}_3\text{CO}_2\text{CH}_2\text{CF}_3 \quad \text{CF}_3\text{CO}_2\text{CH}_2\text{CF}_3 \quad \text{ArSO}_2\text{N}_3 \\
& \quad \text{CH}_3 \quad \text{ArSO}_2\text{N}_3 \quad \text{Et}_3\text{N, H}_2\text{O} \quad \text{Et}_3\text{N, H}_2\text{O} \\
\end{align*}
\]

Scheme 1.11

The following subsection will highlight other routes which are still useful for the synthesis of \(\alpha\)-diazocarbonyl compounds presumably due to their ready availability.

### 1.5.3 Other routes to \(\alpha\)-diazocarbonyl compounds

This brief section aims to highlight other less conventional methods to prepare \(\alpha\)-diazo ketones including the Forster reaction, which involves oxime formation \(31\) at the \(\alpha\)-methylene position of the ketone \(30\), followed by reaction with chloroamine to give diazo ketone \(32\) (Scheme 1.12).\(^{24}\)
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Scheme 1.12

The Bamford-Stevens tosylhydrazone decomposition (Scheme 1.13)\(^{25}\) and the recent

Scheme 1.13

report involving the dehydrogenation of hydrazones with activated dimethylsulfoxide (Scheme 1.14).\(^{26}\)

Scheme 1.14

1.6 Classification of \(\alpha\)-diazocarbonyl compounds

The stability and reactions of metallocarbenes (carbenoids) produced from the decomposition of \(\alpha\)-diazocarbonyl compounds is profoundly affected by several factors including the nature of the substituents. Whilst an acceptor group will tend to make the carbenoid more electrophilic and reactive, a donor group will make the carbenoid more stable and so chemoselective. Based on this factor Davies classified carbenoids into three groups.\(^{5}\)
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- acceptor-substituted carbenoids,
- acceptor-acceptor-substituted carbenoids,
- donor-acceptor-substituted carbenoids.

1.6.1 Acceptor-substituted carbenoids

Carbenoids derived from diazo compounds with a single electron withdrawing substituent belong to this group (Scheme 1.15).

\[
\begin{align*}
\text{diazoacetate} & : & \text{N}_2\text{O} \quad \text{OR} \\
\text{diazoketone} & : & \text{N}_2\text{O} \quad \text{R} \\
\text{diazoacetamide} & : & \text{N}_2\text{O} \quad \text{NR}_2
\end{align*}
\]

Scheme 1.15

Their decomposition leads to the formation of highly reactive metallocarbenoids species with carbenoids from diazoketones more reactive while carbenoids from diazoacetamides are least reactive.

1.6.2 Acceptor-acceptor-substituted carbenoids

This group comprises of carbenoids derived from diazo compounds with two electron-withdrawing substituents (Scheme 1.16).

\[
\begin{align*}
\text{diazoacetoacetate} & : & \text{N}_2\text{O} \quad \text{OR} \\
\text{diazomalonate} & : & \text{N}_2\text{O} \quad \text{OR} \\
\text{diazodiketone} & : & \text{N}_2\text{O} \quad \text{R} \\
\text{diazoacetoacetamide} & : & \text{N}_2\text{O} \quad \text{NR}_2
\end{align*}
\]

Scheme 1.16

The second electron-withdrawing group gives added stabilization to the diazo compound, and therefore requires the use of active catalyst for the decomposition.\(^{27}\) However, once formed the carbenoid is highly electrophilic and easily undergoes C-H activation.
1.6.3 Donor-acceptor-substituted carbenoids

In this group, a donor substituent such as a vinyl or an aryl group stabilises the carbenoid through resonance (Scheme 1.17).

\[ \text{aryldiazoacetate} \quad \text{vinyldiazoacetate} \]

Scheme 1.17

Very active catalysts are required for effective decomposition of this class of diazo compounds.

1.7 Diazocarbonyl compounds in synthesis

\( \alpha \)-Diazocarbonyl compounds have an exceptional flexibility in synthesis. Their most significant reaction proceeds with loss of nitrogen which can be generated thermally, photochemically or catalytically. The reaction intermediates include free carbenes, carbenoids and carbonyl ylids. The most common diazocarbonyl reactions are cyclopropanation, Wolff rearrangement, insertion into unactivated C-H bonds, aromatic cycloaddition, dimerisation, electrophilic aromatic substitution, oxidation and ylid formation followed by sigmatropic rearrangement.

Without exception, each intermolecular process has its intramolecular counterpart, indeed the current high interest in the use of diazocarbonyl compounds as intermediates derives from the success of the intramolecular processes following the development of rhodium (II) carboxylate catalysts by Teyssie, Hubert, and Noels.\(^{28}\) The subsequent sections will describe in detail the main reactions of \( \alpha \)-diazocarbonyl compounds.

1.7.1 Cyclopropanation

Cyclopropanation involves the 1,2-addition of carbenes to alkenes yielding cyclopropanes. The process is arguably the most characteristic reaction of carbene intermediates and provides a facile and powerful means of cyclopropane construction (Scheme 1.18).\(^{29}\)
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Factors which impact on the diastereoselectivity and regioselectivity of cyclopropanation reaction includes steric and the electronics of the substituents on the carbene and/or alkene, as well as the metal catalyst.\textsuperscript{30} Thus, the use of the more hindered \textit{t}-butyl substituent of 33 influences the diastereoselectivity and favours the formation of the \textit{trans}-cyclopropane 35 (Scheme 1.19, Table 1.1).

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Yield (%)</th>
<th>Trans/cis ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=Ph</td>
<td>93</td>
<td>1.6</td>
</tr>
<tr>
<td>R=OEt</td>
<td>88</td>
<td>1.7</td>
</tr>
<tr>
<td>R=\textit{t}-Bu</td>
<td>87</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Table 1.1

With respect to the electronics of substituents on the carbenes for example 37, the diastereoselectivity is controlled by the polarity of the substituents (Scheme 1.20, Table 1.2).
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<table>
<thead>
<tr>
<th>Entry</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>Yield (%)</th>
<th>Ratio $38:39$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Ph</td>
<td>38</td>
<td>23 : 77</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>COOEt</td>
<td>93</td>
<td>62 : 38</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>CONMe$_2$</td>
<td>74</td>
<td>69 : 31</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>NO$_2$</td>
<td>54</td>
<td>71 : 29</td>
</tr>
</tbody>
</table>

Table 1.2

The more polar substituent ($NO_2 > CONMe_2 > COOEt > Ph$) determines the predominant $trans$ stereochemistry, therefore $38 > 39$ (entries 1-4). Doyle reasoned that the nucleophilic oxygen of the polar carbene substituent stabilises the developing electropositive centre of the reacting alkene, thus leading to increased diastereoselectivity (Scheme 1.21).

![Scheme 1.21](image)

In terms of the catalyst, both the metal and its ligands can have significant influences on diastereoselectivity. For example, among rhodium (II) carboxylate and carboxamidate ligands, the effectiveness for diastereocontrol follows the order $Rh_2$(cap)$_4$, $Rh_2$(acam)$_4 > Rh_2$(OAc)$_4$, $Rh_2$(oct)$_4$, $Rh_2$(NHCOCF$_3$)$_4 > Rh_2$(tfa)$_4$, $Rh_2$(pfb)$_4$. This order shows that the greater the acid strength of the ligand’s conjugate acid, the higher is the reactivity of the catalyst and the lower the selectivity.

Regioselectivity in cyclopropanation also depends on electronic and steric factors with the more electron rich double bond reacting preferentially: $ROCH=CH_2 > PhCH=CH_2 > R_2C=CH_2 > RCH=CH_2$, $R$=alkyl. Electron deficient olefins (i.e. $\alpha,\beta$-unsaturated) often fail to generate cyclopropanes but rather form pyrazolines. Conjugated dienes and trienes are also reactive and cyclopropanation at the more nucleophilic double bond is predominant.
1.7.2 Reaction with aromatics

The reaction between diazocarbonyl compounds and aromatics was initiated by Buchner and initially represented a singularly direct route to a vast range of seven-membered carbocyclics many of which were suitable for further elaboration into natural products. In a broad sense, the reaction involves the conversion of an aromatic such as the diazoketone \(40\) into a cycloheptatrienyl derivatives \(41\) (Scheme 1.22). \(^{34}\)

![Scheme 1.22](image)

1.7.3 Ylid formation and subsequent reactions

Carbenoids \(42\) derived from catalytically decomposed \(\alpha\)-diazocarbonyl compounds exhibit highly electrophilic properties and therefore can react with an available heteroatom to generate ylids \(43\) (Scheme 1.23).

![Scheme 1.23](image)

Ylids are reactive intermediates which can undergo a number of useful transformations including \([2,3]\)-sigmatropic rearrangement, \([1,2]\) insertion (Steven’s rearrangement) and \(\beta\)-hydride elimination. The following section will describe in detail the more important \([2,3]\)- and \([1,2]\)- sigmatropic rearrangements.
1.7.3.1 **[2,3]-Sigmatropic rearrangements**

Symmetry-allowed [2,3]-sigmatropic rearrangement is a facile bond reorganisation process which is observed in a broad selection of allylic substrates including allylic sulfides, ethers, selenides, amines, and halides. The rearrangement makes a new C-C σ-bond at the expense of a C-S σ-bond and is believed to proceed due to the greater stability of the sulfur-carbon bond in the product compared to the carbanion in the starting material (Scheme 1.24).

![Scheme 1.24](attachment:image)

Copper catalysts were not particularly successful for this transformation due to the high temperature often required. In contrast, diazo decomposition with rhodium (II) carboxylates which takes place under milder conditions has been successful for such transformations. Therefore, the tandem inter- or intramolecular catalytic ylid generation followed by the [2,3]-sigmatropic rearrangement has found wide application in synthesis. Werner *et al* and Johnson *et al* applied this rearrangement as a novel methodology for the construction six-46, and eight-47 membered oxygen heterocycles from the diazoketones 44 and 45 respectively (Scheme 1.25).
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The major competing reaction in allylic halides, particularly of bromide and chlorides is cyclopropanation reaction. Also several studies have showed that chemoselectivity is strongly dependent upon several factors including the nature of the diazocarbonyl compound, the catalyst choice, olefin geometry and allylic substitution.

The critical nature of catalyst choice is underscored by the following example, from studies by Chappie (Scheme 1.26, Table 1.3).

\[
\text{Scheme 1.26}
\]

<table>
<thead>
<tr>
<th>catalyst</th>
<th>Yield</th>
<th>49:50:51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh(_2)(OAc)(_4)</td>
<td>70</td>
<td>0 : 69 : 31</td>
</tr>
<tr>
<td>Cu(hfacac)(_2)</td>
<td>68</td>
<td>0 : 68 : 32</td>
</tr>
<tr>
<td>Pd(OAc)(_4)</td>
<td>78</td>
<td>0 : 78 : 27</td>
</tr>
<tr>
<td>Rh(_2)(cap)(_4)</td>
<td>71</td>
<td>90: 0 : 10</td>
</tr>
</tbody>
</table>

\[
\text{Table 1.3}
\]

The trans-diazoamide 48 was not expected to undergo a [2,3]-sigmatropic rearrangement because the allylic nucleophile was proposed to be too distant to react with the electrophilic carbenoid centre. However, upon decomposition with the electron rich Rh\(_2\)(cap)\(_4\), the diazoamide formed the unexpected \textit{anti} pyrrolidine 49. In contrast using rhodium, copper and palladium based catalysts with electron withdrawing ligands produced only cyclopropane products 50 and 51.
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1.7.3.2 [1,2]-Sigmatropic rearrangements

The concerted [1,2]-sigmatropic rearrangement also referred to as the Stevens [1,2]-shift is perceived to occur via a homolysis-recombination mechanism leading to the formation of new carbon-carbon bond (Scheme 1.27).41

\[
\begin{align*}
R_C^X \rightarrow R'_{C-X} \rightarrow R'_{R'-X} \rightarrow R_{R'-X} \rightarrow R_{R'-X}
\end{align*}
\]

\[X=O,N,S\]

**Scheme 1.27**

Although, the [1,2] shift is synthetically limited in use apparently due to the competing [2,3]-sigmatropic rearrangement, most of its application has been exploited in intramolecular reactions. A rare application of the rearrangement intermolecularly in ring expansion is shown below (Scheme 1.28).

![Scheme 1.28](image)

The transformation proceeds upon rhodium (II) acetate catalysed decomposition of dimethyl diazomalonate 55, the resulting carbenoid reacts with N-ethylisothiazol-3(2H)-one 52 to form the sulfide ylid 53, which then undergoes ring expansion via a [1,2]-shift process giving the product 54.42

1.7.4 The Wolff rearrangement

In simple terms, the Wolff rearrangement refers to a specific 1,2-rearrangement of a diazo ketone 56 following the loss of nitrogen to a ketene 57, which then reacts with water giving the homologous acid 58 (Scheme 1.29).
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The synthetic utility of the Wolff rearrangement became apparent when it was observed that the ketene reacts with water and other nucleophiles including alcohols, amines, thiols and can also undergo cycloaddition reactions (Scheme 1.30).

The rearrangement can be initiated by thermolysis, photolysis, or metal catalysis, with the latter two being the more widely employed. Whilst the ketene formation is crucial, its subsequent reaction is determined by its structure and the reaction conditions. The versatility of the Wolff rearrangement would make its adequate coverage challenging, at least in this report, however, the subsections below attempt to briefly illustrate its usefulness in synthesis.

1.7.4.1 Arndt-Eistert homologation
Arguably the earliest application of the Wolff rearrangement is the Arndt-Eistert homologation. The reaction is effectively a one-carbon homologation of acyl chlorides and is favoured by either silver ion catalysis or photolysis (Scheme 1.31).
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Scheme 1.31

This strategy was applied in the synthesis of Cbz-protected β-phenylalanine methyl ester 60 from the diazoketone 59 (Scheme 1.32).

Scheme 1.32

In general, the application to open chain diazo ester 61 and diazonamide 62 systems gives low yield due to the presence of less favoured alkoxy and amino migrating groups (Scheme 1.33).

Scheme 1.33

1.7.4.2 Ring contraction reactions

Ring contraction via the Wolff rearrangement reaction is an effective methodology for the synthesis of strained ring systems under temperatures regarded as less extreme, for example the synthesis of the tricycle 65 from the methylester 64 prepared from diazoketone 63 (Scheme 1.34).
The contraction allows small ring formation from larger ring systems, and although there is no limitation as to ring size formation, examples of three membered rings are limited.

1.7.4.3 Wolff rearrangement leading to cycloaddition reactions

Ketenes generated from a Wolff rearrangement can react with olefins in a [2+2] cycloaddition reaction, generally affording four membered ring products. An illustrative example, each of an intermolecular and intramolecular cycloaddition to give products 66 and 67 respectively is shown in Scheme 1.35.

1.7.4.4 The Vinylogous Wolff Rearrangement

The vinylogous Wolff rearrangement is a characteristic reaction of β,γ-unsaturated diazoketones for example 68 initiated mainly by copper catalysis (Scheme 1.36).
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![Scheme 1.36]

It involves an initial cyclopropanation reaction to give the bicyclic intermediate **69**, which subsequently undergoes an unusual skeletal rearrangement, with a yet to be fully understood mechanism,\(^{46}\) to afford ketene **70**. Nucleophilic capture of intermediate **70** using an alcohol yields the \(\gamma,\delta\)-unsaturated carboxylic acid derivative **71**.\(^ {47}\)

### 1.7.5 Reactions with aldehydes and ketones

The carbon-oxygen double bond of a carbonyl forms carbonyl ylids **72** by donating electron density to the electron deficient carbenoid formed from a diazocarbonyl compound (Scheme 1.37).

![Scheme 1.37]

Similarly, the carbonyl group can also accept electron density by participating as an electrophile. Such reactions fall into two broad categories (i) an aldol type reaction promoted by base with retention of the diazo functional group (Scheme 1.38) and (ii) a related Lewis acid mediated reaction which results in the loss of nitrogen and affords \(\beta\)-dicarbonyl compounds. An application of the Lewis acid reaction to the synthesis of ester **78** is shown in Scheme 1.39.\(^ {48}\)

![Scheme 1.38]
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Scheme 1.39

The aldol-type reaction involves a base-promoted ionisation of 73 to give the α-diazocarbonyl anion 74. Addition of the anion to the aldehyde or ketone gives the product 75. Wenkert and McPherson have shown that various bases can be employed for the deprotonation step including n-butyllithium, lithium diisopropylamide, and potassium hydroxide in methanol or ethanol.\textsuperscript{49} A recent synthesis of (±)-atractylenin 79 by Corey incorporates this methodology (Scheme 1.40).\textsuperscript{50}

Scheme 1.40

As earlier mentioned at the beginning of this section, the variety of transformations of diazocarbonyl compounds is enormous and may be difficult to cover in this thesis. Therefore, the last transformation to be discussed is the insertion reaction.

1.7.6 Insertion reactions

Carbenes generated catalytically have proven to be highly versatile for insertion into C-H and X-H bonds where X is O, S, N, Se, P or halogen.\textsuperscript{51} It is worth noting that C-H and Si-H bond insertion have to be separated from the other heteroatom-hydrogen bond insertions. Indeed, their low polarity separates them mechanistically from the other group of insertion reactions.
1.7.6.1 X-H insertion reactions

The X-H insertion reaction of diazocarbonyl compounds is the process which overall represents a general approach to the α-functionalisation of a ketone, in many cases under neutral conditions (Scheme 1.41).

\[
\begin{align*}
R^2N_2O + H-X & \rightarrow \text{R}R'/X \\
R/R' &= \text{alkyl, alkoxy, aryl}; X = O, S, N, Se, P, Halogen
\end{align*}
\]

Scheme 1.41

The X-H insertion reactions are invaluable synthetically and represent a useful way of introducing heteroatom containing substituents adjacent to carbonyl groups. However, the executed research is focused on C-H insertion reactions and will therefore be the subject of discussion in the following section.

1.7.6.2 C-H Insertion reactions

The insertion of “free” carbenes into C-H bonds was first observed by Meerwein, Rathjen, and Werner. However, low yield and lack of chemical control limited their use.

These limitations have been overcome by the use of metal catalyst particularly those of rhodium (II) carboxylates. These catalysts are useful for the catalytic decomposition of α-diazocarbonyl compounds leading to transition-metal carbenoid intermediates that can insert into a C-H bond. Studies have shown that insertion of a carbenoid into a C-H bond could proceed via an intermolecular or an intramolecular process. Intramolecular insertion of a ketocarbene into unactivated C-H bonds allows transformations which would otherwise be difficult to achieve. An illustration of an intramolecular insertion is depicted below for the conversion of diazoketone 80 into cyclopentanone 81 (Scheme 1.42).

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{N}_2 \\
\text{80}
\end{array} & \xrightarrow{\text{R}_{\text{h}}(\text{OAc})_4} \begin{array}{c}
\text{O} \\
\text{81}
\end{array}
\end{align*}
\]

Scheme 1.42
Chapter I: Introduction

For metal induced insertion, the effect of the metal and its ligands is crucial to achieve insertion into an unactivated C-H bond. In general, rhodium based catalysts are perceived to be superior to other catalysts for example copper based catalyst. This is exemplified by the cyclisation of 82 to the cyclopentanone 83 which proceeds in high efficiency (59%) using a rhodium (II) based catalyst. In contrast, a copper (II) catalyst gave only 1% yield (Scheme 1.43).\(^5\)

![Scheme 1.43](image)

**Scheme 1.43**

Furthermore, an appropriate level of electrophilicity at the metallocarbene carbon center is required in order for the C-H insertion to occur. Poor regio- and stereocontrol results when the carbenoid intermediate is too electrophilic and thereby favouring other competing reaction pathways that ultimately leads to low selectivity. On the other hand, if the carbenoid is not sufficiently electrophilic, it will therefore not be reactive enough to insert into the unactivated C-H bond. The degree of electrophilicity is governed by the nature of the ligands on the metal catalyst. Extensive studies by Doyle\(^5\)\(^4\) and Padwa\(^5\)\(^5\) on the reactivities *versus* selectivities of rhodium (II) catalysts resulted in the classification shown (Scheme 1.44).

\[
\text{Rh}_2(\text{cap})_4 > \text{Rh}_2(\text{acam})_4 > \text{Rh}_2(\text{OAc})_4 > \text{Rh}_2(\text{pfb})_4 > \text{Rh}_2(\text{tfa})_4
\]

Increased reactivity for diazodecomposition

Increased stereo- and regioselectivity

**Scheme 1.44**
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It was observed that catalysts with electron withdrawing ligands e.g. Rh$_2$(pfb)$_4$ show a high reactivity for diazo decomposition but gave low stereo- and region-control. In contrast, more electron rich catalyst, e.g. Rh$_2$(cap)$_4$, showed lower reactivity but higher selectivities. Since then, extensive efforts by a number of groups have improved the understanding of the selectivity of insertion reactions. Studies mostly by Taber,$^{56,57}$ Doyle$^{58}$ and Wenkert$^{59}$ have enabled the identification of factors controlling the site-selectivity of intramolecular C-H insertion reactions to include the type of diazo function, the degree of substitution of the carbon atom where insertion takes place, the nature of catalyst and steric and electronic factors. In general cyclisation of these carbenoids preferentially favoured 5-membered rings and the cyclisation of heteroatomic compounds proceeded with a preference for insertion into a C-H bond α to the heteroatom. In terms of ring size, the probable trend is four membered ring ≤ five membered ring > six membered ring > seven membered ring and the preference for five membered rings may be due to proximity between the carbene centre and the C-H bond where insertion is to take place (Scheme 1.45).

![Scheme 1.45]

In the reaction, treatment of 84 with a Rh(II) catalyst afforded the five membered bicyclic cyclopentanone 85, at the expense of the four membered ring (spiro product) and the six membered bicyclic product.

There is also a general trend for insertion into C-H bonds depending on the substitution of the carbon with a preference for the more electron rich carbon, generally insertion into 3°-carbon > 2°-carbon > 1°-carbon > vinyl > aryl (Scheme 1.46).

![Scheme 1.46]
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However, in cyclisation of heteroatom containing compounds exceptions do occur. The C-H insertion site is switched to favour specifically the C-H bond α to the heteroatom. In this case a different ring size than the expected five membered ring may be favoured (Scheme 1.47).

\[
\begin{array}{c}
\text{O} \\
\text{N}_2 \\
\text{O} \\
\text{Bn} \\
\text{O} \\
\text{Bn} \\
\text{Rh}_2(\text{OAc})_4 \\
\end{array} \\
\text{86} \\
\xrightarrow{\text{Rh}_2(\text{OAc})_4} \\
\begin{array}{c}
\text{O} \\
\text{Bn} \\
\end{array} \\
\text{87} \\
\]

Scheme 1.47

The oxygen atom adjacent to the C-H bond in compound 86 influences the formation of the six membered product 87 possibly due to overlap between a filled orbital on the heteroatom and the C-H bond, thereby activating the insertion point by an increase in its electron density. Similarly, a 2°-carbon would become favoured over a 3°-carbon in such heteroatom cyclisations (Scheme 1.48).

\[
\begin{array}{c}
\text{O} \\
\text{N}_2 \\
\text{O} \\
\text{O} \\
\text{Bn} \\
\text{Rh}_2(\text{OAc})_4 \\
\end{array} \\
\text{88} \\
\xrightarrow{\text{Rh}_2(\text{OAc})_4, \text{CH}_2\text{Cl}_2} \\
\begin{array}{c}
\text{O} \\
\text{O} \\
\end{array} \\
\text{89} \\
\]

Scheme 1.48

Clearly, the oxygen atom in 88 activates the adjacent 2°-carbon, favouring the formation of the furanone product 89, as against the 3°-carbon that would lead to a cyclopentane product.

Recent studies have also shown that the nature of the catalyst, substrate and carbenoid substitution affects chemoselectivity and more importantly product yields, these aspects will be discussed in the following sections.

1.8 Selectivity in diazocarbonyl reactions

Extensive studies of dirhodium (II) catalyzed reactions of α-diazocarbonyl compounds demonstrate that chemoselectivity and therefore product yields are highly dependent on three
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factors: catalyst electrophilicity, carbenoid substitution and substrate substitution. Studies over the last two decades have shown that these same factors have profound effects on enantioselectivity in reactions employing chiral Rh (II) catalyst. The following section focuses on these factors with the aim of revealing that subtle electronic, steric, and/or conformational changes often have a monumental impact on reaction pathways.

1.8.1 Nature of catalyst and its effect on selectivity

One of the challenges for modern synthesis is to create distinct types of complex molecules from identical starting materials based solely on catalyst selection. In this context, rhodium (II) catalysts are remarkable, as a relatively small body of related catalysts can cause a diverse range of reactivity. Padwa pioneered the study of the influence of catalyst and its ligands on chemoselectivity. The study revealed that the nature of catalyst and its ligands can effectively, and sometimes completely, switch reaction preference as illustrated using three electronically diverse catalysts 93, 94 and 95 on diazoketone 90 (Scheme 1.49).

In this competitive insertion/cyclopropanation, the observed electrophilicity of the resultant carbenoids increases significantly of the order rhodium(II)caprolactam 95 < rhodium(II)acetate 94 < rhodium(II)perfluorobutyrate 93. Interestingly, a complete reversal of reactivity was observed depending on catalyst choice. The use of catalyst 93 afforded the aryl insertion product 91 exclusively. In contrast, catalyst 95 produced the cyclopropanation product 92 exclusively. This suggests that strongly electron withdrawing ligands favour C-H insertion

\[
\begin{align*}
\text{Scheme 1.49}
\end{align*}
\]
while cyclopropanation is favoured by electron donating ligands. However, a more dramatic reactivity was observed by merely changing the ligand sterics of 94 from methyl to triphenylmethyl in Rh$_2$(tpa)$_4$ 97 (Scheme 1.50).

The reaction of 96 with Rh$_2$(OAc)$_4$ 94 gave exclusively 98 in 94% yield. However, when the Rh$_2$(tpa)$_4$ catalyst 97 was employed, 96 was observed to undergo an exclusive aryl C-H insertion reaction to give 99. Moody, Padwa and co-workers have also investigated the effect of ligands in competitive reaction between benzylic C-H insertion and aryl C-H insertion for diazoamide ester 100. They observed a substantial improvement in yields, as well as selectivities on replacing rhodium (II) acetate 94 with rhodium (II) perfluorobutyramide, [Rh$_2$(NHCOC$_3$F$_7$)$_4$] 102. The latter catalyst afforded the aryl C-H insertion product exclusively which was isolated as the siloxyindole 101 (Scheme 1.51).

**Scheme 1.50**

**Scheme 1.51**
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Taber’s group has also noted the importance of the rhodium (II) catalyst ligand in the C-H insertion process.\textsuperscript{63} They observed that strongly electron withdrawing ligands favour \( \beta \)-hydride elimination while C-H insertion is favoured by electron donating ligands (Scheme 1.52).

\[ \text{Rh}^{(II)} + \text{Rh}_2(\text{tfa})_4 \rightarrow \text{Rh}_2(\text{OAc})_4 : \text{Rh}_2(\text{OBz})_4 : \text{Rh}_2(\text{tfa})_4 \]

\begin{align*}
\text{Rh}_2(\text{OAc})_4 & \quad 70 \quad : \quad 30 \\
\text{Rh}_2(\text{OBz})_4 & \quad 60 \quad : \quad 40 \\
\text{Rh}_2(\text{tfa})_4 & \quad 38 \quad : \quad 62
\end{align*}

Scheme 1.52

The more reactive rhodium carbenoid derived from the trifluoroacetate catalyst \textbf{104} favours the entropically less demanding pathway of \( \beta \)-hydride elimination.

1.8.2 Nature of substrate and its effect on selectivity

The stereoelectronics of substrates for C-H insertion reactions have been investigated. In particular, Davies and co-workers have showed that the electronic nature of the aromatic component is important.\textsuperscript{64} In their study of the reaction of vinyldiazoacetate \textbf{105} with benzene derivatives, they observed benzene \textbf{106}, toluene \textbf{107}, and \( t \)-butylbenzene \textbf{108} allowed access to bicycle [3.2.2]-nonatriene \textbf{112}. In contrast to anisole \textbf{109}, 1,2-dimethoxy- and 1,2,3-trimethoxybenzene which afforded alkylation product \textbf{111}, presumably due to the greater stabilization of transition state \textbf{110} (Scheme 1.53).
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Scheme 1.53

The impact of electronic variations in substrate structure was further echoed by Padwa et al in a study on intramolecular Buchner reaction of diazoacetamide 113 to give a 2:1 ratio of cycloheptatriene 116 and benzylic C-H insertion product 117 (Scheme 1.54). 65

Scheme 1.54
Chapter I: Introduction

This yield improved to 3:1 when the more electron rich ring system 114 was used. In contrast, the electron deficient \( p\)-NO\(_2\)Ph system 115 shut down the Buchner reaction pathway, instead giving a mixture of C-H insertion products 123 and 124. As earlier mentioned, it is worth noting that the substituents of the carbene also influences chemoselectivity, this will be briefly discussed in the next section.

1.8.3 Nature of diazo substitution and its effect on selectivity

Davies and co-workers in an effort at studying the effect of diazo (carbene) substitution on intermolecular aliphatic C-H insertion with cyclohexane 127 prepared \( cis\) 125 and \( trans\)-vinylidiazoacetate 126 (Scheme 1.55). They observed that the \( cis\)-isomer 125 failed to undergo intermolecular C-H insertion with 127. Instead, intramolecular aryl C-H insertion occurred to give indene 128 while the \( trans\)-isomer 126 gave a mixture of products, 129 arising from intermolecular C-H insertion and compound 130, argued to be formed via \( cis\)-\( trans\) isomerisation of the carbenoid followed by aryl C-H insertion and subsequent intermolecular cyclopropanation of the resulting indene.

![Scheme 1.55](image)

Having presented an overview of diazocarbonyl compounds and their attendant reactions in particular the C-H insertion reaction, the next section will now detail the planned research towards exploiting this chemistry.
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1.9 Aims of the project

This introductory chapter has provided an insight into typical transformations of metallocarbenes initiated by rhodium (II) catalyst. In line with present research, emphasis was placed on intramolecular C-H insertion reactions. The intramolecular C-H insertion reaction has been shown to be synthetically invaluable for the construction of carbocycles and heterocycles which can be further elaborated into target natural products with potential biological properties.

As mentioned at the beginning of this introduction, the aim of this project was to develop a method to access the bicyclic acetal core 5, which can be explored in the synthesis of five-, seven- and higher-membered-ring oxygen heterocycles 257, 333, 383. The strategy adopted is a tandem methodology, which involves an intramolecular C-H insertion of diazoketone acetal template 4 as the key step followed by reductive cleavage of the bicyclic acetal core 5 (Scheme 1.56).

![Scheme 1.56](image)

This protocol builds on previous work conducted within the group, which showed that the rhodium (II) acetate treatment of diazoketone 131 generates the bicyclic ketone 132 that was subsequently elaborated into tetrahydrofuran derivatives (Scheme 1.57).
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However, the bicyclic ketones 132 were obtained in low yields. Furthermore, the synthesis of the diazoketone precursors 131 involved the preparation and usage of diazomethane, known to be both toxic and explosive. A further complication resulted from the commercial unavailability of the diazomethane precursor, Diazald® due to its withdrawal from the chemical catalogue. Therefore, with a view to enhance the yields of the bicyclic ketones, the first objective was to prepare the diazo ketones 4. It was hoped that the extra substituent R₄ would enhance the yields of ketones 5 following the rhodium (II) acetate catalysed decomposition of 4. It was also the plan to explore alternative protocol for the synthesis of diazo ketones 4 without the use of diazomethane. One of the secondary aims of this work was to prepare the bicyclic ketones 134 and 135 analogous to 5 and bearing a vinyl and an ester group at R₄ respectively. It was hoped that such systems would allow for further transformation into macrocycles as illustrated using 134 (Scheme 1.58).

Scheme 1.57

Scheme 1.58
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The overall goal of this project is to be able to access the five-membered ring THFs upon reductive cleavage and to explore the possibility of extending this same strategy towards accessing seven-membered ring oxepanes.

Chapter II which follows this introduction will present the results and discussions on work carried out while preparing the aldehyde acetals based on the adopted strategy aimed at circumventing the subsequent use of diazomethane.

Chapter III will present the successful synthesis of the diazoacetoacetates without using diazomethane and a facile one-pot procedure developed for the preparation of diazoacetoacetates.

The next Chapter will describe successful efforts of a high temperature rearrangement reaction that resulted in the novel synthesis of Barceloneic lactones (see scheme 1.56), the first of such reports.

Chapter V will commence with the synthesis of the vinyldiazoketones, in particular their enantioselective conversion into the bicyclic alcohols.

The next two Chapters will present results and discussions of work undertaken towards the synthesis of highly substituted THFs and oxepane derivatives. Particular attention will be given to the two routes explored for the synthesis of the oxepanes.

Following a general conclusion and suggestions of potential areas for future exploration, the final Chapter will detail the experimental procedures and data obtained for the products synthesised.
Chapter I: Introduction

1.10 References

    Weygand, F.; Bestmann, H. Angew. Chem. 1960, 72, 971.
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Thijs, L.; Smeets, F. L. M.; Gillissen, P. J. M.; Harmsen, J.; Zwanenburg, B.


Chapter I: Introduction


53. Wenkert, E.; Davis, L.; Mylari, B.; Solomon, M.; Dasilva, R.; Shulman, S.; Warnet,
Chapter I: Introduction


64. Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova,

65. Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marion, J. P. Jr.;


Chapter II: Synthesis of Aldehyde Acetals

2.1 Introduction

As discussed in the preceding chapter, the successful synthesis of the key aldehyde acetals was fundamental for the project goals and therefore efforts were directed towards their preparation. Although 2-phenylpropane-1,3-diol is commercially available, as are a few other 2-substituted propane-1,3-diols, their cost inhibits usage on a large scale. Reflecting this, other methods for their preparation were required. This chapter will describe the synthesis of these diols and their subsequent conversion into the aldehyde acetals.

2.2 Strategy for synthesis of aldehyde acetals

The retrosynthetic disconnections, which form the basis of the synthetic strategy for the preparation of aldehyde acetals, are illustrated in the following scheme (Scheme 2.1).

It was proposed that the aldehyde acetal (I) could be obtained from the ester acetal (II) by reduction of the ester. This in turn, may be obtained from ketalisation of pyruvate ester (IV) with diol (III), prepared by reduction of the diethylmalonate (V).
Chapter II: Synthesis of Aldehyde Acetals

2.2.1 Preparation of 2-arylpropan-1,3-diols

Although 2-phenylpropane-1,3-diol is commercially available and very expensive, 2-benzylpropane-1,3-diol is not available commercially. However, both of their corresponding diethylmalonates are available and also significantly cheaper, therefore procedures to achieve their reduction were explored.

2.2.1.1 2-phenylpropan-1,3-diol

Lithium aluminium hydride (LiAlH₄) is a valuable reagent employed widely for the reduction of esters. Consequently, a cooled suspension of LiAlH₄ (5 eq) in Et₂O at 0°C was treated dropwise with a solution of diethyl-2-phenylmalonate 140 and the reaction mixture stirred for 3 hours at room temperature (Scheme 2.2).

![Scheme 2.2]

After work-up, the residue was purified by flash column chromatography on silica gel and further recrystallised from cyclohexane. The diol 141 was obtained as a white solid in good yield (60%). Evidence for the formation of the diol was found in the IR and ¹H NMR spectra. A comparison of the IR spectra of the starting material and the product showed the appearance of the broad IR band characteristic of alcohols at ~3440-2990 cm⁻¹ and the disappearance of the ester signal at 1740 cm⁻¹. The absence of any carbonyl signal in the ¹³C spectrum confirmed the total reduction of the ester groups. Confirmation of complete reduction was further supported by the highly symmetrical nature of the ¹H NMR spectrum showing just three signals at 3.98 ppm and 3.91 ppm, attributed to 1-CH₂ and 3-CH₂, together with a signal at 3.30-3.25 ppm attributed to 2-CH. In addition the data obtained was in agreement with that from commercially available material.
2.2.1.2 2-benzylpropan-1,3-diol

Following the same procedure as described above, reduction of diethyl-2-benzylmalonate 142 using LiAlH₄ was carried out and diol 143 was obtained as a solid in high yield (Scheme 2.3).

![Scheme 2.3](image)

As before, evidence for the formation of diol 143 was confirmed by the IR spectrum with the broad signal at 3440-2980 cm⁻¹ characteristic of alcohols and the absence of the signal attributed to the ester carbonyl at 1738 cm⁻¹. The ¹H NMR spectrum showed signals at 3.87 ppm and 3.75 ppm attributed to 2 x CH₂OH, 2.70 ppm attributed to 2-CH₂Ph together with a signal at 2.31 ppm attributed to the hydroxyl functionalities. Finally, the absence of the ester carbonyl signals in the ¹³C NMR spectrum confirmed the formation of 143.

With the diols in hand, the next step of the study was to synthesis the corresponding aldehyde acetals.

2.2.2 Synthesis of ester acetals

The established Ziegler¹ and Wardrop² strategy for the synthesis of acid acetals, which requires the prior formation of the ester acetals by acetalisation of an appropriate diol with a pyruvate, was adopted.

Thus, a solution of 2-phenylpropane-1,3-diol 141 was successively treated with BF₃.OEt₂ and methyl pyruvate 144 in acetonitrile according to the published procedures (Scheme 2.4).
Chapter II: Synthesis of Aldehyde Acetals

![Scheme 2.4](image)

Following work-up, two diastereoisomeric ester acetals 145 and 146 in a ratio of 4:1 were observed in the $^1$H NMR spectrum of the crude reaction mixture. These could be separated easily by flash column chromatography. Key evidence for the formation of the two ester acetals was found in the $^{13}$C NMR spectrum where signals corresponding to the quaternary C-2 were observed for the major and minor isomers at 98.1 and 97.6 ppm respectively, together with signals corresponding to the ester carbonyl carbon observed at 171.0 and 170.3 ppm. In addition, the $^1$H NMR spectrum showed signals for the methoxy units at 3.95 and 3.80 ppm. These data were also in agreement with that reported by Garbi$^3$ who, through X-ray crystallography had shown, in the major isomer 145 that the phenyl group adopted the equatorial position and the C-2 carboxylate group the axial position (Figure 2.1). This is as would be expected under thermodynamically controlled conditions due to anomeric effects.$^4$

![Figure 2.1](image)
Similarly, in the minor isomer 146, the crystal structure shows both the phenyl and C-2 carboxylate groups adopted the axial position (Figure 2.2).

![Figure 2.2](image)

Previous attempts by Garbi\(^3\) to form the major isomer exclusively by careful screening of Lewis acids were unsuccessful and no attempt was made to refine this procedure which was adopted in subsequent ester acetal preparation.

The corresponding ester acetals were obtained by varying the substituents on the diol 155 and the C-2 position of methyl pyruvate 156 (Scheme 2.5).

![Scheme 2.5](image)

The table below summarises the ratios, yields and key spectroscopic evidence for the formation of the ester acetals (Table 2.1).
Table 2.1

In all the compounds examined, mixtures of isomeric acetals were obtained and the nature of the groups R₁ and R₃ had little effect on the ratios of isomers formed. With the exception of the benzyl series (entry 2), the ester acetal isomers could be easily separated by column chromatography. Careful purification of the benzyl series gave small pure samples of each isomer suitable for analysis.

Also, in the cases studied, the C-2 carboxylate group preferentially occupies the axial position. The major isomer formed is believed to be that in which the larger R₁ or R₂ group adopts the
Chapter II: Synthesis of Aldehyde Acetals

preferential equatorial position. Similarly for the minor isomer, the larger R₁ or R₂ group adopts the axial position.

The only exception was the nitro/methyl series (entry 3), where the position of the large nitro group relative to the C-2 carboxylate defines the isomers as established by X-ray crystallographic analysis,⁵ thus the major and minor isomers are trans and cis respectively.

Further confirmation of the equatorial preference of the larger group between R₁ and R₂, emanates from the observation of similar signals and coupling constants for the protons 4,6-H_{ax} and 4,6-H_{eq} of each compound. The results are summarised in the table below (Table 2.2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁/R₂ group</th>
<th>R₃ group</th>
<th>'H NMR of major isomer</th>
<th>'H NMR of minor isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>CH₃</td>
<td>4.10 (dd, J 11.7, 4.8, 4.6-H_{eq})</td>
<td>4.25 (dd, J 12.1, 3.3, 4.6-H_{eq})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.95 (t, J 11.7, 4.6-H_{ax})</td>
<td>4.10 (dd, J 12.1, 2.0, 4.6-H_{ax})</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>CH₃</td>
<td>3.80 (dd, J 11.5, 4.4, 4.6-H_{eq})</td>
<td>3.95-3.90 (m, 4.6-H_{eq})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.50 (t, J 11.5, 4.6-H_{ax})</td>
<td>3.78 (d, J 11.0, 4.6-H_{ax})</td>
</tr>
<tr>
<td>3</td>
<td>NO₂</td>
<td>CH₃</td>
<td>4.70 (d, J 13.3, 4.6-H_{eq})</td>
<td>4.15 (d, J 11.7, 4.6-H_{eq})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.85 (d, J 13.3, 4.6-H_{ax})</td>
<td>4.05 (d, J 11.7, 4.6-H_{ax})</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>4.31 (dd, J 11.6, 4.8, 4.6-H_{eq})</td>
<td>4.05 (t, J 11.8, 4.6-H_{eq})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.10 (t, J 11.6, 4.6-H_{ax})</td>
<td>4.25 (dd, J 11.8, 4.5, 4.6-H_{ax})</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>Ph</td>
<td>4.07 (dd, J 11.5, 4.4, 4.6-H_{eq})</td>
<td>3.78 (dd, J 11.9, 5.8, 4.6-H_{eq})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.69 (2H, t, J 11.5, 4.6-H_{ax})</td>
<td>4.05 (dd, J 11.9, 3.6, 4.6-H_{ax})</td>
</tr>
</tbody>
</table>

**Table 2.2**

Although the signals and the coupling constants were similar in all the cases studied, it became necessary to establish definitely that the bulky R₃ = Ph group (entry 4 and 5) has not resulted in the acetal backbone ‘flipping’ thereby placing the C-2 carboxylate in the equatorial position as this will ultimately limit its usefulness for our intended C-H insertion reactions. Therefore, a sample of the major isomer 151 obtained was recrystallised from cyclohexane to give crystals suitable for X-ray crystallographic analysis (Figure 2.3, Appendix A).
Pleasingly, and consistent with the reported phenyl series, the C-2 carboxylate adopted the axial orientation with both C2 and C5 phenyl rings adopting the equatorial orientations.

In the minor isomer 152, the crystal structure shows that a chair conformation is retained and the C5-phenyl and C2-carboxylate groups adopt the axial orientations as expected (Figure 2.4, X-ray data obtained at 293K and 240K respectively, Appendix B & C).
2.2.2.1 Nitration of ester acetals

Having successfully prepared the ester acetals with varying electronics around the acetal core, it became apparent that a directing group on the aromatics may provide insights into their effects upon an eventual C-H insertion process. Towards this goal, it was decided to synthesise the nitrophenyl derivative 157. Previous efforts within the group involved the lengthy preparation of the nitrophenyl diol 158 from 2-propane-1,3-diol 141. The subsequent reaction of 158 with methyl pyruvate 144 afforded the corresponding nitro ester acetal 157 (Scheme 2.6).
Chapter II: Synthesis of Aldehyde Acetals

Due to the lengthy sequence involved, it was decided to explore an alternative protocol. Having synthesised the ester acetal 145 and taking the sensitive ester group into consideration, protocols for the nitrlation of 145 were explored (Scheme 2.7).

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{145} & \quad \text{159, 89\%} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{145} & \quad \text{160, 7\%} \\
\end{align*}
\]

Scheme 2.7

Initial attempt at nitrating 145 using a 1:1 mixture of concentrated nitric acid and water in glacial acetic acid led to complete decomposition. However, dropwise addition of trifluoroacetic anhydride to a solution containing a mixture of 145 and ammonium nitrate in anhydrous chloroform delivered the nitrated products as a mixture of para-substituted 159 and ortho-substituted 160 in 12:1 ratio as observed in the \(^1\)H NMR spectrum of the crude reaction mixture. Ultimately, the isomers were easily separated by flash column chromatography.

Key evidence for the formation of the two nitro ester acetals was found in the \(^{13}\)C NMR spectrum where signals corresponding to the quaternary C-2 were observed for the para and ortho isomers at 98.1 and 98.2 ppm respectively, together with signals corresponding to the ester carbonyl carbon observed at 170.5 and 170.8 ppm. In addition, the \(^1\)H NMR spectrum showed signals for the methoxy units at 3.85 and 3.89 ppm. In the aromatic region, a set of signals at 8.10 and 7.30 ppm respectively for 3'-H and 2'-H characteristic of para-substitution confirmed the presence of 159 while a set of signals at 7.79, 7.54, 7.40 and 7.29 ppm respectively for 3'-H, 5'-H, 4'-H and 6'-H equally characteristic of ortho-substitution confirmed the presence of 160. Further evidence obtained from the IR shows signals at 1530, 1350 and 1524, 1350 cm\(^{-1}\) attributed to the NO\(_2\) functionality in both isomers.

Similarly, the minor ester acetal 146 was nitrated to give a 10:1 mixture of para-substituted 161 and ortho-substituted 162 isomers, separable by flash column chromatography (Scheme 2.8). Evidence for the formation of 161 and 162 are shown in the table below (Table 2.3).
Chapter II: Synthesis of Aldehyde Acetals

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

146

\[
\begin{align*}
\text{NH}_4\text{NO}_3 \ (1.1\text{eq}) & \quad \text{EtO}_2\text{C} \quad \text{O} \\
(CF_3\text{CO})_2\text{O} \ (4\text{eq}), \text{CHCl}_3 & \quad \text{H} \\
0^\circ\text{C} \text{ for } 2\text{ h} \text{ then } \text{rt } \text{ for } 10\text{ h}
\end{align*}
\]

161, 86%

162, 8%

10:1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isomers</th>
<th>$^{13}$C NMR (ppm)</th>
<th>$^1$H NMR (ppm)</th>
<th>IR (cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>161</td>
<td>170.6 (CO), 98.3 (C-2), 3.85 (OMe)</td>
<td>8.12 (3’-H), 7.65 (2’-H)</td>
<td>1516, 1346 (NO$_2$)</td>
</tr>
<tr>
<td>2</td>
<td>162</td>
<td>170.6 (CO), 98.5 (C-2), 3.83 (OMe)</td>
<td>8.13 (6’-H), 7.89 (3’-H), 7.64 (5’-H), 7.43 (4’-H)</td>
<td>1511, 1339 (NO$_2$)</td>
</tr>
</tbody>
</table>

Scheme 2.8, Table 2.3

With the ester acetals in hand, attention turned towards converting each into the corresponding alcohol acetals and ultimately, the key aldehyde acetals. The following section will present efforts towards achieving this goal.

2.3 Synthesis of aldehyde acetal

Diisobutylaluminium hydride (DIBAL) is a reagent that can be used to reduce esters to aldehydes. For example, Ito et al employed this reagent to reduce ester 163 to aldehyde 164 in the synthesis of cyclohexynnorstatine isopropyl ester 165 (Scheme 2.9).$^6$

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{DIBAL, Et}_3\text{O} \quad -78^\circ\text{C}, 86\% \\
\text{OHC} & \quad \text{H}_2\text{N} \\
\text{COO} & \quad \text{OH}
\end{align*}
\]

Scheme 2.9
However, initial attempts to submit the ester acetal 145 for reduction using DIBAL resulted in incomplete conversion into the aldehyde acetal 176 and hence the low yield (11%) (Scheme 2.10).

Further attempts to drive the reaction to completion by allowing the reaction to stir at room temperature for a total of 16 h lead to a marginal increase in yield to 16%, while increasing DIBAL to 2 equivalents resulted in a mixture of aldehyde acetal 176, overreduced alcohol acetal 166 and unreacted starting material 145 (Scheme 2.11).

Based on these disappointing results, it was decided to reduce the ester acetal 145 completely to the alcohol 166 before reoxidizing to the aldehyde.

2.3.1 Synthesis of alcohol acetal

Since the preceeding result suggested that the aldehyde was far more readily reduced to the alcohol than anticipated, we opted to reduce the ester acetal completely to the alcohol by further increasing the number of equivalents of DIBAL used (Scheme 2.12).
Chapter II: Synthesis of Aldehyde Acetals

Following work-up and purification by flash column chromatography, the alcohol acetal 166 was obtained in very good yield (95%). Evidence for the formation of the alcohol was found in the IR and $^1$H NMR spectra. A comparison of the IR spectra of the starting material with that of the product showed the appearance of the broad IR band characteristic of alcohols at 3390 cm$^{-1}$ and the disappearance of signal corresponding to the ester carbonyl at 1742 cm$^{-1}$. The $^1$H NMR spectrum showed the disappearance of the methoxy singlet signal at 3.95 ppm and the appearance of the signal at 3.73 ppm attributed to carbinol hydrogens ($1-H_2$) together with a signal at 1.83 ppm attributed to the hydroxyl hydrogen. Further evidence supporting the complete reduction was obtained from the $^{13}$C NMR spectrum which showed the disappearance of the signal attributed to the ester carbon at 171.0 ppm.

In a similar fashion, ester acetals 145, 146, 149-154, 159 and 161 were then reduced to the corresponding alcohol acetals 166-175 with the use of excess DIBAL. Key evidence for the formation of the alcohol acetals are summarised in the following table (Scheme 2.13, Table 2.4).
In all cases, the alcohol acetals 166-175 were obtained in good to quantitative yields as pure samples and were subsequently taken through to the next step of the synthesis.

With an efficient protocol for the synthesis of the alcohol acetals established, efforts were directed towards their transformation via oxidation into the aldehyde acetals. A host of oxidising agents are available, however most are acidic. Considering the fact that the substrate 166 is thought to be acid sensitive because of the acetal backbone, it was decided to employ the mild Swern oxidation procedure.7,8

Satisfyingly, oxidation of 166 under Swern conditions afforded the desired aldehyde acetal 176 in excellent yield (95%) (Scheme 2.14).
Evidence for the formation of the aldehyde acetal 176 was obtained from the IR, $^1$H and $^{13}$C NMR spectra. Analysis of the IR spectrum showed the disappearance of the characteristic broad signal attributed to the alcohol at 3390 cm$^{-1}$ and the appearance of a signal corresponding to the aldehyde at 1744 cm$^{-1}$. The $^1$H NMR spectrum contained a characteristic signal corresponding to the aldehyde at 9.63 ppm, whilst the disappearance of the signal at 3.73 ppm confirmed the oxidation at C-1 of the carbinol. The $^{13}$C NMR spectrum provided key evidence with the appearance of a characteristic signal corresponding to the aldehyde at 201.4 ppm.

The alcohol acetals 166-175 were then oxidized to the corresponding aldehyde acetals 176-185 using the Swern protocol. Evidence for the formation of the aldehyde acetals 176-185 was as discussed above and is summarised in the table below (Scheme 2.15, Table 2.5).
Chapter II: Synthesis of Aldehyde Acetals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituent</th>
<th>Yield (%)</th>
<th>IR (cm⁻¹)</th>
<th>$^1$H and $^{13}$C NMR (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R₁=Ph, R₂=H, R₃=CH₃</td>
<td>95</td>
<td>1744 (CHO)</td>
<td>176 : 9.63 (CHO), 201.4 (CHO)</td>
</tr>
<tr>
<td>2</td>
<td>R₁=H, R₂=Ph, R₃=CH₃</td>
<td>94</td>
<td>1747 (CHO)</td>
<td>177 : 9.55 (CHO), 199.2 (CHO)</td>
</tr>
<tr>
<td>3</td>
<td>R₁=Ph, R₂=H, R₃=Ph</td>
<td>95</td>
<td>1729 (CHO)</td>
<td>178 : 9.54 (CHO), 197.6 (CHO)</td>
</tr>
<tr>
<td>4</td>
<td>R₁=H, R₂=Ph, R₃=Ph</td>
<td>98</td>
<td>1727 (CHO)</td>
<td>179 : 9.35 (CHO), 192.3 (CHO)</td>
</tr>
<tr>
<td>5</td>
<td>R₁=Bn, R₂=H, R₃=Ph</td>
<td>91</td>
<td>1736 (CHO)</td>
<td>180 : 9.42 (CHO), 196.0 (CHO)</td>
</tr>
<tr>
<td>6</td>
<td>R₁=H, R₂=Bn, R₃=Ph</td>
<td>94</td>
<td>1733 (CHO)</td>
<td>181 : 9.30 (CHO), 193.6 (CHO)</td>
</tr>
<tr>
<td>7</td>
<td>R₁=p-NO₂C₆H₄, R₂=H, R₃=CH₃</td>
<td>88</td>
<td>1737 (CHO)</td>
<td>182 : 9.63 (CHO), 200.2 (CHO)</td>
</tr>
<tr>
<td>8</td>
<td>R₁=H, R₂=p-NO₂C₆H₄, R₃=CH₃</td>
<td>80</td>
<td>1741 (CHO)</td>
<td>183 : 9.61 (CHO), 199.5 (CHO)</td>
</tr>
<tr>
<td>9</td>
<td>R₁=CH₃, R₂=NO₂, R₃=CH₃</td>
<td>79</td>
<td>1741 (CHO)</td>
<td>184 : 9.52 (CHO), 198.6 (CHO)</td>
</tr>
<tr>
<td>10</td>
<td>R₁=NO₂, R₂=CH₃, R₃=CH₃</td>
<td>86</td>
<td>1759 (CHO)</td>
<td>185 : 9.40 (CHO), 196.7 (CHO)</td>
</tr>
</tbody>
</table>

Table 2.5

In most cases studied, excellent yields of aldehyde acetals were obtained, with only the yields of the nitro-substituted aldehydes 182-185 (entry 7-10) falling below 90%.
2.4 Conclusions

The reduction of diethyl-2-benzylmalonate and diethyl-2-phenylmalonate to the corresponding diols was successfully achieved in good yields, the diols were subsequently transformed sequentially into the ester acetal, alcohol acetal and finally into the key aldehyde acetals.

In forming the ester acetals, isomeric mixtures of products were obtained which are generally separable by flash column chromatography and variations in the electronic nature of the aryl group had little effect on the stereoselectivity of the acetalisation step.

Initial attempts at transforming the ester acetals to the aldehyde acetals in one step proved unsuccessful. However, their reduction with excess DIBAL delivered the alcohol acetals in good to quantitative yields.

Subsequent oxidation using the Swern protocol proceeded uneventfully to give the desired aldehyde acetals in reasonably good yields without any undesired effect on the acetal core.

Having developed an efficient protocol for the preparation of the aldehyde acetals, attention turned towards their conversion into the corresponding diazoacetoacetates. This will be the object of the next Chapter.
Chapter II: Synthesis of Aldehyde Acetals

2.5 References


5. Wardrop, D. J.; Forslund, R. E.; Landrie, C. L.; Velter, A. I.; Wink, D.; Surve, B.

3.1 Introduction

Previous research by Garbi\(^1\) involved the elegant synthesis of trisubstituted tetrahydrofurans 187 from a study conducted on the acceptor substituted class of carbenoids,\(^2\) such as 186 (Scheme 3.1).

\[\text{HO} \quad \text{HO} \quad \text{HO} \]
\[\text{MeO} \quad \text{O} \quad \text{N}_2 \quad \text{2} \quad \text{O} \quad \text{H} \quad \text{EtO} \quad \text{2} \quad \text{O} \quad \text{Et} \]
\[145 \quad \rightarrow \quad 186 \quad \rightarrow \quad 187 \quad \rightleftharpoons \quad 188 \quad \text{several steps} \]

Scheme 3.1

However, the preparation of the carbenoid 186 from the ester 145 was achieved in low yields. Moreover, the transformation of ester 145 into the diazoketone 186 involved the use of the toxic and explosive diazomethane solution. Therefore, further extension to this project resulted in investigating the acceptor-acceptor-substituted carbenoids, such as 205. It was the plan to efficiently convert the ester 145 into the diazoacetoacetate 205 without the use of the diazomethane solution. Ultimately, further transformations of 205 were anticipated to deliver the highly substituted tetrahydrofuran 188 with an increased functionality that could be exploited. This chapter will describe the synthesis of the diazoacetoacetates, an acceptor-acceptor-substituted carbenoids and the development of a one-pot procedure for the preparation of diazoacetoacetate derivatives.
3.2 Synthetic strategy

The retrosynthetic disconnections for the preparation of the target acetal substrate (I) are illustrated in the following scheme (Scheme 3.2).

![Scheme 3.2](image)

It was proposed that the diazoacetoacetate acetal (I) could be obtained from the diazo ketol acetal (II) by oxidation of the alcohol. An aldol-type condensation between diazo ester (III) and aldehyde (IV) was then expected to deliver II.

After having successfully prepared the set of aldehydes acetals 176-185, attention now turned to the study of their aldol-type condensation.

3.2.1 Preparation of diazoketol acetals

In 1972, Wenkert and McPherson\(^3\) developed a method for the synthesis of \(\alpha\)-diazo-\(\beta\)-hydroxy esters 191 using various aldehydes 189 and ethyl diazoacetate 190 (Scheme 3.3).

![Scheme 3.3](image)
Chapter III: Synthesis of Diazooacetate Derivatives

The reaction involves a condensation between the aldehyde 189 and ethyldiazoacetate (EDA) 190 giving high yields of the α-diazo-β-hydroxy ester products 191. The mechanism involves deprotonation of the diazo compound 190 with the resulting diazo substituted anion acting as the nucleophile in an aldol type addition with the aldehyde 189.

Since then, various bases have been employed for this important deprotonation step including, sodium hydride\(^4\), lithium diisopropylamide (LDA)\(^5\) and butyllithium\(^6\). Recently, Varala\(^7\), Davies\(^8\) and Wang\(^9\) expanded the scope of applicable bases when they independently reported the use of quarternary ammonium hydroxide, diethyl zinc and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) respectively under milder conditions to give good yields of products. However, of these, by far the most widely employed base is LDA.

3.2.1.1 Application

Based on the wide acceptability, it was decided to evaluate the condensation reaction employing the use of LDA in the aldol-type conversion of 176 into 194 (Scheme 3.4). Thus, a cooled solution of LDA was added to ethyldiazoacetate 190 in THF at -78°C followed by the addition of the aldehyde acetal 176.

![Scheme 3.4](image)

Although analysis of the \(^1\)H NMR spectrum of the crude reaction mixture provided evidence to suggest the formation of the product 194 with the appearance of a signal at 4.85 ppm attributed to the C-3 proton, attempts to isolate this from the complex mixture of products were unsuccessful. One possible reason for the formation of such a complex mixture might be the self condensation of ethylidiazoacetate (5 eq) under the influence of LDA.
Since the failure of the above reaction was attributed to the strong basic nature of LDA, it was decided to evaluate the use of a milder base. Wang et al has shown that DBU can be efficiently used for the deprotonation of ethyldiazoacetate 190 to give good to excellent yields of products 193 following a condensation reaction with various aldehydes 192 (Scheme 3.5).

![Scheme 3.5](image)

Following this precedent, solutions of DBU and aldehyde 176 in acetonitrile were successively added to ethyldiazoacetate 190 at room temperature. Following work-up and purification by flash column chromatography on silica gel, the diazoketol acetal 194 was obtained in good yield (86%).

Evidence for the formation of the diazoketol acetal 194 was obtained from the $^1$H NMR, $^{13}$C NMR and IR spectra. The $^1$H NMR spectrum clearly indicated the disappearance of the signal attributed to the aldehyde proton at 9.63 ppm whilst the appearance of three additional signals at 4.85 ppm, 4.27 ppm and 1.28 ppm could be assigned to 3- $H$, 1-OCH$_2$CH$_3$ and 1-OCH$_3$CH$_3$ respectively. Further evidence for the diazoketol 194 was obtained from a signal at 2.84 ppm in the $^1$H NMR spectrum assigned to the 3- $OH$ group which disappeared when the sample was shaken with deuterated water (D$_2$O). The $^{13}$C NMR spectrum showed the disappearance of the signal corresponding to the aldehyde carbon at 201.4 ppm and the appearance of signals corresponding to the ester carbon (C-1) at 166.4 ppm and diazo carbon (C-2) at 57.9 ppm together with the signals at 67.8 ppm, 60.8 ppm and 14.4 ppm corresponding to C-3, 1-OCH$_3$CH$_3$ and 1-OCH$_2$CH$_3$ respectively. Finally, a comparison of the IR spectrum of the starting aldehyde 176 and diazoketol acetal 194 showed the disappearance of the signal at 1744 cm$^{-1}$ attributed to the aldehyde and the appearance of a broad signal corresponding to the alcohol at 3520-3410 cm$^{-1}$, a characteristic ester signal at 1683 cm$^{-1}$ and a signal at 2096 cm$^{-1}$ diagnostic of the diazo functional group.

In a similar fashion, the aldehyde acetals 176-180, 182 and 184 were then transformed to the corresponding diazoketol acetals 194-200 by the use of EDA and DBU. Key evidence for the
formation of the diazoketol acetals are summarised in the following table (Scheme 3.6, Table 3.1).

![Scheme 3.6]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituents</th>
<th>Yield (%)</th>
<th>IR (cm⁻¹)</th>
<th>¹³C and ¹H NMR (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R₁=Ph, R₂=H, R₃=CH₃</td>
<td>86</td>
<td>2096 (CN₂)</td>
<td>194 : 166.4 (CO), 2.84 (OH)</td>
</tr>
<tr>
<td>2</td>
<td>R₁=H, R₂=Ph, R₃=CH₃</td>
<td>79</td>
<td>2103 (CN₂)</td>
<td>195 : 166.7 (CO), 3.07 (OH)</td>
</tr>
<tr>
<td>3</td>
<td>R₁=Ph, R₂=H, R₃=Ph</td>
<td>80</td>
<td>2114 (CN₂)</td>
<td>196 : 166.1 (CO), 3.04 (OH)</td>
</tr>
<tr>
<td>4</td>
<td>R₁=H, R₂=Ph, R₃=Ph</td>
<td>79</td>
<td>2103 (CN₂)</td>
<td>197 : 166.0 (CO), 3.11 (OH)</td>
</tr>
<tr>
<td>5</td>
<td>R₁=Bn, R₂=H, R₃=Ph</td>
<td>64</td>
<td>2098 (CN₂)</td>
<td>198 : 166.0 (CO), 3.30 (OH)</td>
</tr>
<tr>
<td>6</td>
<td>R₁=p-NO₂C₆H₄, R₂=H, R₃=CH₃</td>
<td>94</td>
<td>2099 (CN₂)</td>
<td>199 : 166.4 (CO), 1.29 (OCH₂CH₃)</td>
</tr>
<tr>
<td>7</td>
<td>R₁=CH₃, R₂=NO₂, R₃=CH₃</td>
<td>96</td>
<td>2107 (CN₂)</td>
<td>200 : 166.2 (CO), 2.83 (OH)</td>
</tr>
</tbody>
</table>

Table 3.1

In all the cases studied, the diazoketol acetals 194-200 were obtained in good to excellent yields as pure samples and were subsequently taken through to the next step of the synthesis.
Chapter III: Synthesis of Diazoacetoacetate Derivatives

With an efficient synthetic protocol of the diazoketol acetals established, attention turned towards their oxidation.

### 3.2.2 Oxidation of diazoketol acetals

Deng in a recent study showed that manganese (IV) oxide (MnO$_2$) can be conveniently used to oxidise $\alpha$-diazo-$\beta$-hydroxycarbonyls such as 201 to the corresponding $\alpha$-diazo-$\beta$-dicarbonyl products 202 in very good yields (Scheme 3.7).

![Scheme 3.7]

With this precedent, it was decided to evaluate the use of manganese (IV) oxide for the oxidation of the ketol 194. Thus, activated MnO$_2$ (10 eq) was added in two portions over 4 hours to a solution of diazoketol acetal 194 in dichloromethane (Scheme 3.8). After stirring for 10 hours at room temperature, the MnO$_2$ was then removed by filtration. This initial experiment however, resulted in poor yield of the product 205 (7%) and unreacted starting material 194 was recovered.

![Scheme 3.8]

Further efforts at increasing the yield involved variation of the reaction parameters including the amount of MnO$_2$ added, the reaction time and the number of portions over which the oxidant was added. The results obtained are shown in the table below (Table 3.2).
The best yield of 80% (entry 4) was obtained when 10 eq of MnO₂ was added in three portions over 48 hours. This result indicates the time dependence of the oxidation, as using the same 10 eq for a shorter time period afforded lower yields (entries 1-3). An increase to 30eq had no affect on the yield obtained (entries 5 vs 3).

Evidence for the formation of the diazodiketone acetal 205 was obtained from IR, ¹H NMR and ¹³C NMR spectra. The IR spectrum showed the disappearance of the broad stretch at 3520-3410 cm⁻¹ attributed to the alcohol and the appearance of a characteristic signal at 1732 cm⁻¹ corresponding to the carbonyl group. A comparison of the ¹H NMR spectra of the starting material 194 and the diazodiketone acetal 205 showed the disappearance of the signals at 4.85 ppm and 2.84 ppm attributed to 3-H and hydroxyl group respectively. The ¹³C NMR spectrum showed a signal at 188.6 ppm attributed to the carbonyl at C-3, further confirming the formation of the diazodiketone.

Similarly, acceptable results were obtained for the independent oxidations that resulted in the isolation of the diazodiketones 206, 210 and 211 (Figure 3.1).
Chapter III: Synthesis of Diazoacetoacetate Derivatives

Despite the optimisation of the oxidation reaction to obtain the diazodiketones 205, 206, 210 and 211 in respectable yields, it was felt that the required 48 hours reaction time represented a significant synthetic limitation. Therefore, it was decided to evaluate alternative oxidation conditions for this transformation. Initially, the diazoketol 194 was subjected to the Swern oxidation protocol. Gratifyingly, this led to the formation of diazodiketone acetal 205 in good yield of 76% after a reaction time of only 1 hour.

In a second experiment, the use of IBX as the oxidizing reagent was probed based on the precedent of Davies who independently reported the conversion of aldehyde 203 into 2-indolyl diazoketoester 204 (Scheme 3.9).8

![Scheme 3.9](image)

Thus, IBX dissolved in DMSO was added to a solution of ketol 194 in DMSO. Pleasingly, the diazodiketone acetal 205 was obtained in an excellent yield of 90% with both the diazo group and acetal backbone intact. More importantly, in comparison to the Swern reaction, this procedure provided a more facile purification which simply involved the wash of the crude reaction mixture with copious quantity of aqueous sodium bicarbonate to neutralise the excess acid. As before, all analytical data were in agreement with that previously obtained.

Having established an efficient protocol, the diazoketol acetals 194, 196, 198-200 were then oxidized to the corresponding diazodiketone acetals 205-209 using IBX. Key evidence for the formation of the diazodiketone acetals are summarised in the following table (Scheme 3.10, Table 3.3).

![Scheme 3.10](image)
In all cases, the diazodiketone acetals 205-209 were all obtained in good to quantitative yields as pure samples.

3.3 Development of a one-pot synthesis of diazoacetoacetate derivatives

Concurrent with the development of an efficient two step sequence for the preparation of diazodiketone acetals, Weinreb reported a conceptually similar protocol. The first step of this involved the LDA assisted condensation of ethyldiazoacetate with aldehydes 212 at -78 °C followed subsequently by a Dess-Martin periodinane (DMP) oxidation (Scheme 3.11).

![Scheme 3.11](image)

Although the reported yields of the diazoacetoacetate products 213 were good, we considered our methodology better and more appealing to a synthetic chemist because it involves the use of milder reagents under ambient conditions.
Towards this end, it was decided to investigate the generality of our methodology. Therefore, a select set of aliphatic, aromatic and heterocyclic aldehydes were investigated. Following the same procedures as described previously, efforts were made to transform the aldehydes 176, 214-219 into the corresponding diazoacetoacetates. Table 3.4 below summarises the results obtained.

Gratifyingly, for most compounds examined, good to excellent yields of $\alpha$-diazo-$\beta$-hydroxyl carbonyl products 194, 220-224 were obtained. Lower yields were obtained for aldehydes with electron donating groups for example 216 which gave a yield of 32% (entry 3).

Importantly, the subsequent oxidation using IBX was highly efficient, giving good to quantitative yields of diazoacetoacetate products 205, 226-230. Furthermore, in comparison with the Weinreb method, overall yields for this protocol were significantly enhanced. For example, while the use of benzaldehyde gave a yield of 62%, our protocol delivered a yield of 78% (entry 4).
### Table 3.4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde substrate</th>
<th>α-Diazo-β-hydroxyl compound&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Diazooacetoacetate derivative&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Overall yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Aldehyde 214" /></td>
<td><img src="image2" alt="α-Diazo-β-hydroxyl compound 220" /></td>
<td><img src="image3" alt="Diazooacetoacetate derivative 226" /></td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image4" alt="Overall yield (95 %)" /></td>
<td><img src="image5" alt="Overall yield (80 %)" /></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image6" alt="Aldehyde 215" /></td>
<td><img src="image7" alt="α-Diazo-β-hydroxyl compound 221" /></td>
<td><img src="image8" alt="Diazooacetoacetate derivative 227" /></td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image9" alt="Overall yield (93 %)" /></td>
<td><img src="image10" alt="Overall yield (100 %)" /></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image11" alt="Aldehyde 216" /></td>
<td><img src="image12" alt="α-Diazo-β-hydroxyl compound 222" /></td>
<td><img src="image13" alt="Diazooacetoacetate derivative 228" /></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image14" alt="Overall yield (32 % (85 %)&lt;sup&gt;c&lt;/sup&gt;)" /></td>
<td><img src="image15" alt="Overall yield (93 %)" /></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image16" alt="Aldehyde 217" /></td>
<td><img src="image17" alt="α-Diazo-β-hydroxyl compound 223" /></td>
<td><img src="image18" alt="Diazooacetoacetate derivative 229" /></td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image19" alt="Overall yield (81 %)" /></td>
<td><img src="image20" alt="Overall yield (96 %)" /></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image21" alt="Aldehyde 218" /></td>
<td><img src="image22" alt="α-Diazo-β-hydroxyl compound 224" /></td>
<td><img src="image23" alt="Diazooacetoacetate derivative 230" /></td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image24" alt="Overall yield (67 %)" /></td>
<td><img src="image25" alt="Overall yield (64 %)" /></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image26" alt="Aldehyde 176" /></td>
<td><img src="image27" alt="α-Diazo-β-hydroxyl compound 194" /></td>
<td><img src="image28" alt="Diazooacetoacetate derivative 205" /></td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image29" alt="Overall yield (86 %)" /></td>
<td><img src="image30" alt="Overall yield (90 %)" /></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image31" alt="Aldehyde 219" /></td>
<td><img src="image32" alt="α-Diazo-β-hydroxyl compound 225" /></td>
<td><img src="image33" alt="Diazooacetoacetate derivative 226" /></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image34" alt="Overall yield (0 %)" /></td>
<td><img src="image35" alt="Overall yield (0 %)" /></td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields after column chromatographic purification.

<sup>c</sup> The yield is based on recovered starting material.

<sup>nd</sup> Yield not determined.

---

Table 3.4
For all the compounds 194, 220-224 and 205, 226-230, satisfactory analytical and spectroscopic data were obtained. Key evidence for the formation of the α-diazo-β-hydroxyl carbonyl compounds 194, 220-224 are summarised below in Table 3.5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-Diazo-β-hydroxyl compound</th>
<th>IR (cm⁻¹)</th>
<th>¹³C and ¹H NMR (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2089 (CN₂)</td>
<td>220 : 166.8 (CO), 71.1 (CN₂), 2.50 (OH), 1.28 (OCH₂CH₃)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2092 (CN₂)</td>
<td>221 : 166.0 (CO), 77.2 (CN₂), 2.90 (OH), 1.31 (OCH₂CH₃)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2091 (CN₂)</td>
<td>222 : 166.4 (CO), 62.5 (CN₂), 2.96 (OH), 1.30 (OCH₂CH₃)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2093 (CN₂)</td>
<td>223 : 166.3 (CO), 66.4 (CN₂), 2.96 (OH), 1.30 (OCH₂CH₃)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>2091 (CN₂)</td>
<td>224 : 166.3 (CO), 65.9 (CN₂), 2.51 (OH), 1.27 (OCH₂CH₃)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>2096 (CN₂)</td>
<td>194 : 166.4 (CO), 57.9 (CN₂), 2.84 (OH), 1.28 (OCH₂CH₃)</td>
</tr>
</tbody>
</table>

Table 3.5

Likewise, key evidence for the formation of the diazoacetoacetates 205, 226-230 are summarised in Table 3.6 below.
Chapter III: Synthesis of Diazoacetoacetate Derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazoacetoacetate derivative</th>
<th>IR (cm⁻¹)</th>
<th>¹³C NMR (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Diazoacetoacetate structure" /></td>
<td>2130 (CN₂)</td>
<td>226 : 196.7 (CO)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Diazoacetoacetate structure" /></td>
<td>2146 (CN₂)</td>
<td>227 : 186.0 (CO)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Diazoacetoacetate structure" /></td>
<td>2139 (CN₂)</td>
<td>228 : 185.3 (CO)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Diazoacetoacetate structure" /></td>
<td>2139 (CN₂)</td>
<td>229 : 186.8 (CO)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Diazoacetoacetate structure" /></td>
<td>2133 (CN₂)</td>
<td>230 : 190.2 (CO)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Diazoacetoacetate structure" /></td>
<td>2127 (CN₂)</td>
<td>205 : 188.6 (CO)</td>
</tr>
</tbody>
</table>

Table 3.6

In general, this two-step sequence proved to be robust with a variety of aliphatic, alicyclic, heterocyclic and aromatic aldehydes including those with electron withdrawing and donating groups being converted in good yield to the corresponding diazoacetoacetate. Importantly, the oxidation reaction was very clean requiring minimal purification, which simply involved the removal of excess IBX using sodium bicarbonate. The only limitation is that highly electron-rich and α,β-unsaturated aldehydes gave only moderate conversions in the initial condensation step.

As only a catalytic amount of DBU was required for the synthesis of the α-diazo-β-hydroxyl carbonyl intermediates and the presence of small quantities of DBU is not deleterious to the action of IBX. It was speculated that this two-step procedure could be further simplified to a
one-pot method. The key parameter in this development would be the choice of a suitable common solvent. Initial attempts at dissolving IBX in acetonitrile, the solvent employed for the initial aldol condensation, indicated its limited solubility. Therefore the use of DMSO was explored. Pleasingly, aldehyde acetal 176, ethyldiazoacetate and DBU were all soluble in DMSO. In the event, treatment of a DMSO solution of aldehyde acetal 176 with ethyldiazoacetate and DBU for 8 hours, followed by the addition of a solution of IBX in DMSO, afforded the desired diazodiketone acetal 205 in an excellent yield (91%) (Scheme 3.12).

![Scheme 3.12](image)

Analytical and spectroscopic data obtained were in agreement with that previously obtained. Pleased with this result and having established the compatibility of all the reagents, it was decided to examine the possibility of further telescoping the procedure by adding the oxidant at the outset of the reaction, which would make the transformation a genuine one-pot, one-step protocol (Scheme 3.13).

![Scheme 3.13](image)

Again this proved successful, providing the diazodiketone acetal 205 in 89% yield. Similarly, the aldehydes 214-219 were each converted to the corresponding diazoacetoacetates. Table 3.7 summarises the results obtained.
### Entry | Aldehyde substrate | Diazoacetoacetate derivative<sup>a</sup>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
</tr>
<tr>
<td>7</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields after column chromatographic purification.

Table 3.7
Chapter III: Synthesis of Diazooacetooacetate Derivatives

The diazoacetooacetate derivatives 205, 226-231 were obtained in good to excellent yields that are equal to or greater than that obtained by the standard two-step protocol. Again, a variety of aldehydes were tolerated including aliphatic, heterocyclic and aromatics bearing both electron withdrawing and donating groups. Most importantly, this one-pot procedure allowed both electron-rich 216 (entry 3) and α,β-unsaturated 219 (entry 7) aldehydes to be converted to the desired diazoacetooacetates in moderate to good yield. As before, satisfactory analytical and spectroscopic data were obtained for the products.
Chapter III: Synthesis of Diazoacetoacetate Derivatives

3.4 Conclusions

The transformation of the aldehyde acetals to the diazoketol acetals and ultimately to the target diazodiketone acetals was successfully achieved.

The synthesis of the diazoketol acetals involved an aldol-type condensation between an appropriate aldehyde acetal and ethyl diazoacetate. Although, initial efforts using LDA were unsuccessful, however DBU proved to be the base of choice.

Oxidation of the diazoketol acetals to the diazodiketone acetals was equally a success, initial choice of oxidants including MnO₂ and Swern oxidation had issues of practicability and purification. However, the choice of IBX proved optimal, delivering products in exceptional yields.

Harmonisation of the aldol-type condensation with the oxidation reactions, led to the development of a simple and efficient one-pot protocol for the synthesis of diazoacetoacetate derivatives from aldehydes in good yields.

Having successfully synthesised the diazoacetoacetates – acceptor/acceptor substituted carbenoids, subsequent efforts were directed at their catalytic decomposition. This will constitute the subject of the next chapter.
3.5 References

Chapter IV: Synthesis of Barceloneic Lactone Derivatives

4.1 Introduction

The preceding chapter discussed the preparation of a range of diazodiketone acetics, representative of the acceptor-acceptor substituted class of carbenoids. This chapter aims to present studies of C-H insertion reactions, undertaken with this class of carbenoids when exposed to metal catalyst(s) and efforts that resulted in the successful preparation of Barceloneic lactone derivatives.

4.2 Studies of diazodiketone C-H insertion reactions

As discussed in Chapter 1, a large variety of metal catalysts have been reported for the decomposition of diazo compounds. The choice of an appropriate metal catalyst depends on many subtle factors including the nature of ligands on the metal centre and electronics of the substituent on the diazo group. Previous studies by Garbi within the group, have shown that the rhodium (II) acetate catalysed decomposition of diazo ketone acetal 131 gives the bicyclic ketone acetal 132 in reasonable yields (Scheme 4.1).

![Scheme 4.1](image)

Based on the precedent developed by Garbi, it was decided to evaluate the use of Rh$_2$(OAc)$_4$ catalyst in the transformation of the diazodiketone acetal 205 to the bicyclic ketone acetal 232 (Scheme 4.2). It was hoped that the additional ester substituent on the diazo carbon would enhance the yield for the formation of the functionalised bicyclic ketone 232 and also provide an opportunity to further elaborate the product.
Scheme 4.2

In a typical reaction, a solution of the diazodiketone acetal 205 in DCM was added dropwise via a syringe pump to a stirred solution of Rh\(_2\)(OAc)\(_4\) (1 mol%) in DCM at room temperature. Unfortunately, initial attempts were unsuccessful, with the majority of reactions leading generally to recovery of starting material 205. Further attempts towards preparing the bicyclic ketone product 232 involved varying the catalyst loading and the temperature of the reaction. Various solvents were also screened and the results are presented below in table 4.1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (mol%)</th>
<th>Rate of addition</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>over 24 hours</td>
<td>CH(_2)Cl(_2)</td>
<td>Room temp</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>over 24 hours</td>
<td>CH(_2)Cl(_2)</td>
<td>Room temp</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>over 24 hours</td>
<td>CH(_2)Cl(_2)</td>
<td>Room temp</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>over 24 hours</td>
<td>CH(_2)Cl(_2)</td>
<td>Reflux</td>
<td>SM + CM</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>over 24 hours</td>
<td>Toluene</td>
<td>Reflux</td>
<td>SM + CM</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>3 portions</td>
<td>Toluene</td>
<td>Reflux</td>
<td>SM + CM</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>over 24 hours</td>
<td>Benzene</td>
<td>Reflux</td>
<td>SM + CM</td>
</tr>
</tbody>
</table>

SM = Starting material; CM = Complex mixture

Table 4.1

Disappointingly, in all cases the product(s) of the reaction were unidentifiable, irrespective of the increases in catalyst loading to 5 mol% and the varying of solvent temperatures from room temperature to reflux. However, two deductions became apparent;
Chapter IV: Synthesis of Barceloneic Lactone Derivatives

1. Since an increase in the catalyst loading and the temperature of the reaction did not give the desired products, it was thought that either the catalyst was not suitable to effect the decomposition of the diazodiketone acetal 205 or presumably diazodiketone 205 was too stable to be reactive. Towards this end, a more reactive electrophilic rhodium (II) carboxylate catalyst was thought to be appropriate.

2. Although 1,3-dioxanes-2-carboxylic acid derivatives display a pronounced preference (~3 to 4 kcal/mol) for an axially oriented 2-carboxylate group, the bulkiness of this derivative in diazodiketone acetal 205 may have caused a ring inversion or ‘flip’, leading to an orientation that places it in an equatorial position as in 233 (Scheme 4.3).

![Scheme 4.3](image)

In this conformation, a combination of 1,3 interactions, the large distance between the C-2 diazo group and the heteroatom activated C-4’/6’-H bond together with their loss of ideal coplanar arrangement precludes the C-H insertion reaction from taking place.
Hence, in an effort to rule out the possibility of a ring inversion, it was decided to attempt the rhodium (II) acetate catalysed decomposition reaction of diazodiketone acetal 206 (Scheme 4.4). It was anticipated that the bulky C-2’ phenyl ring in 206 would ‘lock’ the orientation, thereby preventing ring inversion.

Unfortunately, the reaction gave a complex mixture which included recovered starting material and unidentifiable products without a trace of the desired bicyclic ketone acetal product 234. Further attempts to increase the temperature of the reaction only resulted in a complex mixture.

Having established that the ring inversion was an unlikely reason for the non-observance of C-H insertion products, attention turned towards the former hypothesis.

4.2.1 Formation of insertion products

From an extensive literature survey, it was established that C-H insertions of diazocarbonyl compounds can show high levels of chemoselectivity that varies according to the nature of the catalyst employed. Therefore it was decided to evaluate the use of rhodium (II) catalyst with differing electron demands of the ligands. Rhodium (II) octanoate [Rh₂(oct)₄] and rhodium (II) heptafluorobutyrate [Rh₂(pfb)₄] catalysts were investigated because they represented both ends of the rhodium (II) catalysts reactivity/selectivity spectrum. According to the spectrum, Rh₂(oct)₄ catalyst bearing electron donating ligands is noted to show low reactivity but high selectivity while Rh₂(pfb)₄ with electron withdrawing ligands shows high reactivity accompanied with low selectivity. Therefore, following the same procedure outlined above, the diazodiketone acetal 205 was submitted to C-H insertion mediated by Rh (II) catalyst. Initial attempts using the Rh₂(oct)₄ catalyst resulted in recovery of the starting material (entry 1 & 2,
Chapter IV: Synthesis of Barceloneic Lactone Derivatives

Table 4.2). However, further attempts made using the Rh$_2$(pfb)$_4$ catalyst led to a 20% yield of product 235 (entry 3, Table 4.2, Scheme 4.5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cat. loading (mol%)</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Rate of addition of SM</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh$_2$(oct)$_4$</td>
<td>2</td>
<td>rt</td>
<td>DCM</td>
<td>Over 24h</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>Rh$_2$(oct)$_4$</td>
<td>2</td>
<td>Reflux</td>
<td>DCM</td>
<td>Over 24h</td>
<td>SM + CM</td>
</tr>
<tr>
<td>3</td>
<td>Rh$_2$(pfb)$_4$</td>
<td>2</td>
<td>rt</td>
<td>DCM</td>
<td>Over 24h</td>
<td>20</td>
</tr>
</tbody>
</table>

SM = Starting material; CM = Complex mixture

Table 4.2

Evidence for the formation of the trioxabicyclic product 235 was obtained from the IR, $^1$H NMR and $^{13}$C NMR spectra. Comparison of the IR spectrum of 205 with that of product 235 showed the disappearance of the signal at 2127 cm$^{-1}$ attributed to the diazo functionality (C=N$_2$) and the appearance of a signal at 1705 cm$^{-1}$ assigned to the enol ether. The $^1$H NMR spectrum showed the disappearance of the signal at 3.91 ppm attributed to 4'/6'-H and the appearance of two singlets at 6.00 ppm and 5.16 ppm corresponding to 5'-H and 2-H respectively. The $^{13}$C NMR spectrum showed the disappearance of the signal at 188.6 ppm attributed to the carbonyl at C-3 and the appearance of a signal at 162.7 ppm assigned to the carbon of the enol ether (C-7').
Surprisingly, the isolated product was not the desired bicyclic ketone acetal 232. Although most signals obtained from IR, 1D and 2D NMR spectra could be assigned to compound 232, a critical analysis of the 2D NMR spectra (particularly NOESY and HMBC) obtained supported the structure 235 (Figure 4.1).

These data suited compound 235 better than 232 due to the IR and $^{13}$C NMR signals at 1705 cm$^{-1}$ and 162.7 ppm respectively, which are considered too low for the carbonyl group (C-7) present in 232 but suitable for an enol ether in 235. In addition, in the $^1$H NMR spectrum of 232, the signals corresponding to 5'-H and 6'-H would be expected to be doublets, however those attributed to 2'-H and 5''-H in compound 235 appeared as singlets.

More convincing evidence for structure 235 was provided by NOESY experiment (Figure 4.2, A) which showed correlation between 1'-CH$_3$ and 2-H, and the HMBC spectrum (Figure 4.2, B) which indicated correlations between 5'-H and C-7’, 1’-CH$_3$ and C-7’, and finally 2-H and C-7’.
Chapter IV: Synthesis of Barceloneic Lactone Derivatives

The trioxabicyclic ester 235 is however not an entirely strange product. Its formation by an O-H insertion is due to the highly electron withdrawing nature of the perfluorobutyrate ligands and hence confirmed that generation of the intermediate carbenoid was accessible. Clark and co-workers recently reported the formation of analogous products such as 238 during the diazo decomposition of \( \alpha \)-diazo-\( \alpha' \)-alkoxy ketones 236 in their studies of Rh (II) carboxylate mediated C-H insertion (Scheme 4.6).\(^6\)

![Scheme 4.6](image)

The generally accepted mechanistic rationale for the formation of 235 is shown below (Scheme 4.7).

![Scheme 4.7](image)
Chapter IV: Synthesis of Barceloneic Lactone Derivatives

In this mechanism, catalytic decomposition of diazodiketone acetal 205 gives the carbenoid 239. Subsequent oxygen assisted hydride transfer to the electrophilic carbon of the carbenoid affords the reactive intermediate 240, which contains both an enolate and oxonium ion. Intramolecular attack on the oxonium ion by the oxygen of the enolate then gives the observed O-H insertion product 235.

Having tried unsuccessfully to access the C-H insertion product from diazo diketone acetal 205 using a rhodium (II) catalyst, efforts were diversified towards the screening of other metal catalysts known to be suitable for similar insertion reactions (Scheme 4.8). The results obtained are summarised in table 4.3.

![Scheme 4.8](image)

**Table 4.3**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temp.</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>rt</td>
<td>205</td>
</tr>
<tr>
<td>2</td>
<td>Pd(acac)$_2$</td>
<td>rt</td>
<td>205</td>
</tr>
<tr>
<td>3</td>
<td>Cu(acac)$_2$</td>
<td>rt</td>
<td>205</td>
</tr>
<tr>
<td>4</td>
<td>Cu(hfacac)$_2$</td>
<td>rt</td>
<td>205</td>
</tr>
<tr>
<td>5</td>
<td>Cu(hfacac)$_2$</td>
<td>35 °C</td>
<td>205 + decomposition</td>
</tr>
<tr>
<td>6</td>
<td>Rh$_2$(DOSP)$_4$</td>
<td>rt</td>
<td>235</td>
</tr>
<tr>
<td>7</td>
<td>Rh$_2$(MEPY)$_4$</td>
<td>rt</td>
<td>205</td>
</tr>
<tr>
<td>8</td>
<td>Rh$_2$(tfa)$_4$</td>
<td>rt</td>
<td>205</td>
</tr>
</tbody>
</table>
Chapter IV: Synthesis of Barceloneic Lactone Derivatives

Disappointingly, none of the catalysts attempted led to the formation of the desired product 232. However, Davies’s asymmetric catalyst Rh$_2$(DOSP)$_4$ afforded a 20% yield of the O-H insertion product 235.$^7$

Having attempted to prepare 232 using a series of metal catalysts without success, it was decided to investigate the ambitious possibility of efficiently synthesising 235 using Rh$_2$(pfb)$_4$ and then explore the possibility of a Ferrier-type rearrangement$^8$ towards obtaining 232 (Scheme 4.9).

![Scheme 4.9](image)

It was anticipated that a Lewis acid would coordinate to the carbonyl oxygen of the ester 235 giving the intermediate 241. Thereby triggering a global shift in electrons, that would ultimately result in intermediate 242, containing both an enolate and oxonium ion. Finally, upon work-up, intramolecular attack by the carbon of the enolate on the oxonium ion was expected to give 232.

In order to investigate the rearrangement, it was necessary to be able to prepare 235 efficiently. Therefore optimisation studies was conducted on the Rh$_2$(pfb)$_4$ catalysed decomposition of
diazoketone 205 (Scheme 4.5), which included varying the catalyst loading and the rate of substrate addition. The results obtained are shown in Table 4.4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cat. loading (mol%)</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Rate of addition of SM</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh₂(pfb)₄</td>
<td>2</td>
<td>rt</td>
<td>DCM</td>
<td>Over 24h</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Rh₂(pfb)₄</td>
<td>2</td>
<td>Reflux</td>
<td>DCM</td>
<td>Over 24h</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>Rh₂(pfb)₄</td>
<td>2</td>
<td>rt</td>
<td>DCM</td>
<td>Instant</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Rh₂(pfb)₄</td>
<td>5</td>
<td>rt</td>
<td>DCM</td>
<td>Over 24h</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>Rh₂(pfb)₄</td>
<td>5</td>
<td>rt</td>
<td>DCM</td>
<td>Instant</td>
<td>40</td>
</tr>
</tbody>
</table>

SM = Starting material; CM = Complex mixture

**Table 4.4**

The best yield of 40% (entry 5) was obtained at a loading of 5 mol% in DCM and with both the substrate and the catalyst present in the reaction flask at the outset of the reaction as opposed to the addition of the substrate via a syringe pump into a solution of the catalyst over time (cf entry 4 vs 5). The result also indicates that the reaction does not tolerate prolonged high temperature due to instability of the product under these conditions (entry 2 vs 3). Notably, increasing the catalyst loading to 5 mol% resulted in an increase in yield of 13% (entry 3 vs 5).

To explore this rearrangement, three Lewis acids BF₃.OEt₂, TiCl₄ and Sc(OTf)₃ were screened. In a typical experiment, a solution of the trioxabicycle 235 (1 eq) in DCM was cooled to -78 °C and then a solution of the Lewis acid (1 eq) in DCM was added. After 6 hours, TLC indicated only starting material, it was then allowed to warm up to room temperature and stirred overnight.

Following work-up and purification, the BF₃.OEt₂ and Sc(OTf)₃ mediated reactions gave only starting material 235. However the ¹H NMR spectrum of the crude TiCl₄ mediated reaction was more promising as it showed complete consumption of starting material but analysis was difficult owed to a complex mixture of products.
Having tried to accomplish the synthesis of 232 from 205 by the choice of a suitable metal catalyst and also by Lewis acid catalysed rearrangement from 235 without success, it was decided to modify the substrate.

4.2.2 Modification of substrate

4.2.2.1 Methylenation reaction

Considering that the formation of the O-H insertion product 235 proceeds through a rearrangement involving the carbonyl oxygen in diazodiketone acetal 205, it was thought that this oxygen assisted rearrangement could be prevented by converting the carbonyl oxygen to a carbon via methylenation reaction (Scheme 4.10).

Scheme 4.10

The first attempt was to evaluate the Wittig reaction in the methylenation step. Thus, a solution of methyltriphenylphosphonium bromide (CH₃PPh₃Br) in THF was cooled to 0 °C before the addition of a strong base. The reaction mixture turned brick red colour after 30 min, followed by adding a solution of 205 before warming to room temperature. A range of conditions were explored for the methylenation procedure and the results obtained are summarised in table 4.5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA, CH₃PPh₃Br, THF, 0 °C</td>
<td>SM recovered</td>
</tr>
<tr>
<td>2</td>
<td>n-BuLi, CH₃PPh₃Br, THF, 0 °C</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>NaH, CH₃PPh₃Br, DMSO, rt</td>
<td>SM recovered</td>
</tr>
</tbody>
</table>

SM = Starting material

Table 4.5
Chapter IV: Synthesis of Barceloneic Lactone Derivatives

The Wittig reactions involving LDA and NaH were unsuccessful (entry 1 and 3), reactions led to recovery of starting material 205. When n-butyllithium was used as the base (entry 2), a complex mixture of unidentifiable products were obtained. Since efforts to obtain product 244 by preforming the Wittig reagent were unsuccessful, it was decided to attempt the methylenation reaction using the commercially available Tebbe’s reagent. Thus, a solution of Tebbe’s reagent in toluene was added to a solution of diazodiketone acetal 205 in THF at 0 °C. The reaction mixture was then allowed to warm up to room temperature and quenched after 30 min. Following flash column chromatography, the diazodiketone acetal 205 was recovered together with 6% of the O-H insertion product 235. Surprisingly, neither the oxygen of the carbonyl nor the ester group was methylenated. Although, it is not quite clear why this was the case, it was thought that steric effects could have played a role.

4.2.3 Barceloneic lactone synthesis

Since attempts at preparing the bicyclic ketone acetal 232 at room temperature were unsuccessful and the previous use of prolonged high temperature led to mainly decomposition. It was decided to alter the sequence and rate of addition at elevated temperature, with the aim of isolating any product formed prior to decomposition. In a typical experiment, a solution of diazo diketone acetal 205 was slowly added over time to a pre-heated solution of a catalyst. Initial attempts involved the use of Rh$_2$(OAc)$_4$ in refluxing DCM to give a 3% yield of product 248 and mainly decomposition (Scheme 4.11).

![Scheme 4.11](image)

Following isolation and $^1$H NMR analysis, the structure of the isolated compound was inconclusive and complete characterisation was impossible as the reaction was carried out on a
small scale. Further attempts using benzene at reflux for a 2 hour period, surprisingly, gave the product 248 in 40% isolated yield. However, data obtained clearly showed that 248 was not the desired bicyclic ketone acetal 232.

Analysis of the $^{13}$C NMR spectrum indicated two ester carbonyl signals at 168.1 ppm and 166.2 ppm that were clearly conjugated to an alkene at 168.5 ppm. Moreover, the $^1$H NMR chemical shift corresponding to the C-4 methyl group at 2.29 ppm suggested that this too was coupled to the conjugated system. These, combined with mass spectral data (ES$^+$) which suggested a molecular ion of $m/z = 291 [M+Na]^+$ led to the suggestion that the unusual lactone 248 has been obtained.

Stronger evidence for such a proposal came from careful analysis of correlations in the various 2D NMR experiments undertaken. Notably, a significant NOESY correlation was observed between 1′-OCH$_2$CH$_3$ and the 4-CH$_3$ signal, consistent with a cis alkene and thereby confirming the cyclic nature of the lactone. Further evidence was obtained from HSQC and HMBC experiments, with the HMBC correlations of C-2 to 8-H, C-4 to 6-H and C-3 to 4-CH$_3$ providing strong support for the proposed structure (Figure 4.3).

A search of various databases revealed that this structure was novel with the closest analogue being found in the fungal natural products barceloneic lactone 245, isolated from a fungus of the genus Phoma in a screen for protein-farnesyl tranferase (PFT-ase) inhibitors, and penicillide 246 and dehydropenicillide 247, found in the ascomycetous fungus Talaromyces derxii, Figure 4.4.
Chapter IV: Synthesis of Barceloneic Lactone Derivatives

Figure 4.4

Since synthetic approaches to these compounds have not been reported, it was considered that a brief examination of the scope and mechanism of this rearrangement was merited. Further attempts to perform the reaction at a higher temperature and for a shorter period of time necessitated the search for a higher boiling solvent. Happily, the use of toluene for this reaction had no effect on the reaction outcome. By-passing the slow addition process and simply heating the diazo diketone acetal 205 with Rh₂(pfb)₄ in toluene afforded a mixture of 235 (45%) and 248 (22%) (Scheme 4.12).

Scheme 4.12
Chapter IV: Synthesis of Barceloneic Lactone Derivatives

The formation of 235 (as a result of the electron withdrawing ligands on Rh\textsubscript{2}(pfb)\textsubscript{4} catalyst) represented a background reaction occurring prior to reaching the critical reaction temperature for the rearrangement. This was confirmed by repeating this process in a microwave reactor (Scheme 4.13).

\[ \text{EtO}_2\text{C} \rightleftharpoons \text{N}_2 \rightleftharpoons \text{EtO}_2\text{C} \]

Under these conditions, a cleaner reaction with no evidence for the formation of 235 could be achieved at much lower reaction temperatures (70 °C) and shorter reaction times (10 min). Whilst heating is essential, it is not a sole requirement, as all attempts to achieve this transformation in the absence of a Rh (II) complex failed leading to a complex mixture of products with no evidence for any lactone formation. Similarly, all attempts to reproduce this transformation using diazo ketone 186 which lacks the additional stabilising element failed leading only to extensive decomposition. However, in terms of the scope of the reaction, variation in both components of the acetal is tolerated giving various derivatives of barceloneic lactone. Key evidence for the formation of these derivatives are summarised in the following table (Scheme 4.14, Table 4.6).
In all the cases, reactions led to similar yields of products. However, to account for the aforementioned observations, we propose a pathway in which initial carbene generation is achieved under promotion by a Rh (II) complex, Scheme 4.15. At room temperature this reacts to afford the O-H insertion product 235. However, at elevated temperatures, potentially through dissociation of the metal carbenoid 253 to afford the free carbene, a Wolff rearrangement can occur leading to the ketene 255.\textsuperscript{11} In the absence of the stabilising group (alkene or ester unit) this is unstable and undergoes decomposition at these high temperatures, \textit{cf.} diazo ketone acetal 186. However, when substituted this is sufficiently long-lived to allow a formal 1,3 shift of one of the acetal oxygen atoms to occur to give the observed lactones 257.
In support of such a hypothesis, heating of diazodiketone acetal 209 with Rh₂(pfb)₄ in a mixture of toluene and methanol (1:1) afforded the diester acetal 258 in modest yield of 18% along with trace amounts of lactone 251 (Scheme 4.16).
Key evidence for the formation of diester acetal 258 was obtained from the IR, $^1$H NMR and $^{13}$C NMR spectra. Comparison of the IR spectrum of diazo diketone acetal 209 with that of product 258 showed the disappearance of the signals at 2132 cm$^{-1}$ and 1735 cm$^{-1}$ attributed to the diazo functionality (C=N$_2$) and carbonyl at C-3 respectively and the appearance of two signals at 1756 and 1731 cm$^{-1}$ assigned to the diester units. The $^1$H NMR spectrum showed the appearance of two singlets at 4.24 ppm and 3.75 ppm corresponding to 2-H and the methoxy group respectively. The $^{13}$C NMR spectrum provided key evidence with the disappearance of the signal at 186.8 ppm attributed to the carbonyl at C-3 and the appearance of a signal at 165.9 ppm corresponding to the methoxy ester.
Chapter IV: Synthesis of Barceloneic Lactone Derivatives

4.3 Conclusions

The study undertaken in this chapter led to the novel synthesis of Barceloneic lactone derivatives.

Although several attempts to prepare the desired C-H insertion product from prepared diazo diketone acetals were unsuccessful, the synthesis of the competing (in this case more favourable) O-H insertion product was achieved in modest yield using Rh$_2$(pfb)$_4$.

Interestingly, exposure of the diazo diketone acetals to elevated temperature for a short period of time resulted in a complete switch of the reaction pathway. In this case, the barceloneic lactone derivatives obtained had profitable biological properties derived from the parent compound.

The scope and mechanism of the reaction were subsequently investigated. The reaction was shown to be general for acetals bearing a diazo group with dual stabilisation. The mechanism is postulated to proceed via a Wolff rearrangement.

Having tried to prepare the desired bicyclic ketones using the acceptor-acceptor substituted carbenoids without success, the next chapter would describe further efforts using the donor-acceptor substituted carbenoids with the aim of achieving the synthesis.
Chapter IV: Synthesis of Barceloneic Lactone Derivatives

4.4 References

11. For a similar example of Wolff rearrangement occurring at elevated temperatures see:
5.1 Introduction

As efforts, discussed in the preceding chapter, aimed at the synthesis of the desired C-H insertion product using acceptor-acceptor substituted carbenoids were unsuccessful. Attention then turned to investigate donor-acceptor carbenoids. A secondary aim was to avoid the use of the toxic and explosive diazomethane in the preparation of the carbenoids.

This chapter will describe the work undertaken towards these goals including the synthesis of the donor-acceptor-substituted carbenoids and their insertion chemistry.

5.2 Synthetic strategy

The retrosynthetic disconnections for the preparation of the target bicyclic vinylketone acetal (I) are illustrated in the following scheme (Scheme 5.1).

\[
\begin{align*}
(I) & \quad \rightarrow \quad (II) & \quad \rightarrow \quad (III) \\
& \quad \downarrow \\
& \quad \rightarrow \\
& \quad \rightarrow \\
(VI) & \quad + \quad (V) & \quad \rightarrow \quad (IV)
\end{align*}
\]

Scheme 5.1

The synthetic plan involved four key steps. It was proposed that the bicyclic vinylketone acetal (I) would be obtained from a Rh (II) catalysed C-H insertion reaction from the
vinyl diazoketone acetal (II). This in turn could be obtained by a diazo transfer reaction on an allylketone acetal (III), prepared by the oxidation of the allylalcohol acetal (IV). A Grignard reaction between the reagent (VI) and aldehyde (V) was expected to deliver IV.

Following a successful preparation of the set of aldehydes acetals (176-185), attention now turned to the study of their condensation with an appropriate Grignard reagent to prepare the corresponding allylalcohol acetals.

### 5.2.1 Preparation of allylalcohol acetals

The synthesis of allylalcohol acetal 259 proceeded successfully using allylmagnesium bromide as the Grignard source at -78 °C (Scheme 5.1). The product was isolated in excellent yield (94%) as a racemic mixture at carbon 1.

![Scheme 5.1](image)

Evidence for the formation of the allylalcohol acetal 259 was provided by the IR, $^1$H and $^{13}$C NMR spectra. Analysis of the IR spectrum showed the disappearance of the characteristic signal attributed to the aldehyde at 1744 cm$^{-1}$ and the appearance of a broad signal corresponding to the alcohol at 3620-3310 cm$^{-1}$ together with a signal corresponding to the alkene unsaturation at 1641 cm$^{-1}$. The $^1$H NMR spectrum contained characteristic alkene signals at 5.95 ppm (3-H), 5.19 ppm (4-H), 5.13 ppm (4-H) and the disappearance of the aldehyde signal at 9.63 ppm confirmed its consumption. The $^{13}$C NMR spectrum provided key evidence with the appearance of a C-1 butenol signal at 70.8 ppm and the disappearance of the characteristic signal attributed to the aldehyde at 201.4 ppm.

In a similar fashion, aldehyde acetals 178-180, 182, 184 were then converted to the corresponding allylalcohol acetals 259-263 using the Grignard reagent (allylmagnesium...
Chapter V: Enantioselective Synthesis of Bicyclic Alcohol Acetals

bromide). Key evidence for the formation of the allylalcohol acetals was as discussed above and is summarised for each example in the table below (Scheme 5.2, Table 5.1).

![Chemical reaction](image)

Scheme 5.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituent</th>
<th>Yield (%)</th>
<th>IR (cm⁻¹)</th>
<th>¹H and ¹³C NMR (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R₁=Ph, R₂=H, R₃=CH₃</td>
<td>94</td>
<td>3390 (OH) 1641 (C=C)</td>
<td>259 : 4.12 (1-H), 70.8 (C-1)</td>
</tr>
<tr>
<td>2</td>
<td>R₁=H, R₂=Ph, R₃=CH₃</td>
<td>92</td>
<td>3437 (OH) 1641 (C=C)</td>
<td>260 : 3.60 (1-H), 76.5 (C-1)</td>
</tr>
<tr>
<td>3</td>
<td>R₁=Ph, R₂=H, R₃=Ph</td>
<td>72</td>
<td>3521 (OH) 1641 (C=C)</td>
<td>261 : 3.72 (1-H), 77.2 (C-1)</td>
</tr>
<tr>
<td>4</td>
<td>R₁=H, R₂=Ph, R₃=Ph</td>
<td>65</td>
<td>3503 (OH) 1640 (C=C)</td>
<td>262 : 3.69 (1-H), 77.3 (C-1)</td>
</tr>
<tr>
<td>5</td>
<td>R₁=Bn, R₂=H, R₃=Ph</td>
<td>81</td>
<td>3560 (OH) 1641 (C=C)</td>
<td>263 : 3.68 (1-H), 77.5 (C-1)</td>
</tr>
<tr>
<td>6</td>
<td>R₁=p-NO₂Ph, R₂=H, R₃=CH₃</td>
<td>nd</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>R₁=CH₃, R₂=NO₂, R₃=CH₃</td>
<td>nd</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

nd = not determined

Table 5.1

In most of the cases studied, the allylalcohol acetals 259-263 were obtained in good yields from the corresponding aldehydes with the exception of aldehydes 182, 184 bearing electron
withdrawing nitro group. In these later cases, trace amounts of the desired products (which were not isolated) were observed in the $^1$H NMR spectrum of the crude reaction mixture.

With the allylalcohol acetals in hand, attention turned towards converting each to the corresponding allylketone acetals and ultimately, the bicyclic vinylketone acetals. The following section will present efforts towards achieving these goals.

### 5.2.2 Preparation of allylketone acetals

Having previously successfully synthesised the aldehyde 176 from the alcohol 166 using the Swern oxidation protocol, it was decided to explore the oxidation of allylalcohol 259 using the same conditions (Scheme 5.3).

![Scheme 5.3](image)

In the event, allylalcohol 259 was oxidised to afford an isomeric mixture of two ketone acetals 264 and 268 in a 78% yield (1:10 ratio). The two products were inseparable by column chromatography on silica. Key evidence for the formation of two ketone acetals was obtained in the IR and $^{13}$C NMR spectra. In the IR spectrum, two characteristic carbonyl bands were observed for 264 and 268 at 1728 and 1705 cm$^{-1}$ respectively. Similarly, in the $^{13}$C NMR spectrum, two signals corresponding to the carbonyl groups were observed for the minor allyl ketone acetal 264 and the major enone acetal 268 products at 208.1 and 198.2 ppm respectively. Further evidence for the formation of 264 and 268 was obtained in the $^1$H NMR spectrum which showed a signal at 3.41 ppm for 2-$H_2$ in 264, while two signals at 7.23 and 6.63 ppm for 3-$H$ and 2-$H$ respectively were observed in 268. Confirmation of the trans
stereochemistry in the enone 268 was obtained from the observed coupling constant of 15 Hz in the $^1$H NMR spectrum between the 3-$H$ and 2-$H$ protons.

Since, the oxidation afforded the desired allyl ketone acetal 264 as the minor isomer and was inseparable by column chromatography from the major enone acetal 268, it was decided to explore alternative oxidation protocols. The results are summarised in the table below (Scheme 5.4, Table 5.2).

![Scheme 5.4](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction condition</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IBX, DMSO, rt, 4 h</td>
<td>SM + complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>NMO, TPAP, DCM, rt, 24 h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>3</td>
<td>PDC, 4Å mol. sieves, DCM, rt, 4 h</td>
<td>76%, 11:1 (264:268)</td>
</tr>
</tbody>
</table>

SM = starting material

Table 5.2

Initial attempt using IBX led to recovery of allylalcohol acetal 259 and mainly a complex mixture of products which proved difficult to purify and identify (entry 1). Surprisingly, in the case of NMO/TPAP combination (entry 2), the reaction resulted in only the recovery of the starting material. However, the best conditions found for the oxidation of allylalcohol acetal 259 was using pyridinium dichromate (PDC) (entry 3). This gave a similar yield (76%) compared to the Swern oxidation procedure but a greater ratio of 11:1, pleasingly in favour of the allylketone acetal product 264. Although the ketone mixtures from the PDC oxidation were inseparable, we anticipated the conversion of 268 into 264 in the subsequent step.
Therefore, PDC was maintained as the oxidant of choice for the oxidation of the allylalcohol acetals. In a typical experiment, powdered 4Å mol. sieves and PDC were added to a solution of the allylalcohol in DCM at room temperature.

In a similar manner, the allylalcohol acetals 259-261, 263 were then converted to the corresponding ketone mixtures using PDC (Scheme 5.5). The ratios and yields of products are shown below together with the key spectroscopic evidence for the desired major allyl ketone isomers (Table 5.3).

![Scheme 5.5]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituents</th>
<th>Ratio</th>
<th>Yield (%)</th>
<th>IR (cm⁻¹)</th>
<th>¹³C and ¹H NMR (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R₁=Ph, R₂=H</td>
<td>11:1</td>
<td>76</td>
<td>1728 (CO)</td>
<td>264 : 208.1 (CO), 3.41 (2-H₂)</td>
</tr>
<tr>
<td></td>
<td>R₃=CH₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R₁=H, R₂=Ph</td>
<td>12:1</td>
<td>69</td>
<td>1729 (CO)</td>
<td>265 : 206.0 (CO), 3.49 (2-H₂)</td>
</tr>
<tr>
<td></td>
<td>R₃=CH₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R₁=Ph, R₂=H</td>
<td>13:1</td>
<td>68</td>
<td>1730 (CO)</td>
<td>266 : 205.6 (CO), 3.29 (2-H₂)</td>
</tr>
<tr>
<td></td>
<td>R₃=Ph</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R₁=Bn, R₂=H</td>
<td>13:1</td>
<td>71</td>
<td>1738 (CO)</td>
<td>267 : 204.5 (CO), 3.33 (2-H₂)</td>
</tr>
<tr>
<td></td>
<td>R₃=Ph</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.3

In all the examined compounds, mixtures of isomeric ketone acetals were obtained and the nature of the substituents (R₁ and R₃) had no significant effect on the ratios of isomers formed. In all cases, the allyl ketones 264-267 were obtained in good yields.
With a protocol for the synthesis of the allyl ketones established, efforts were directed towards their subsequent transformation with an appropriate diazo transfer reagent to the vinyldiazoketone acetals.

### 5.2.3 Synthesis of vinyldiazoketone acetals

#### 5.2.3.1 Diazo-transfer reaction

##### 5.2.3.1.1 Introduction

A widely used method for the formation of diazoketones is a diazo transfer reaction. This involves the transfer of a diazo group from a diazo donor (usually a sulfonyl azide) to the $\alpha$-methylene proton of an acceptor (usually a carbonyl group).

Two main classes of acceptors based on the acidity of the $\alpha$-methylene proton are known:

- **Simple ketone enolates**

  In this case, the diazo transfer process is not very efficient and often gives poor yields. However, diazo transfer can be achieved by an indirect deformylative diazo-transfer (Scheme 5.6).

\[
\begin{align*}
\text{R, R'} &= \text{alkyl} \\
\text{R}^\prime &\text{HCOOEt, EtONa} \\
\text{R}^\prime &\text{H} \\
\text{R} &\text{TsN}_3 \\
\text{R}^\prime &\text{N}_2 \\
\text{TsNHCHO} \\
\end{align*}
\]

**Scheme 5.6**

- **$\beta$-Keto esters, $\beta$-diketones, malonic esters**

  In these cases, the enhanced reactivity of the $\alpha$-methylene position permits diazo transfer and the substrates are readily converted into 2-diazo-1,3-dicarbonyl compounds by the standard Regitz procedure (Scheme 5.7).
Chapter V: Enantioselective Synthesis of Bicyclic Alcohol Acetals

\[
\text{R} \quad \text{R}' = \text{aryl, alkyl}
\]

\[
\text{R} \quad \text{R}'
\]

\[
\text{O} \quad \text{O}
\]

\[
\text{+ TsN}_3 \quad \text{Et}_3\text{N}
\]

\[
\text{R} \quad \text{R}'
\]

\[
\text{O} \quad \text{O}
\]

\[
\text{N}_2
\]

\[
\text{Et}_3\text{N}
\]

\[
275 276
\]

Scheme 5.7

Davies has applied this methodology in the preparation of donor-acceptor substituted carbenoids 278 following the successful development of \(p\)-acetamidobenzensulfonyl azide (\(p\)-ABSA) as the suitable diazo transfer reagent (Scheme 5.8).\(^4\)

\[
\text{O} \quad \text{O}
\]

\[
\text{R'} \quad \text{R}
\]

\[
p\text{-ABSA, DBU}
\]

\[
\text{CH}_3\text{CN, 0 oC}
\]

\[
\text{N}_2
\]

\[
\text{R'} \quad \text{R}
\]

\[
277 278, 84-86\%
\]

Scheme 5.8

Davies and co-workers obtained the vinyldiazo ketone products in good yields of 84-86%. More importantly, \(p\)-ABSA had the added advantage of being safer to handle, bench stable, less toxic and easily separable from desired products than previously known diazo transfer reagents such as tosyl azide.

In view of this precedent, it was decided to evaluate the use of \(p\)-ABSA in the diazo transfer reaction to convert ketone mixture 264 and 268 into the vinyldiazoketone acetal 279 (Scheme 5.9). Thus a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1 eq) was added to a stirred solution of an inseparable mixture of 264:268 (11:1) (1 eq) and \(p\)-ABSA in CH\(_3\)CN at 0 °C.
Initial attempts using \( p \)-ABSA (1 eq) and DBU (1.5 eq) led to the formation of the desired vinyl diazoketone acetal 279, however as an inseparable mixture with unreacted enone acetal 268 in 40% combined yield. Surprisingly, the choice of the more basic DBU over triethylamine (Et\(_3\)N) for the \textit{in-situ} isomerisation of enone acetal 268 to allylketone acetal 264 prior to diazo transfer was unsuccessful therefore leading to the inherent separation problem. Based on this, attempts were made to form the desired vinyl diazoketone acetal 279 exclusively.

Therefore, further efforts were directed at varying the reaction parameters including the choice of diazo transfer reagent, the base and the temperature of the reaction. A summary of the results obtained are as shown in Table 5.4.

A greater ratio of the desired vinyl diazoketone acetal 279 was obtained using \( p \)-ABSA (entry 2 & 4) compared to mesyl azide (MsN\(_3\)) (entry 3 & 5). This result shows the superiority of \( p \)-ABSA as a better reagent for diazo transfer reactions involving allyl ketone compounds. Whilst the use of lithium bis(trimethylsilyl)amide (LiHMDS) as a base gave mainly enone acetal 268 and decomposition products (entry 6), subsequent addition of tetramethylethylenediamine (TMEDA) had no effect on the reaction outcome. Furthermore, the use of triethylamine (Et\(_3\)N) resulted in a clean conversion of 264 to 268, without any evidence of diazo transfer to give the desired product 279 (entry 7). However, when the reaction was conducted with DBU at room temperature or at 0 °C and subsequently warmed-up to room temperature, higher ratios of product 279 were obtained (entry 8, 10-12). Gratifyingly, it was noted that an excess amount of DBU was needed to achieve an efficient transformation of 268 into 279 (entry 13 & 14). In addition, the reaction proceeded under ambient conditions without any effect on the yield (entry 15).
## Table 5.4

Evidence for the formation of the vinyl diazoketone acetal 279 was provided by the IR, $^1$H and $^{13}$C NMR spectra. Analysis of the IR spectrum showed the appearance of a diagnostic signal corresponding to the diazo ketone at 2082 cm$^{-1}$. The $^1$H NMR spectrum which showed the disappearance of the signal at 3.41 ppm confirmed the diazo transfer exclusively into the kinetically favoured $\alpha$-position (C-2). The $^{13}$C NMR spectrum provided key evidence with the appearance of a characteristic signal corresponding to the diazo ketone at 66.7 ppm.

With the optimum conditions necessary for the diazo transfer reaction determined, the reaction was carried out on the inseparable mixtures of ketone acetals 264-271. Evidence obtained for
the formation of the vinylidiazoketone acetals 279-282 was as discussed above and is summarised in the table below (Scheme 5.10, Table 5.5).

![Scheme 5.10](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituents</th>
<th>Yield (%)</th>
<th>IR (cm⁻¹)</th>
<th>¹³C (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R₁=Ph, R₂=H</td>
<td>90</td>
<td>2082 (CN₂)</td>
<td>279 : 66.7 (CN₂)</td>
</tr>
<tr>
<td></td>
<td>R₃=CH₃</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R₁=H, R₂=Ph</td>
<td>72</td>
<td>2088 (CN₂)</td>
<td>280 : 68.6 (CN₂)</td>
</tr>
<tr>
<td></td>
<td>R₃=CH₃</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R₁=Ph, R₂=H</td>
<td>69</td>
<td>2081 (CN₂)</td>
<td>281 : 69.1 (CN₂)</td>
</tr>
<tr>
<td></td>
<td>R₃=Ph</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R₁=Bn, R₂=H</td>
<td>71</td>
<td>2083 (CN₂)</td>
<td>282 : 77.2 (CN₂)</td>
</tr>
<tr>
<td></td>
<td>R₃=Ph</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 5.5**

In all of the cases studied, the vinylidiazoketone acetals 279-282 were obtained in good yields as pure samples and were subsequently taken through to the next step of the synthesis.

With a practically reproducible and efficient synthetic protocol of the vinylidiazoketone acetals established, attention turned towards investigating the key metal catalysed decomposition to access the corresponding C-H insertion products.
5.2.4 Rhodium catalysed C-H insertion reactions

With the vinyl diazoketone acetal 279 in hand, it was decided to explore the key step in the methodology as it was anticipated that 279 was favourably set-up for C-H insertion reaction. In a typical experiment, a dilute solution of 279 was slowly added into a solution of catalyst at room temperature (Scheme 5.11).

Disappointingly, initial attempts which involved the use of 1 mol% Rh$_2$(OAc)$_4$ at room temperature did not afford the desired bicyclic vinyl ketone acetal 283. Further attempts to increase the catalyst loading gradually to 10 mol% had no effect on the outcome of the reaction. (Table 5.6, entry 2-4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst loading</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>1 mol %</td>
<td>DCM</td>
<td>Rt</td>
<td>SM recovered</td>
</tr>
<tr>
<td>2</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>2 mol %</td>
<td>DCM</td>
<td>Rt</td>
<td>SM recovered</td>
</tr>
<tr>
<td>3</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>5 mol %</td>
<td>DCM</td>
<td>Rt</td>
<td>SM recovered</td>
</tr>
<tr>
<td>4</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>10 mol %</td>
<td>DCM</td>
<td>Rt</td>
<td>SM recovered</td>
</tr>
</tbody>
</table>

SM = starting material

Table 5.6

Based on previous results (Chapter IV) which involved the use of Rh$_2$(pfb)$_4$ in the microwave preparation of barceloneic lactone derivatives, it was decided to examine the same procedure on the vinyl diazoketone 279 (Scheme 5.12).
Following the reaction of 279 with 5 mol% Rh$_2$(pfb)$_4$ under microwave conditions, the barcelonic lactone derivative 284 was isolated in 45% yield. Evidence for the formation of 284 was provided by the IR, $^1$H and $^{13}$C NMR spectra. Analysis of the IR spectrum showed the disappearance of a diagnostic signal at 2082 cm$^{-1}$ attributed to the diazo ketone and the appearance of a signal at 1714 cm$^{-1}$ corresponding to the ester carbonyl. The $^1$H NMR spectrum showed the appearance of a signal at 2.11 ppm corresponding to the C-4 methyl group. The $^{13}$C NMR spectrum provided key evidence with the appearance of characteristic signals at 169.7 and 157.4 ppm corresponding to the ester carbonyl and alkene (C-3/4) respectively.

The formation of 284 confirmed the accessibility of the carbenoid from 279 under the influence of a rhodium (II) catalyst. Intrigued by this, it was decided to explore this catalyst system further. Thus, a solution of 279 was slowly added to Rh$_2$(pfb)$_4$ catalyst in DCM at room temperature. Gratifyingly, the bicyclic C-H insertion products 285 and 286 (geometrical isomers) were obtained in moderate yield together with the O-H insertion product 287 in a ratio of 2.25:0.75:1 respectively (Scheme 5.13). Importantly, all products were easily separated by column chromatography.
As before, evidence for the isolated products 285, 286 and 287 obtained from analytical and spectroscopic data were satisfactory. The E/Z stereochemistry was assigned based on NOESY correlations. For example, in 285 there was a significant correlation between the 5-H and 6-CHCH₃ protons while in 286, there was a significant correlation between the 5-H and the 6-CHCH₃ protons (Figure 5.1).

Irrespective of the solvent and Rh (II) catalyst system, conducting the reaction under forcing conditions suppresses the formation of O-H insertion product 287 and leads to the formation of mainly 284 (entry 1-7). In addition, refluxing for long periods of time resulted in the decomposition of 284 (entry 4 vs 5). Therefore the formation of the barceloneic lactone derivative 284 requires a Rh (II) catalyst over a short reflux time (entry 4). Notably, whilst all of the achiral Rh (II) catalyst system investigated did not suppress the formation of the O-H
insertion product 287 (entry 8-14), the Davies chiral tetrakis[1-[(4-tert-butylphenyl)sulfonyl]-
(25)-pyrrolidinecarboxylate]dirhodium (II), [Rh$_2$(S-TBSP)$_4$] catalyst led to the exclusive
formation of the C-H insertion products 285 and 286 in ratio 96:4 respectively. The specific
rotation, $[\alpha]^{28.1}_D$ for the enriched mixture was +24.0° obtained at a concentration of 0.8 g/ml in
CDCl$_3$.

Table 5.7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Catalyst</th>
<th>Catalyst Loading (mol%)</th>
<th>Yield 287 (%)</th>
<th>Yield 285+286 (%)</th>
<th>Ratio$^{d}$ 285:286</th>
<th>Yield 284 (%)</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>reflux</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>1</td>
<td>0</td>
<td>30</td>
<td>ND</td>
<td>38</td>
<td>b$^e$</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>reflux</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>5</td>
<td>0</td>
<td>7</td>
<td>5:1</td>
<td>25</td>
<td>a</td>
</tr>
<tr>
<td>3</td>
<td>C$_6$H$_6$</td>
<td>reflux</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>1</td>
<td>0</td>
<td>ND</td>
<td>1:1</td>
<td>4</td>
<td>a</td>
</tr>
<tr>
<td>4</td>
<td>C$_6$H$_6$</td>
<td>reflux</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>5</td>
<td>0</td>
<td>trace</td>
<td>ND</td>
<td>45</td>
<td>b$^f$</td>
</tr>
<tr>
<td>5</td>
<td>C$_6$H$_6$</td>
<td>reflux</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>5</td>
<td>0</td>
<td>-$^c$</td>
<td>-</td>
<td>16</td>
<td>b$^g$</td>
</tr>
<tr>
<td>6</td>
<td>DCM</td>
<td>reflux</td>
<td>Rh$_2$(pfb)$_4$</td>
<td>5</td>
<td>0</td>
<td>trace</td>
<td>ND</td>
<td>14</td>
<td>a</td>
</tr>
<tr>
<td>7</td>
<td>C$_6$H$_6$</td>
<td>reflux</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>5</td>
<td>0</td>
<td>10</td>
<td>3:1</td>
<td>20</td>
<td>a</td>
</tr>
<tr>
<td>8</td>
<td>C$_6$H$_6$</td>
<td>rt</td>
<td>Rh$_2$(pfb)$_4$</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>ND</td>
<td>0</td>
<td>a$^n$</td>
</tr>
<tr>
<td>9</td>
<td>C$_6$H$_6$</td>
<td>rt</td>
<td>Rh$_2$(pfb)$_4$</td>
<td>5</td>
<td>10</td>
<td>40</td>
<td>3:1</td>
<td>0</td>
<td>b$^f$</td>
</tr>
<tr>
<td>10</td>
<td>DCM</td>
<td>rt</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>b$^g$</td>
</tr>
<tr>
<td>11</td>
<td>DCM</td>
<td>rt</td>
<td>Rh$_2$(pfb)$_4$</td>
<td>5</td>
<td>10</td>
<td>30</td>
<td>3:1</td>
<td>0</td>
<td>b$^f$</td>
</tr>
<tr>
<td>12</td>
<td>C$_7$H$_8$</td>
<td>rt</td>
<td>Rh$_2$(pfb)$_4$</td>
<td>5</td>
<td>10</td>
<td>33</td>
<td>2:1</td>
<td>0</td>
<td>b$^g$</td>
</tr>
<tr>
<td>13</td>
<td>C$_7$H$_8$</td>
<td>0</td>
<td>Rh$_2$(pfb)$_4$</td>
<td>5</td>
<td>9</td>
<td>30</td>
<td>2:1</td>
<td>0</td>
<td>b$^f$</td>
</tr>
<tr>
<td>14</td>
<td>C$_7$H$_8$</td>
<td>rt</td>
<td>Rh$_2$(pfb)$_4$</td>
<td>5</td>
<td>11</td>
<td>22</td>
<td>ND</td>
<td>0</td>
<td>b$^g$</td>
</tr>
<tr>
<td>15</td>
<td>C$_7$H$_8$</td>
<td>rt</td>
<td>Rh$_2$(S-TBSP)$_4$</td>
<td>5</td>
<td>0</td>
<td>30</td>
<td>96:4</td>
<td>0</td>
<td>b$^g$</td>
</tr>
</tbody>
</table>

(a) substrate and pre-heated catalyst solution mixed together at once in a flask; (b) substrate
added via syringe pump into solution of catalyst over time; $^c$ reaction mixture appeared black
probably due to decomposition of products; $^d$ ratio obtained after purification by chromatography;
$^e$ substrate added over 10 min; $^f$ substrate added over 7 h; $^g$ substrate added over 20 h; $^n$ substrate added at once.

Table 5.7
5.2.4.1 Preparation of rhodium (II) heptafluorobutyramide catalyst

Pleased with this result, attention turned to explore this catalyst system further. However, due to its high commercial cost (£66.40 per 100mg, Aldrich), and the intention to gain insight of potential asymmetry induction, it was decided to investigate the achiral (racemic) catalyst system ($\pm$)-Rh$_2$(TBSP)$_4$. By so doing, comparisons could be drawn between the results from the chiral and the achiral reactions and hence allow the determination of enantiomeric ratios. As this achiral catalyst system was not available commercially, its preparation became inevitable. A literature search revealed that most catalyst systems based on rhodium (II) metal which are not commercially available are prepared by a high temperature ligand exchange reaction between the commercially available Rh$_2$(OAc)$_4$ and the desired ligand. For example, Doyle applied this protocol in the preparation of rhodium (II) acetamide catalyst Rh$_2$(acam)$_4$ by exchanging the acetate ligands in 288 for acetamides 289 (Scheme 5.14).\(^7\)

\[\text{Scheme 5.14}\]

Based on this precedent, preparation of the ($\pm$)-1-(4-tert-butylphenylsulfonyl)pyrrolidine-2-carboxylic acid precursor 293 needed for the ligand exchange reaction became necessary as this was not commercially available (Scheme 5.15).
Thus, 4-\(\text{tert}\)-butylbenzene-1-sulfonylchloride \(292\) was added to (DL)-proline \(291\) in a sodium/carbonate/water mixture. Following work-up, the desired product \(293\) was obtained in good yield (70%). Evidence for the formation of \(293\) was obtained from \(^1\text{H}\) NMR spectrum which showed a signal at 4.25 ppm corresponding to the proton at C-2. As before, additional analytical and spectroscopic data obtained were satisfactory.

With the precursor \(293\) in hand, attention turned towards exploring the high temperature ligand exchange reaction with \(\text{Rh}_2(\text{OAc})_4\). Thus, a mixture of \(293\) and \(\text{Rh}_2(\text{OAc})_4\) in chlorobenzene was refluxed in a Soxhlet extraction apparatus for six days. Following the removal of chlorobenzene by distillation, a mixture containing mainly residual \(\text{Rh}_2(\text{OAc})_4\), decomposed starting material and traces of the desired product was obtained. However, no attempt was made to isolate the product and the reaction was not repeated for a longer period of time due to time constraints.

Moreover, considering that \(\text{Rh}_2(\text{pfb})_4\) gave C-H insertion products \(285\) and \(286\) in appreciable yield (40%) and ratio (3:1) in contrast to the O-H insertion product \(287\) (10%) (Table 5.7, entry 9). It was thought that the corresponding rhodium (II) heptafluorobutyramide catalyst \(\text{Rh}_2(\text{hfb})_4\) (conceptually lesser in reactivity but with a higher selectivity) might suppress the formation of the undesired O-H insertion product \(287\). Towards this goal, the preparation of \(\text{Rh}_2(\text{hfb})_4\) following the same high temperature ligand exchange reaction between \(\text{Rh}_2(\text{OAc})_4\) \(288\) and the commercially available heptafluorobutyramide \(294\) was conducted (Scheme 5.16).
Chapter V: Enantioselective Synthesis of Bicyclic Alcohol Acetals

Following purification by alumina chromatography, the Rh$_2$(hfb)$_4$ catalyst 295 was isolated in excellent yield. As before, satisfactory analytical data was obtained.

Having prepared the Rh$_2$(hfb)$_4$ catalyst, attention turned to the study of its reactivity and ultimately its selectivity towards the vinyldiazoketone acetal 279. Thus, a solution of diazoketone 279 was slowly added to Rh$_2$(hfb)$_4$ catalyst in DCM at room temperature (Scheme 5.17).

As expected, the bicyclic C-H insertion products 285 and 286 (geometrical isomers) were obtained exclusively, although in poor yield (15%). Further attempts involved the screening of different solvents and satisfyingly an improved yield of 40% in ratio 3:1 was obtained using benzene (Table 5.8, entry 3).
Table 5.8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>Ratio ($E,285$:$Z,286$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>15</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td>$C_7H_8$</td>
<td>30</td>
<td>3:1</td>
</tr>
<tr>
<td>3</td>
<td>$C_6H_6$</td>
<td>40</td>
<td>3:1</td>
</tr>
</tbody>
</table>

More importantly, the reaction could be performed without any need for the slow addition sequence giving similar yields of products. Curiously, in this case, there was no evidence for the formation of by-products including dimers. Analytical and spectroscopic data obtained for 285 and 286 were in agreement with that acquired previously.

5.2.4.2 Attempted deconjugation of bicyclic ketones

As described in Chapter 1, one of the basic goals was to elaborate the bicycle 283 into macrocycles. Following the successful identification of a suitable catalyst system for the decomposition of vinyldiazoketone acetal 279, it was obvious that the isolated bicyclic enones 285 and 286 were not the desired bicyclic vinyl ketone 283 necessary for the subsequent elaborations as anticipated. For example, the transformation of 283 to macrocycles 298 or 299, involves three key steps including vinylation, Cope rearrangement and finally reductive cleavage (Scheme 5.18).
The first step in this sequence involved a 1,2 addition to the ketone of 283 which was proposed to suffer from a competing 1,4 addition in enone mixtures 285 and 286. Therefore, it was decided to isomerise the enone mixtures to the vinyl ketone 283 or its analogues. Initial attempt involved the use of lithium diisopropylamide (LDA) and methyl iodide at low temperature (Scheme 5.19).

Following work-up, the reaction led to a complex mixture of products which proved difficult to analyse. The addition of TMEDA had no effect on the reaction outcome. Further attempts using LDA/acetic acid combination was equally unsuccessful as was the use of alternative bases including sec.butyllithium (sec BuLi) and LiHMDS. However, in the course of
conducted these trials, the $^1$H NMR spectrum of the crude reaction mixture involving the Rh$_2$(hfb)$_4$ catalysed decomposition of vinyl diazoketone acetal 279 was acquired. Surprisingly, this $^1$H NMR spectrum was different from that of the enone mixtures 285 and 286 obtained following purification by chromatography. Significantly, the $^1$H NMR spectrum of the crude reaction mixture for this latter reaction showed signals for three protons in the alkene region at 5.35, 5.22 and 5.20 ppm corresponding to 6-CHCH$_2$, 6-CH$_2$CH$_2$ and 6-CHCH$_2$ respectively in 283. Moreover, there was no evidence for the proton at 6.28 ppm attributed to 6-CHCH$_3$ in the $^1$H NMR spectrum of the enone compound 285 (Figure 5.2).

![Figure 5.2](image)

It was felt that the isomerisation which leads to the enone mixtures must have occurred during chromatographic purification due to the acidic nature of silica gel. Therefore efforts were made to reduce the acidity of the silica gel prior to being used for the purification. Initial effort resulted in the addition of varying amounts of triethylamine. However, the isomerisation was still observed. The attempted use of basic alumina also led to the enones 285 and 286 and it was concluded that the isomerisation was promoted by both acid and basic media.

### 5.2.4.3 Attempted in-situ trapping of bicyclic vinyl ketone

In an effort to isolate the desired unisomerised product 283), it was decided to perform subsequent reactions using the crude reaction mixture without prior purification. In one such effort, vinylation was attempted on the crude reaction mixture obtained from the Rh$_2$(hfb)$_4$ catalysed diazo decomposition of 279 (Scheme 5.20).
Thus, to a solution of vinylmagnesium bromide in THF at -78 °C was added the resulting crude mixture containing 283. The progress of the reaction was subsequently monitored by TLC. After 4 hour no new spot was observed by TLC and the reaction was allowed to warm up to room temperature and quenched. Analysis of the $^1$H NMR spectrum showed the presence of only isomerised starting material. As the isomerisation occurred in the presence of benzene carried through from the initial catalysis step, it was decided that subsequent vinylations should be conducted after concentration of the crude mixture. However, further attempts which involved performing the reaction at room temperature and increasing the number of equivalents of the Grignard reagent and heating at 50 °C and then at 90 °C failed to give any product. The attempted use of methylmagnesium bromide (MeMgBr) was equally unsuccessful. In all cases isomerised starting material was obtained.

As the addition of Grignard reagents over the electrophilic carbon of ketone 283 proved difficult to achieve. It was decided to explore the use of organolithiums due to the enhanced nucleophilicity associated with this class of reagents. However, efforts to add a butyl group using $n$-butyllithium ($n$-BuLi) at -78 °C also resulted in isomerisation of starting material. Further attempts led to the use of vinyllithium reagent prepared separately from the transmetallation reactions of both methyllithium (MeLi) and $n$-BuLi with tributylvinyltin at -78 °C. After 3 hours, TLC indicated no new spot and subsequent work-up of reaction mixture led to the isolation of isomerised starting material. At this stage, it was felt that the enolisation of the acidic $\alpha$-proton may be the reason for the unsuccessful attempts at achieving a 1,2 addition.

In 1992, Greeves reported an improved ultrasound procedure for the preparation of organocerium reagents. These lanthanide based reagents are prepared from organolithium or Grignard reagents and can undergo clean addition to a wide range of carbonyl compounds for example 301 to give high yields of products 302. More importantly, enolisation, reduction and
conjugate addition to \( \alpha,\beta \)-unsaturated substrates which present problems with the addition of simple organometallics are almost completely suppressed (Scheme 5.21).

![Scheme 5.21](image)

Based on this precedent, it was decided to explore this procedure in the conversion of 283 to 296. Thus, a sonicated \( \text{CeCl}_3 \cdot 7\text{H}_2\text{O} \) solution in THF was added to a stirred solution of vinyllithium (prepared in the same manner as before) at -78 \( ^\circ \text{C} \). After 1 hour, crude mixture 283 was added slowly and the reaction mixture was monitored by TLC. Disappointingly, after 3 hours, TLC indicated no new spot and the reaction mixture was worked-up. However, only isomerised starting material was isolated. Although one reason attributed for the failure was the enolisation of the acidic \( \alpha \)-proton, it was also considered that the residual rhodium (II) catalyst complex in the crude mixture of 283 could also be having a significant effect.

5.2.4.4 Modification of substrate

With the isomerisation process proving difficult to circumvent, efforts were directed towards modifying the substrate 279. It was hoped that having an aromatic ring in conjugation with the alkene unsaturation could prevent the isomerisation into enone mixtures following Rh (II) catalysed C-H insertion reaction and chromatographic purification. The desired substrate 304 was anticipated to be prepared from an olefin cross metathesis reaction between 279 and styrene 303 using the Grubbs’ second-generation ruthenium catalyst 305, reputed for its air stability and functional group tolerance (Scheme 5.22).
Thus, to a homogenous mixture of 279 and styrene 303 in DCM at 40 °C was added Grubbs’ catalyst. Disappointingly, a complex mixture of products which proved difficult to identify was obtained together with recovered starting material 279 (10%). Curiously, not even the reduced form of the expected cross metathesised product or that resulting from homo-couplings were observed. Moreover, it is interesting to note that Snapper has reported a one-pot enyne-cross metathesis-cyclopropanation reaction between 306, 307 and 308 to give vinylcyclopropanes 309 in moderate to good yields using the same catalyst system functioning in a dual role (Scheme 5.23).

Scheme 5.22

\[
\text{Scheme 5.23}
\]
However, there was no observation of a similar product when the reaction was conducted following this protocol. Having tried to prepare 304 from vinyldiazoketone 279 unsuccessfully due to the labile and unstable diazo group, it was decided to attempt its preparation from the allylalcohol 259. The retrosynthetic disconnections which form the basis of the strategy are shown in Scheme 5.24.

![Scheme 5.24](image)

It was anticipated that 304 would be obtained by a diazo transfer reaction from 311, prepared by the oxidation of 310. An olefin cross-metathesis reaction between allylalcohol 259 and styrene 303 was expected to give 310.

Having prepared the allylalcohol acetal 259 as previously described, it was decided to explore the subsequent olefin cross-metathesis reaction with 303 using the Grubbs’ second generation catalyst 305 (Scheme 5.25).
Thus, Grubbs’ catalyst 305 was added to a mixture of allylalcohol acetal 259 and styrene 303 in DCM at 40 °C. Following work-up and purification using the Diver protocol, the cross coupled product 310 was isolated in good yield. Evidence for the formation of 310 was obtained from the $^1$H NMR spectrum which showed signals at 6.52 ppm and 6.37 ppm corresponding to the 4-$H$ and 3-$H$ protons respectively of the alkene unsaturation. Additional analytical and spectroscopic data obtained were satisfactory.

With the product 310 in hand, attention turned towards its oxidation. Initial attempts involving the use of IBX led to an unidentifiable product without any trace of the expected product. Further attempts exploring the Swern oxidation protocol and the PDC reagent led to similar observations. Due to time constraints, this protocol was abandoned.

The preparation of an alternative substrate 313 bearing a disubstituted alkene was expected to be easily amenable to PDC oxidation and equally anticipated to stabilise the alkene from isomerisation upon an eventual Rh (II) catalysed C-H insertion reaction. It was considered that 313 could be obtained from a condensation reaction between aldehyde 176 and (2-methylallyl)magnesium bromide 312 (Scheme 5.26).
Scheme 5.26

Thus, following the same procedure as described previously, the product 313 was obtained in good yield. As before, evidence for its formation obtained from analytical and spectroscopic data were satisfactory.

With the alcohol acetal 313 in hand, it was decided to convert it to the corresponding ketone acetal 314 using PDC as the oxidant (Scheme 5.27).

Scheme 5.27

Satisfyingly, the expected ketone 314 was obtained in good yield as a single isomer without any trace of the enone form. Evidence for the formation of ketone acetal 314 was obtained from the IR and $^{13}$C NMR spectra which showed signals at 1726 cm$^{-1}$ and 207.7 ppm respectively corresponding to the carbonyl at C-1. Additional analytical and spectroscopic data obtained was satisfactory.

Having synthesised the ketone acetal 314, efforts were directed towards its conversion into the diazoketone acetal 315 adopting the same diazo transfer conditions involving the use of $p$-ABSA as described previously (Scheme 5.28).
Scheme 5.28

Following purification, the desired diazoketone acetal 315 was isolated in good yield. As expected, the diazo group transfer proceeded exclusively into the kinetically favoured α-position. As before, analytical and spectroscopic data obtained were satisfactory.

With the diazoketone acetal 315 in hand, attention turned to the study of its catalytic decomposition using Rh₂(S-TBSP)₄ as the catalyst (Scheme 5.29).

Scheme 5.29

Thus, a solution of diazoketone acetal 315 was slowly added to a dilute solution of the catalyst at room temperature. Analysis of the ¹H NMR spectrum of the crude reaction mixture indicated the presence of two acetal products 316 and 317 in ratio 2:1, which subsequently proved inseparable by column chromatography. As before, evidence for the formation of acetals 316 and 317 obtained from analytical and spectroscopic data was satisfactory.

However, the desired product was not obtained. The doubly substituted alkene of diazoketone acetal 315 was not sufficient to prevent the alkene isomerisation upon diazo decomposition with Rh (II) catalyst. This accounted for the formation of the thermodynamically stable enone acetal 316, while the formation of acetal 317 is believed to be due to insertion into adventitious water.¹² Further effort to deconjugate bicycle 316 was complicated by the presence of the α-
dicarbonyl 317. As efforts to prevent the isomerisation of the alkene in vinylidiazoketone 279, following catalytic decomposition, by modification of the substrate proved unsuccessful. It was decided to explore the in-situ reduction of the crude bicyclic ketone 283. The following section will present efforts towards achieving this objective.

5.2.4.5 In-situ reduction of bicyclicvinyl ketone

Having tried to prevent the isomerisation process unsuccessfully, it was decided to explore the possibility of selectively reducing the carbonyl functional group in 283 without affecting the alkene bond to give 320 (Scheme 5.30).

![Scheme 5.30]

Initial attempts involved investigating the use of diisobutylaluminiumhydride (DIBAL) as a suitable reagent for the reduction. Thus, following the same procedure as earlier described for the Rh (II) catalysed decomposition of 279, the resulting crude reaction mixture containing 283 was added into DIBAL at room temperature (Scheme 5.31).

![Scheme 5.31]
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Following work-up and purification, an isomeric mixture of bicyclic enols 318 and 319 were obtained in overall moderate yield (40%) in the ratio 1:1. As before, evidence for the formation of the bicyclic enols obtained from analytical and spectroscopic data was satisfactory. The stereochemistry of the E/Z isomers and the 7-OH group was assigned on the basis of 2D NMR analysis, in particular of the NOESY correlations. For example, in 319 (Z isomer), there were significant correlations between the 6-CHCH₃ and 5-H, 6-CHCH₃ and 7-H protons (Figure 5.3, A). The stereochemistry of the 7-OH group was assigned based on correlations between the axial 3-H proton and 7-OH group, 1-CH₃ and 7-H protons (Figure 5.3, B) and was in agreement with previous observations involving a similar study by Garbi.¹³

![Diagram](image)

**Figure 5.3**

The formation of the enols was preceeded by isomerisation to the conjugated enone followed by a 1,2 reduction of the ketone to an alcohol. The isomerisation was thought to be a result of conducting the reaction at room temperature which favoured the Lewis acid (DIBAL) mediated isomerisation to the thermodynamically stable enone products prior to reduction. In an effort to prevent the rearrangement, it was decided to perform the reaction at a lower temperature of -78 °C (Scheme 5.32).

![Scheme](image)

**Scheme 5.32**
Gratifyingly, the reaction proceeded uneventfully and the desired bicyclic alcohol 320 was isolated in good overall yield (41%) as a single product. Evidence for the formation of bicyclic alcohol 320 was obtained from the IR and $^1$H NMR spectra. The IR spectrum showed the appearance of the signal at 3410 cm$^{-1}$ corresponding to the hydroxyl functionality and the $^1$H NMR spectrum confirmed the formation of alcohol 320 with the signal at 4.17 ppm attributed to the C-7 proton. Additional analytical and spectroscopic data obtained was satisfactory. The C-6, C-7 stereochemistry and the 6,7 cis relationship were assigned based on 2D NMR analysis particularly the NOESY correlations. Significantly, irradiation of the 6-CH=CH$_2$ proton gave a strong correlation to the axial 3- H proton, which implied that the 6-CH=CH$_2$ group and the axial 3- H proton were on the same side of the molecule. Consistent with this, irradiation of the 7- H proton gave a strong correlation to the 6- H and 1-CH$_3$ protons (Figure 5.4).

Similarly, the vinyldiazo ketone acetal 280 was subjected to the same reaction conditions. Happily, the desired bicyclic alcohol 322 was isolated in good overall yield (Scheme 5.33).
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As before, evidence for the formation of the bicyclic alcohol 322 obtained from analytical and spectroscopic data was satisfactory. More importantly, the formation of 322 indicated that the entire reaction procedure was reproducible and the alternate stereochemistry at C-5 of the vinylidiazoketone acetal 280 did not have significant effects on the insertion step. Furthermore, the enhanced overall yield of 41% obtained over the two step reaction for the conversion of 279 into 320 confirms the instability of the bicyclic ketone 283 framework to silica gel chromatography. In contrast, yields (often irreproducible) which ranged between 15-40% were obtained for the conversion of 279 into 285 and 286 in the initial step.

Having been able to develop a procedure that allows access to the bicyclic alcohols, it was decided to investigate their preparation using a chiral Rh (II) catalyst for the initial diazo decomposition step. The following section will describe efforts directed at achieving this objective and progress made to gain insights into potential asymmetric induction.

5.2.4.6 Asymmetric synthesis of bicyclic alcohols

In order to investigate the degree of asymmetric induction following the use of the chiral Rh$_2$(S-TBSP)$_4$ catalyst for the insertion step ([α]$^{28.1}_{1D}$ = + 24.0°), it was necessary to establish a suitable analytical method that would enable the identification of the enantiomers. In particular, using a racemic mixture as this would provide a 1:1 signal ratio. However, initial efforts targeted at the screening of various chiral high performance liquid chromatography (HPLC) columns for the separation of the racemic alcohols 320, obtained following the two step procedure of achiral Rh$_2$(hfb)$_4$ catalytic decomposition and DIBAL reduction, were unsuccessful. Therefore, it was decided to derivatise the bicyclic alcohol 320 into the corresponding diastereomeric esters using the Mosher’s acid chloride, (R)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl) (Scheme 5.34).
Disappointingly, initial attempts using commercially available (R)-(−)-(MTPA-Cl) in the derivatisation of 320 led to recovery of starting material (95%) and trace amounts of hydrolysed (R)-(−)-(MTPA-Cl). Further attempts involving the use of excess (R)-(−)-(MTPA-Cl) also led to recovery of starting material (75%) and an unidentified product, which proved difficult to assign.\textsuperscript{14} However, when (R)-(−)-(MTPA-Cl) was freshly prepared from the commercially available acid, (S)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), the reaction proceeded successfully. Thus, to a concentrated mixture of oxalyl chloride, (S)-(−)-(MTPA) and dimethylformamide (DMF) in deuterated chloroform was added alcohol 320, Et\textsubscript{3}N and DMAP. Following work-up and purification, two diastereomeric Mosher’s ester derivatives inseparable by column chromatography were obtained in good yield (60%). Analysis of the $^1$H NMR spectrum confirmed, as expected the formation of the diastereoisomers in the ratio 1:1 (Figure 5.5).
Significantly, the signals at 4.95 and 4.87 ppm in the $^1$H NMR spectrum (Figure 5.5, see inset) which have good baseline resolutions, correspond to the 6'-CH=CHH proton in each of the diastereoisomers. While in the $^{19}$F NMR spectrum, the signals at -71.28 and -71.75 ppm were attributed to the CF$_3$ groups (Figure 5.7). More importantly, under the conditions used for the reaction, there was no evidence for kinetic resolution as conducting and stopping the reaction at ca 20% conversion also gave a ratio of 1:1. Evidence for the formation of the esters 323 and 324 was obtained from the IR and $^1$H NMR spectra of the diastereomeric mixture. The IR spectrum showed the disappearance of the signal at 3410 cm$^{-1}$ attributed to the hydroxyl group and the appearance of the signal at 1752 cm$^{-1}$ corresponding to the carbonyl ester of the diastereoisomers. The formation of the diastereoisomers 323 and 324 was confirmed from the $^1$H NMR spectrum which showed signals at 3.62 and 3.55 ppm corresponding to the 2-OCH$_3$ group respectively. Additional analytical and spectroscopic data obtained was satisfactory.

Having successfully developed a practical and reproducible procedure for identification of the enantiomeric mixture using freshly prepared Mosher’s acid chloride. Attention then turned to
Chapter V: Enantioselective Synthesis of Bicyclic Alcohol Acetals

the screening of chiral rhodium (II) catalyst complexes, with the aim of forming a scalemic mixture.

The study toward an asymmetric synthesis of bicyclic alcohols commenced with investigating the potential of Davies chiral $\text{Rh}_2(\text{S-TBSP})_4$ catalyst to induce asymmetry, having had success previously with this catalyst system in the diazo decomposition of vinyl diazoketone acetal 279. Thus, following the same two step diazo decomposition and reduction but using $\text{Rh}_2(\text{S-TBSP})_4$ catalyst and DIBAL in successions, the vinyl diazoketone acetal 279 was converted into the bicyclic alcohol 320 in a good overall yield of 45% (Scheme 5.35).

![Scheme 5.35](image)

In a similar manner, the vinyl diazoketone 280 was transformed into the bicyclic alcohol 322 in an overall yield of 36%. Evidence obtained from analytical and spectroscopic data were in agreement with that acquired previously and were satisfactory. The specific rotation, $[\alpha]_{20.1}^{20.1}$ of the product 320 obtained at a concentration of 0.4 g/ml in CDCl$_3$ was -31.2°. Encouraged by this result, it was decided to examine the extent of asymmetric induction in the scalemic mixture, if any, following the use of the chiral catalyst. Therefore, the bicyclic alcohol 320 was converted into the corresponding esters by derivatisation with Mosher’s acid chloride using the same protocol as described previously (section 5.2.4.6). Gratifyingly, a mixture of two Mosher’s ester derivatives 323 and 324 which were inseparable by column chromatography was obtained in a good yield of 86%. Analysis of the $^1$H NMR spectrum confirmed that the diastereoisomeric esters resulted from a scalemic mixture of bicyclic alcohols in the ratio 77:23 (Figure 5.6).
The alphabetical signs (a) and (b) as used in Figure 5.6 (inset) corresponds to the major and minor ester derivatives 323 and 324 respectively. To highlight the degree of asymmetric induction, a stackplot each for the $^1$H and $^{19}$F NMR spectra obtained using both catalyst complexes are shown in Figure 5.7.
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Figure 5.7
Pleased with the degree of asymmetry induction using the chiral $\text{Rh}_2(\text{S-TBSP})_4$ catalyst, the enantiomeric excess (ee) of the scalemic mixture was calculated from the $^{19}\text{F}$ NMR spectrum to be a modest value of 54%. More importantly, this is the first report of asymmetry induction using the vinyl diazoketone i.e donor-acceptor carbenoids in intramolecular C-H insertion reactions. Compelled by this result, it was decided to explore the use of other chiral catalyst complexes in the initial diazo decomposition step with the aim of improving the enantiomeric excess.

In 2006, Davies developed and demonstrated that higher enantioselectivities (ee) are obtained when the intermolecular reactions of, in particular, donor-acceptor carbenoids are catalysed by the bulky tetrakis[(S)-(1-adamantyl)-(N-phthalimido)acetate]dirhodium (II), $\text{Rh}_2(\text{S-PTAD})_4$ in comparison to other well recognised chiral catalysts for example tetrakis[1-[(4-alkyl(C_{11}-C_{13})phenyl)sulfonyl]-2(S)-pyrrolidinecarboxylate]dirhodium (II), $\text{Rh}_2(\text{S-DOSP})_4$ and the Hashimoto’s tetrakis[N-phthaloxy]-2-tert-leucinate]dirhodium (II), $\text{Rh}_2(\text{S-PTTL})_4$ (Figure 5.8).

In one such study, Davies showed that ee’s of up to 91% can be achieved with $\text{Rh}_2(\text{S-PTAD})_4$ when N-Boc-pyrrole $\text{328}$ reacts with the vinyldiazoacetate $\text{329}$ to give the tropane derivative $\text{330}$ as the only product (Scheme 5.36, Table 5.9). In contrast, $\text{Rh}_2(\text{S-DOSP})_4$ $\text{326}$ and $\text{Rh}_2(\text{S-PTTL})_4$ $\text{327}$ gave ee’s of 29% and 88% respectively (entry 1 & 2).
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\[
\text{N-Boc} + \text{N}_2\text{CO}_2\text{Me} \xrightarrow{\text{Rh (II) catalyst (1 mol%)}} \text{328} \xrightarrow{2,2\text{-DMB, rt}} \text{330}, 38\% \text{ yield}
\]

91\% ee

Scheme 5.36

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield of 330 (%)</th>
<th>ee of 330 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(_2)(S-DOSP)(_4) 326</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>Rh(_2)(S-PTTL)(_4) 327</td>
<td>34</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Rh(_2)(S-PTAD)(_4) 325</td>
<td>38</td>
<td>91</td>
</tr>
</tbody>
</table>

2,2-DMB = 2,2-dimethylbutane

Table 5.9

Based on this precedence, it was decided to screen the Rh\(_2\)(S-PTAD)\(_4\) 325 and the Rh\(_2\)(S-DOSP)\(_4\) 326 catalysts. The choice of the latter catalyst was to enable comparison with the closely related Rh\(_2\)(S-TBSP)\(_4\) catalyst. Furthermore, both Rh\(_2\)(S-PTAD)\(_4\) 325 and Rh\(_2\)(S-DOSP)\(_4\) 326 catalysts were commercially available. The table below summarises the results obtained (Table 5.10).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Overall yield of bicyclic alcohol 320 (%)</th>
<th>Specific rotation of bicyclic alcohol 320</th>
<th>Yield of Mosher’s ester derivatives (%)</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(_2)(S-TBSP)(_4)</td>
<td>45</td>
<td>([\alpha]^{20.1}\text{D} = -31.2^\circ) c = 0.4, CDCl(_3)</td>
<td>86</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Rh(_2)(S-DOSP)(_4)</td>
<td>44</td>
<td>([\alpha]^{19.4}\text{D} = +44.9^\circ) c = 0.3, CHCl(_3)</td>
<td>57</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Rh(_2)(S-PTAD)(_4)</td>
<td>20</td>
<td>([\alpha]^{19.7}\text{D} = -70.3^\circ) c = 0.4, CHCl(_3)</td>
<td>75</td>
<td>86</td>
</tr>
</tbody>
</table>

Table 5.10
Both Rh$_2$(S-DOSP)$_4$ 326 and Rh$_2$(S-PTAD)$_4$ 325 catalysts gave good yields of the Mosher’s ester derivatives respectively 57% and 75% (entry 2 & 3). Although, Rh$_2$(S-PTAD)$_4$ catalyst 325 had the highest asymmetric induction with ee value of 86% (entry 3) compared to 54% and 50% for Rh$_2$(S-TBSP)$_4$ and Rh$_2$(S-DOSP)$_4$ 326 catalysts respectively. However, its decomposition of vinyl diazoketone acetal 279 afforded the bicyclic alcohol 320 in low yield (20%). The levorotary prefix [(−) sign] of the specific rotation obtained using Rh$_2$(S-PTAD)$_4$ catalyst 325 is consistent with published data. Furthermore, the catalysed decomposition involving Rh$_2$(S-DOSP)$_4$ 326 has been noted to preferentially deliver the opposite enantiomer to that obtained following the use of Rh$_2$(S-PTAD)$_4$ catalyst 325. The dextrorotary [(+) sign] ability of the products obtained using the Rh$_2$(S-DOSP)$_4$ catalyst 326 (entry 2) is in agreement with this observation.
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5.3 Conclusions

The synthesised aldehyde acetals were sequentially transformed into the allylalcohol acetals, allylketone acetals, vinyldiazoketone acetals and finally into the bicyclic acetals.

The allylalcohol acetals were formed in generally good yield as racemic mixture of products except in the case of acetals bearing a nitro group where complex mixtures of products were obtained.

The oxidation of the allylalcohol acetals led to the formation of an inseperable mixture of two products, the desired allylketone acetal and the enone acetal. Gratifyingly, the enone acetals could be readily equilibrated into the former by the choice of DBU under favourable reaction conditions.

The subsequent diazo transfer reaction proceeded successfully using a combination of p-ABSA, and DBU to give acetals with the diazo group transferred into the desired kinetically favoured α-position.

Initial catalytic decomposition of diazo acetals with Rh₂(pfb)₄ gave separable mixtures of both C-H and O-H insertion bicyclic acetals. However, the use of the less reactive although more selective Rh₂(hfb)₄ gave only C-H inserted bicyclicketone acetals. The bicyclicketone acetals were prone to both base and acid catalysed rearrangement and this led to the development of a simultaneous two-step catalytic diazo decomposition and DIBAL reduction giving acceptable yields of bicyclic alcohols.

Further study involved investigating the efficiency of asymmetric catalysis in the diazo decomposition step. This led to the screening of a set of chiral catalysts with Rh₂(S-PTAD)₄ giving the best ee of 86%.

Having developed a robust procedure for the synthesis of the bicyclic alcohol acetals, the next chapter will present efforts directed at converting these acetals into highly functionalised tetrahydrofurans by reductive cleavage.
5.4 References

5. The preparation of this reagent followed the standard procedure of Hazen, G. G.;
7. Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh,
    5714.
    **2007**, 9, 1203.
    2107.
14. Further attempts to use 2,6 lutidine in either case equally resulted in the same conclusion.
6.1 Introduction

As discussed in Chapter 1 (Section 1.9), one of the strategic plans was to explore the reductive cleavage of the insertion product 332 towards generating highly functionalised tetrahydrofuran derivatives 333 (Scheme 6.1).

Scheme 6.1

Having successfully prepared the set of bicyclic acetals 320, 322, 370 and 373, attention then turned to the study of their reductive cleavage. After a concise summary of the reductive cleavage reaction conducted on a closely related substrate within the group, the results of subsequent efforts will be presented herein.

6.2 Reductive cleavage of bicyclic alcohols

Previous reports by Garbi et al revealed that the bicyclic alcohol acetal 334 can undergo reductive cleavage of the acetal in a regioselective manner to give an inseparable mixture of trisubstituted tetrahydrofuran diastereoisomers 335 and 336 (Scheme 6.2).\(^1\) This reaction outcome proved to be general for a series of substrate analogue in which the C-4 substituent was varied.

Scheme 6.2
The reaction is believed to proceed via nucleophilic (in this case triethylsilane, Et₃SiH) attack on the cationic centre of an oxocarbenium ion intermediate 337 formed upon coordination of the Lewis acid with the more accessible oxygen of the acetal (Scheme 6.3).

![Scheme 6.3](image)

Two Lewis acids, titanium tetrachloride (TiCl₄) and boron trifluoride etherate (BF₃.Et₂O) were explored, with both giving similar yields and diastereoselectivities (Table 6.1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Yield (%)</th>
<th>Ratio 335:336</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TiCl₄</td>
<td>65</td>
<td>6:4</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>BF₃.Et₂O</td>
<td>60</td>
<td>7:3</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 6.1

Yamamoto et al in a related study exploring acetal 338 noted that the nature of solvents can influence the stereoselectivity of reductive cleavage using diisobutylaluminium hydride (DIBAL) (Scheme 6.4, Table 6.2).² The trans alcohol 340 formed by an intramolecular hydride attack, was the predominant product from reactions performed in non-polar solvents. In contrast, the cis alcohol 339 was obtained in polar solvents by hydride attack of a second molecule of DIBAL on the cationic center of the oxocarbenium ion.
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Scheme 6.4

\[
\text{DIBAL (6-eq) solvent, rt} \quad \begin{array}{c}
\text{cis 339} \\
\text{trans 340}
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio (cis:trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>12</td>
<td>56</td>
<td>17:83</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>15</td>
<td>51</td>
<td>82:18</td>
</tr>
</tbody>
</table>

Table 6.2

However, attempts by Garbi et al to explore this precedent by varying solvent and temperatures led in each case to complicated mixtures that were difficult to purify. Subsequent efforts by Garbi et al to enhance the stereoselectivity of the products obtained from the reductive cleavage reaction involved the formation of the acetate 341 and tert-butyldimethylsilyl (TBDMS) ether 342 derivatives of the alcohol 334 to explore the effect of steric bulk at C-7 (Scheme 6.5). Following the previously identified optimum conditions, the acetate 341 and TBDMS ether 342 derivatives were subjected to reductive cleavage (Scheme 6.5, Table 6.3).

Scheme 6.5

\[
\text{Et}_3\text{SiH (1.5eq), L.A (1.2 eq) DCM, -78 °C} \quad \begin{array}{c}
341 \quad \text{R=acetate} \\
342 \quad \text{R=TBDMS ether}
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio (cis:trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>343</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>344</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>345</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>346</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6.3

Whilst the use of the acetate derivative 341 failed to improve the selectivity, the reductive cleavage of the TBDMS derivative 342 led to an improved selectivity (95:5).

The stereochemistry could be explained using the stereoelectronic model for highly substituted five-membered-ring oxocarbenium ions devised by Woerpel et al (Scheme 6.6).\textsuperscript{3}

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Entry & Substrate & Lewis acid & Time (h) & Yield (%) & Ratio\textsuperscript{a} \\
\hline
1 & 341, R=Ac & TiCl\textsubscript{4} & 6 & 85 & 343:344 (6:4) \\
 & & BF\textsubscript{3}.Et\textsubscript{2}O & 8 & 70 & 343:344 (7:3) \\
\hline
2 & 342, R=TBDMS & TiCl\textsubscript{4} & 8 & 80 & 345:346 (95:5) \\
 & & BF\textsubscript{3}.Et\textsubscript{2}O & 9 & 70 & 345:346 (95:5) \\
\hline
\end{tabular}
\caption{Synthesis of Highly Functionalised Tetrahydrofurans}
\textsuperscript{a}Results taken from Ref[1].
\end{table}
Chapter VI: Synthesis of Highly Functionalised Tetrahydrofurans

The model proposes that nucleophilic attack occurs from the “inside attack” of the preferred envelope conformation of the five-membered-ring oxocarbenium ion. This forms the product in the lowest energy conformation with the observed selectivity increasing with the bulk of the R group.

6.3 Proposed study

The Lewis acid catalysed nucleophilic cleavage of bicyclic acetals is therefore a well established method within the group for the stereoselective synthesis of tetrahydrofurans (THF). Consequently, the reductive cleavage of the acetals, for example 320 was examined en route to the construction of highly functionalised THF derivatives 347 as shown below (Scheme 6.7).

![Scheme 6.7](image)

Tetrasubstituted THF derivatives such as 347 are challenging motifs to construct by conventional methods and are ubiquitous in many bioactive natural products. For example, Virgatusin 348 which inhibits the endogenous DNA polymerase of hepatitis B virus (HBV)\(^4\) and trilobatin B 349, a lignan from the liverwort *Bazzania trilobata*\(^5\) (Figure 6.1).

![Figure 6.1](image)
The study and results of the current efforts are presented below.

### 6.3.1 Reductive cleavage of bicyclic acetals

According to the basis of the “inside attack” model, the C-3 substituent of the oxocarbenium ion greatly influences the stereoselectivity of the nucleophilic substitution reactions as can be seen from the results of the nucleophilic substitution reactions involving 350, 352, 354 and allyltrimethylsilane catalysed by BF$_3$.OEt$_2$ (Scheme 6.8).$^6$

![Scheme 6.8]

The selectivity of the products formed from 350 and 354, bearing no substituent at C-3 were 68:32 and 60:40 for the products 351 and 355 respectively (eqs. 1 & 3). In contrast, the selectivity observed for the product 353 obtained from 352, bearing a C-3 substituent was 95:5 favouring the 1,3 trans product (eq 2).
In an effort to take advantage of this influence, considering that the alkyl substituent at C-6 of the acetal \( \text{320} \) translates into the C-3 substituent in the oxocarbenium ion intermediate \( \text{356} \) (Scheme 6.9),\(^7\) it was decided to explore the substituent effect in the reductive cleavage reaction.

![Scheme 6.9](image)

Following the method established by Garbi et al, the acetal \( \text{320} \) in DCM was treated with TiCl\(_4\) at -78 °C followed by the addition of Et\(_3\)SiH (Scheme 6.10).

![Scheme 6.10](image)

Analysis of the \(^1\)H NMR spectrum of the crude reaction mixture obtained showed the presence of two diastereoisomeric products \( \text{357} \) and \( \text{358} \) in a 3:2 ratio (Figure 6.2), which could be separated by careful column chromatography.
Both structures were deduced to be tetrahydrofuran (THF) derivatives and the relative stereochemistry of the products was established by a detailed analysis of the NMR data for each isolated derivative.

Evidence for the formation of the THF derivatives was found in the $^1$H NMR spectrum for 357 and 358 which showed signals appearing at 1.18 ppm and 1.22 ppm respectively and corresponding to the 2-$CH_3$ group, with the disappearance of the singlet signal at 1.53 ppm attributed to the 1-$CH_3$ group of alcohol 320 confirming the cleavage of the acetal. Furthermore, these signals appeared as a set of doublets due to the coupling of the 2-$CH_3$ and the 2-$H$ protons, having a determined coupling constant of 6.4 Hz in each case. Additional evidence obtained from analytical and spectroscopic data were satisfactory in each case.

The stereochemistry of the isolated products was determined by 2D NMR experiments particularly the NOESY. For example, in the NOESY of the major THF derivative 357, the 2-
A $CH_3$ signal showed a significant correlation to the 4-$CH=CH_2$ proton which implied that the 2-$CH_3$ and 4-$CH=CH_2$ groups were on the same side of the molecule (Figure 6.3).

Consistent with this suggestion, the 2-$H$ proton showed a strong correlation to the 5-$H$ proton. In contrast, the NOESY of the minor isomer 358 showed significant correlations between the 2-$H$ and 4-$CH=CH_2$ protons and also between the 2-$CH_3$ and 5-$H$ protons.

Similarly, the bicyclic alcohol acetal 322 was subjected to the same reductive cleavage conditions to give a separable mixture of diastereomeric THF derivatives 359 and 360 in a ratio of 6:4 (Scheme 6.11).

Evidence for the formation of the THF derivatives 359 and 360 obtained from analytical and spectroscopic data was satisfactory and consistent with that described above. It is noteworthy that the alternate stereochemistry at C-4 of the bicyclic alcohol acetal 322 had no effect on the stereochemical outcome of the reductive cleavage reaction.
Surprisingly, although the transient intermediate oxocarbenium ion was bearing a substituent at the C-3 position, the reductive cleavages of the acetals 320 and 322 using TiCl$_4$ gave poor selectivity. No further attempts were made to improve the selectivity of the products from the reductive cleavage reaction by varying the Lewis acid as both Garbi and Woerpel have independently shown that the Lewis acid has only limited influence on selectivity. Given this and the precedent established by Garbi et al., it was decided to explore the effect of steric bulk at the C-7 position of the bicyclic alcohol acetal 320. Towards this end, the benzoate and TBDMS ether were prepared. A detailed description of the preparation follows in the next section.

### 6.4 Bicyclic alcohol protection as benzoate and TBDMS derivatives

#### 6.4.1 Benzoate protection of bicyclic alcohol acetal

The alcohol 320 was converted into the benzoate derivative by treating successively with triethylamine (Et$_3$N) and 4-bromobenzoyl chloride in the presence of catalytic amount of 4-dimethylamino pyridine (DMAP) (Scheme 6.12).$^8$

![Scheme 6.12](image)

Evidence for the formation of the benzoate 361 was found in the IR spectrum with the disappearance of the hydroxyl (OH) signal at 3410 cm$^{-1}$ and the appearance of a carbonyl signal at 1725 cm$^{-1}$ corresponding to the ester carbonyl. The $^{13}$C NMR spectrum confirmed the formation of the benzoate with the appearance of a signal at 164.8 ppm attributed to the carbon of the ester functionality in benzoate 361.
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Having prepared the benzoate 361, attention turned towards the preparation of the TBDMS ether derivative of alcohol 320.

6.4.2 TBDMS ether formation from bicyclic alcohol acetal

To prepare the TBDMS ether 362, the procedure of Corey\textsuperscript{9} and Igarashi\textsuperscript{5} for the silylation of hindered alcohols using silyl triflates was followed. Thus, the alcohol 320 in DCM was treated at room temperature with tert-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) in the presence of 2,6-lutidine. However, initial efforts led to only 8\% of the desired product and a number of other products which proved difficult to identify. Further efforts resulted in investigating other bases and in this case Et\textsubscript{3}N proved successful giving the desired product in good yield (Scheme 6.13).

![Scheme 6.13](image)

Evidence for the formation of the silylated product 362 was obtained from the IR spectrum with the disappearance of the signal at 3410\,cm\textsuperscript{-1} corresponding to the hydroxyl stretch. Formation of the silylated product 362 was confirmed by the \textsuperscript{1}H NMR spectrum which showed the appearance of three singlet signals at 0.95 ppm, 0.10 ppm and 0.01 ppm, corresponding respectively to the 9 protons of the \textit{t}-butyl, and 3 protons each for the two methyls on the silicon atom.

With both the benzoate 361 and the TBDMS ether 362 of the bicyclic alcohol acetal 320 in hand, attention turned towards their reductive cleavage.
6.5 Reductive cleavage of benzoate and TBDMS derivatives

The benzoate 361 and TBDMS ether 362 derivatives were subjected to reductive cleavage using the TiCl₄ and Et₃SiH combination as described earlier. Following this procedure, the benzoate 361 in solution was converted into the corresponding THF derivative in excellent yield (Scheme 6.14).

![Scheme 6.14](image)

Analysis of the ¹H NMR spectrum of the crude reaction mixture showed the presence of two diastereomeric THF derivatives 363 and 364 in a ratio of 8:2 which were subsequently separated by column chromatography. As before, evidence for the formation of the THF derivatives 363 and 364 obtained from analytical and spectroscopic data was satisfactory.

The slight increase in THF isomers ratio (8:2) from benzoate 361, compared to the ratio obtained from the reductive cleavage of the bicyclic alcohol 320 (6:4), was attributed to the steric bulk of the benzoate group. Disappointingly, this ratio is far less than that from the chemoselective reaction anticipated as a consequence of this protecting group (Scheme 6.15).
It was hoped that the O-benzoyl group could block the approach of the hydride nucleophile from the top face of the formed oxocarbenium ion 365, inducing then a reverse attack from the bottom face to give exclusively the major isomer 363. However, considering that the THF products 363 and 364 were formed as diastereomeric mixtures in low ratio, other factors which include the position of the O-benzoyl group (possibly unfavourable) and the conformational bias of the intermediate ion 365 could be destabilising the transition state. Curiously, there was no evidence for equilibration of the benzoyl group between positions C-2 and C-1 of the cationic centre of 365.

As efforts to form the major THF isomer 363 selectively from the benzoate derivative 361 was unsuccessful, it was decided to examine the TBDMS ether derivative 362 in the hope that the bulkier TBDMS group would induce a much higher selectivity.

Thus, the TBDMS ether derivative 362 in solution was subjected to the same reductive cleavage reaction as earlier described (Scheme 6.16).
Following work-up, analysis of the $^1$H NMR spectrum of the crude reaction mixture indicated the presence of three isomers 366, 367 and 368 in a ratio of 2:1:2. The isomeric mixture was obtained in an 81% yield but could not be readily separated by column chromatography. However, small pure samples of the silylated major THF isomer 366 and oxepane isomer 368 were obtained and used for analysis. The minor THF isomer 367 could not be obtained pure. As before satisfactory evidence for the formation of the silylated major THF 366 and oxepane 368 isomers were obtained from analytical and spectroscopic data. The data for the silylated minor THF isomer 367 are not reported as the signals in the acquired $^1$H NMR spectrum were too weak.

Further evidence for the formation of the silylated THF isomers 366, 367 and in particular the oxepane isomer 368 was obtained after a subsequent silicon group deprotection protocol. Thus, following the reductive cleavage reaction of TBDMS ether derivative 362 to give the silylated mixtures 366, 367 and 368, the crude reaction mixture containing all three isomers was immediately treated with tetrabutylammonium fluoride (TBAF) at room temperature, to afford the corresponding alcohols (Scheme 6.17).
The mixture of alcohol products 357, 358 and 369 were obtained in good yield and were easily separated into the individual isomers by column chromatography. Evidence for the formation of the isomeric THFs 357 and 358 obtained from analytical and spectroscopic data were satisfactory and were in agreement with that previously acquired. Also, satisfactory evidence for the formation of the oxepane 369 was obtained.

The formation and stereochemistry of the 7-membered ring oxepandiol 369 were confirmed by 2D NMR experiments, in particular the HMBC and NOESY correlations (Figure 6.4, A and B respectively).
For example, in the HMBC spectrum, strong three (3) bond couplings were observed between 4-H and 4-CH=CH₂, 4-H and C-2 and the correlation across the oxygen heteroatom of the oxepane derivative between C-2 and 7-H₂ confirmed the formation of the seven membered ring nucleus. The stereochemistry as obtained from analysis of the NOESY spectrum showed correlations across the ring, significantly, there were correlations between the 2-CH₃ and 3-H protons, 3-H and 4-H, 4-H and 6-H and across 2-H to 7-H₂ protons.

In summary, the desilylation reaction conducted confirmed that the reductive cleavage of the TBDMS ether derivative 362 afforded the silylated oxepane 368 together with the silylated THF isomers 366 and 367. However, the isomers were obtained in an unexpectedly low ratio of 2:1:2, in contrast with previous observations by Garbi et al in which a selectivity of 95:5 was obtained for the formation of only THF isomers from a related substrate.

It was considered that the presence of bulky substituents on the bicyclic alcohol 320 did not significantly improve the selectivity of the products obtained from the reductive cleavage reaction and in fact may have impaired the reaction. Therefore, it was decided to attempt the reductive cleavage on the bicyclic alcohol 370, without the protecting group on the alcohol and bearing an ethyl substituent at the C-6 position compared to the ethenyl group as in previous examples (Scheme 6.18).¹⁰

![Scheme 6.18](image)

Treatment of 370 with triethylsilane and titanium tetrachloride in DCM at -78 °C gave two diastereomeric THF derivatives 371 and 372 in a ratio of 7:3 as observed in the ¹H NMR spectrum of the crude reaction mixture. The two diastereoisomers were subsequently separated by column chromatography. Evidence for the formation of the major THF isomer 371 obtained from analytical and spectroscopic data was satisfactory. However, the data for the minor THF
isomer 372 are not reported as the signals, in the acquired $^1$H NMR spectrum, were too weak. This is attributed to the small scale used in conducting the reaction.

Similarly, the reductive cleavage reaction conducted on the bicyclic alcohol 373 indicated that the alternative stereochemistry at the C-4 position had no effect on the stereoselectivity. In this case, THF diastereoisomers 374 and 375 obtained were separated by column chromatography and isolated in a ratio of 7:3 (Scheme 6.19).

![Scheme 6.19](image)

As before, satisfactory evidence for the formation of the THF derivatives 374 and 375 was obtained from analytical and spectroscopic data.

Although the selectivity obtained from the reductive cleavage reactions were modest. Analysis of the products obtained showed that similar selectivity and same stereochemistry were observed leading to the major THF isomers 357, 359, 363, 366, 371 and 374. Initial application of solely steric did not account for the observed selectivity. A possible rationale which accounts for both the selectivity and stereochemistry is provided when the stereoelectronic model for ‘highly substituted five-membered-ring oxocarbenium ion’ developed by Woerpel et al is invoked together with chelation control. This model postulates that nucleophilic attack occurs from the “inside attack” of the preferred envelope conformation of the five-membered-ring oxocarbenium ion to form the product in the lowest energy conformation (Scheme 6.20).
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Scheme 6.20

Application of this model using the bicyclic alcohol substrate 320 is shown below, following an initial Lewis acid chelation between the more accessible acetal oxygen i.e O-2 to the C-7 oxygen substituent (Scheme 6.21).
By this model, transition state 376 is disfavoured as attack by the nucleophile from the “outside” of the oxocarbenium ion gives rise to the eclipsed product. In contrast, transition state 377 gives the more stable staggered product following an “inside” attack by the nucleophile. However, the oxocarbenium ion of transition state 377 can exist as an additional conformer 378 (Scheme 6.22).
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Both of these ‘‘envelope’’ conformers 378 and 377 would favour ‘‘inside’’ attack by an approaching nucleophilic. Furthermore, certain alkoxy-substituted six-membered-ring oxocarbenium ions have been noted to assume conformations in which the alkoxy group resides preferentially in the pseudoaxial position (Scheme 6.23).\(^\text{11}\)

Whilst 379 is the favoured conformation when R is an alkyl substituent, 380 becomes the preferred conformation when R is an alkoxy group. Logically, this has been successfully extended to five-membered-ring oxocarbenium ions.\(^3\) In addition, this conformational preference has been shown to be consistent with computational investigations.\(^\text{12}\) Based on these, the conformation 377 bearing the 2-alkoxy substituent in a pseudoaxial position is more likely to be the preferred transition state for the nucleophilic addition reaction giving the major isomers 357, 359, 363, 366, 371 and 374 as obtained.

Woerpel et al and Reißig et al have independently observed that both the conformational preference of the oxocarbenium ion intermediate and the steric interactions that arise in the transition structures with nucleophilic attacks influences the stereochemical outcomes of such
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reactions. Inside attack of the nucleophile on the conformers 377 and 378 each involve destabilised transition structures. The transition structure for ‘‘inside’’ attack on conformer 378 develops a destabilising interaction between the approaching nucleophile and the C-3 alkyl substituent, known to bias nucleophilic attack in favour of products with high 1,3–anti stereoselectivity.3 Whilst ‘‘inside’’ attack on conformer 377 circumvents this unfavourable interaction with the nucleophile, the imposed steric interactions between the C-2 and C-4 substituents destabilise this transition structure leading to the product. It is these unfavourable interactions in both transition states that appear to account for the low selectivity obtained from the reductive cleavage reactions and suggest the difference in transition energies between both conformers is negligible. Thus, nucleophilic attack on conformer 378 leads to the minor isomers 358, 360, 364, 367, 372 and 375 as obtained.

Intriguing, the strong dependence of selectivity on the substituent at C-3 of the oxocarbenium ion intermediate was less pronounced.5 One plausible explanation is that the cis relationship of the C-2 and C-4 substituents in the oxocarbenium ion intermediate overshadows the effect of the C-3 substituent. The C-2, C-4 cis relationship has also been implicated in nucleophilic additions to oxocarbenium ions that resulted in low selectivity.13

The formation of the oxepane derivative 368 together with the THF isomers 366 and 367 from the reductive cleavage of the TBDMS derivative 362 is also believed to be due to unfavourable interactions caused by the bulky TBDMS protecting group on the C7-oxygen atom of 362. This distorts the presumed ‘exclusive’ chelation of the accessible O-2 oxygen of the acetal to the C7-oxygen by the Lewis acid in 381 and simultaneously favours the chelation of both acetal oxygens (i.e O-2 and O-8) by the Lewis acid as in 382 (Scheme 6.24).
The formation of the oxepane and THF isomers in a ratio of 2:3 respectively, indicates that the transition structures 381 and 382 are comparable in energy. This leads to a loss of the regiospecific cleavage of the C-1/O-2 bond as both C-1/O-2 and C-1/O-8 bonds becomes amenable to cleavage. Lewis acid chelation via path ‘a’ leads to structure 381 and subsequently gives the THF isomers 377 and 367 as earlier explained using the “inside” attack model. While chelation of both acetal oxygens due to sterics inflicted by the bulky TBDMS group limits path ‘a’ and therefore leads to structure 382 via the alternative path ‘b’. Simultaneous attack of the oxocarbenium ion by the hydride nucleophile from the opposite face of the complexing Lewis acid gives the observed stereochemistry obtained in the formation of the oxepane derivative 368.
6.6 Conclusions

The stereoselective preparation of 2,3,4,5-tetrasubstituted tetrahydrofurans by a Lewis acid mediated reductive cleavage of bicyclic acetals has been achieved in good yields and modest stereoselectivity.

The bicyclic vinyl alcohol including its benzoate and TBDMS ether derivatives together with the bicyclic ethyl alcohol were each successfully cleaved. The bicyclic vinyl alcohol, its benzoate derivative and the bicyclic ethyl alcohol gave only mixtures of THF diastereoisomers easily separated by column chromatography. However, the TBDMS derivative of the bicyclic vinyl alcohol led to a mixture of THF and oxepane isomers.

The reductive cleavage reaction proceeded via an oxocarbenium ion intermediate, initiated by a Lewis acid subsequently followed by attack of a nucleophile. The titanium tetrachloride/triethylsilane combination proved to be an effective system for the reductive cleavage.

The stereochemistry and selectivity of the products obtained from the reductive cleavage reaction is explained using a combination of chelation control and the “inside” attack stereoelectronic model developed by Woerpel et al.

Having synthesised the tetrasubstituted tetrahydrofurans from the bicyclic alcohols, the next chapter aims to present progress made in efforts to synthesise oxepanes from the bicyclic framework.
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6.7 References

10. The bicyclic alcohols 370 and 373 were prepared from the bicyclic ketones 436 and 437 (section 7.5.1) respectively by sodium borohydride (NaBH₄) reduction. Satisfactory analytical and spectroscopic data were obtained and are reported.
Chapter VII: Oxepane Synthesis

7.1 Introduction

The preceding chapter described the use of the combination of titanium tetrachloride and triethylsilane that resulted in the successful synthesis of tetrasubstituted tetrahydrofurans (THF) \textbf{333} (Scheme 7.1, path ‘a’). To enhance the utility of this robust methodology, efforts were directed at developing a divergent synthetic protocol using the bicyclic acetals with the intent of preparing highly functionalised oxepanes \textbf{383} and \textbf{384} (Scheme 7.1, paths ‘b’ and ‘c’ respectively).

![Scheme 7.1](image)

The following sections of this chapter will aim to present detailed descriptions of two separate but similar routes explored towards the synthesis of the target oxepane molecules.

7.2 Inverting the stereochemistry of the alcohol group on bicyclic acetals

Previous work by Garbi et al has shown that the treatment of the diazoketone \textbf{131} (representative of the acceptor substituted class of carbenoids) with rhodium (II) acetate gives the bicyclic ketone \textbf{132}. Subsequent reduction of \textbf{132} affords \textbf{385} and a series of further
transformations leads to 387 with inversion of the C-7 hydroxyl group stereochemistry.\(^1\) It was strongly proposed that the stereochemistry of the C-7 hydroxyl or alkoxy substituent directs the regiochemistry in the reductive cleavage step leading to THF 386 and oxepane 388 derivatives respectively (paths ‘d’ and ‘e’, Scheme 7.2).

![Scheme 7.2](image)

Based on this observation, it was decided to examine both the reaction and the robustness of the reductive cleavage step (path ‘e’), by exploring a bicyclic alcohol analogous to 387 but with a different substitution pattern. It was hoped that this would provide access to pentasubstituted oxepane derivatives which are challenging motifs in organic synthesis. The diazoketones such as 131 required for the transformations can be obtained from the corresponding ester acetal 145 prepared previously (chapter II, section 2.2.2). The following section will describe the preparation of the bicyclic alcohols (of type 387) and efforts made towards the synthesis of oxepanes.
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7.3 Preparation of the bicyclic alcohol 389

The Garbi protocol for the synthesis of bicyclic alcohols, which requires the formation of the acid acetals from the corresponding esters, was adopted. It was decided to explore the mixture of the acetals 147 and 148 for the purpose of probing the entire sequence of reactions, in particular the reductive cleavage step that will lead to the target molecules.

7.3.1 Preparation of the acid acetals 390, 391

The isomeric mixture of esters 147, 148 was treated with NaOH in THF/H₂O mixture (1:1) to afford the corresponding acids 390, 391 in an 80% yield (Scheme 7.3).

![Scheme 7.3](image)

The acid acetals 390, 391 were inseparable by column chromatography. However, recrystallisation from petroleum ether afforded the major acid acetal 390 as a pure sample while the mother liquor was enriched with the minor acid acetal 391. Analytical and spectroscopic data was obtained for the pure major isomer 390 while that of the minor isomer 391 was obtained as an enriched sample.

Evidence confirming the formation of 390 and 391 was obtained from the ¹H NMR spectrum which showed the disappearance of the methoxy singlet signals at 3.83 ppm and 3.81 ppm and the appearance of signals at 8.10 ppm and 7.95 ppm, respectively attributed to the carboxylic acid proton. Additional analytical and spectroscopic evidence obtained were satisfactory.

With the pure major acid acetal 390 in hand, attention turned towards preparing the corresponding diazoketone. This will be the subject of the following section.
7.3.2 Preparation of the diazoketone 397

The efficient preparation of diazoketones requires the acylation of diazomethane with an appropriate molecule bearing the acyl group. However, diazomethane and its precursor Diazald® are not commercially available and therefore methods for their preparation were explored. The precursor, Diazald® 394 was prepared following the De Boer procedure from p-toluenesulfonylchloride 392 and methylamine 393 (Scheme 7.4).³

\[
\text{H}_3\text{C} \quad \text{O} \quad \text{Cl} \quad + \quad \text{2CH}_3\text{NH}_2 \quad \rightarrow \quad \text{H}_3\text{C} \quad \text{O} \quad \text{NCH}_3 \quad + \quad \text{CH}_3\text{NH}_2\text{HCl}
\]

\[
\text{CH}_3\text{NH}_2\text{HCl} \quad + \quad \text{NaOH} \quad \rightarrow \quad \text{CH}_3\text{NH}_2 \quad + \quad \text{NaCl} \quad + \quad \text{H}_2\text{O}
\]

\[
\text{H}_3\text{C} \quad \text{O} \quad \text{NCH}_3 \quad + \quad \text{HNO}_2 \quad \rightarrow \quad \text{H}_3\text{C} \quad \text{O} \quad \text{NCH}_3 \quad + \quad \text{H}_2\text{O}
\]

Scheme 7.4

Once Diazald® 394 was prepared, it was used in a non-ethanolic diazomethane preparation by dissolution in anhydrous ether. The Diazald® 394 solution was then slowly dripped into a mixture of KOH and di(ethyleneglycol)methyl ether in a 1:1 mixture of H₂O/ether at 60 °C.⁴ The resultant diazomethane 395 was distilled as an ethereal solution (Scheme 7.5).

\[
\text{H}_3\text{C} \quad \text{O} \quad \text{NCH}_3 \quad + \quad \text{ROH} \quad \text{KOH} \quad \rightarrow \quad \text{H}_3\text{C} \quad \text{O} \quad \text{OR} \quad + \quad \text{CH}_2\text{N}_2 \quad + \quad \text{H}_2\text{O}
\]

\[\text{R}=\text{CH}_3\text{O(}\text{CH}_2\text{CH}_2\text{)}_2\text{O}\]

Scheme 7.5

The mechanistic rationale for the above process that leads to the formation of diazomethane is depicted below (Scheme 7.6).⁴
Concurrently with the preparation of diazomethane, the acid 390 was activated by treating with isobutyl chloroformate in the presence of triethylamine (Et$_3$N) to form the intermediate mixed anhydride 396. The reaction was followed by TLC and upon complete consumption of the acid indicating the formation of the mixed anhydride, the ethereal solution of freshly prepared diazomethane 395 was added to the reaction mixture (Scheme 7.7).

Following purification by flash column chromatography, the target diazoketone 397 was obtained in 85% yield. Evidence confirming the formation of the diazoketone 397 was obtained
from the IR spectrum which showed a characteristic signal at 2107 cm\(^{-1}\) corresponding to the diazo functional group. The \(^1\)H and \(^{13}\)C NMR spectra showed diagnostic signals at 5.70 ppm, 194.4 ppm and 53.8 ppm corresponding to 2-\(H\), C-1 and C-2 respectively.

### 7.3.3 Preparation of the bicyclic ketone 398

After the successful preparation of the diazoketone 397, application of the Rh (II) mediated C-H insertion protocol earlier outlined (section 5.2.4), using Rh\(_2\)(OAc)_4 as the catalyst afforded the bicyclic ketone 398 in 50% yield following chromatography (Scheme 7.8).

![Scheme 7.8](image)

Evidence for the formation of 398 was obtained from the IR spectrum which showed the disappearance of the signal attributed to the diazo carbon at 2107 cm\(^{-1}\) and the appearance of the signal at 1752 cm\(^{-1}\), shifted from 1626 cm\(^{-1}\) in the starting material, corresponding to the carbonyl group. Additional evidence obtained from analytical and spectroscopic data was satisfactory.

### 7.3.4 Reduction of the bicyclic ketone 398

With the bicyclic ketone 398 in hand, it was submitted for reduction using sodium borohydride (NaBH\(_4\)). In a typical reaction, the bicyclic ketone 398 was treated with NaBH\(_4\) in methanol at room temperature for 12 hours (Scheme 7.9).
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Scheme 7.9

Following chromatography, the desired bicyclic alcohol 399 was isolated in good yield (70%) as a white crystalline solid. Evidence for the formation of 399 was confirmed by the IR spectrum which showed a characteristic broad signal at 3670-2950 cm\(^{-1}\) corresponding to the hydroxyl group and the absence of the signal at 1752 cm\(^{-1}\) corresponding to the carbonyl group. Further evidence obtained from the \(^1\)H NMR spectrum showed the appearance of a signal at 4.05 ppm attributed to the 7-H proton and the \(^{13}\)C NMR spectrum showed the disappearance of the signal at 211.0 ppm attributed to the carbonyl group and the presence of a signal at 75.4 ppm corresponding to the C-7 carbinol carbon.

The full assignment of the \(^1\)H NMR and \(^{13}\)C NMR spectra was accomplished by analysis of the 2D NMR experiments in particular HSQC and HMBC. The stereochemistry of the hydroxyl group at the C-7 position was ascertained by a NOESY experiment, with the significant correlation being that between the 7-OH group and the axial 3-H proton (Figure 7.1). All data obtained were in agreement with previous reports by Garbi.\(^1\)

Figure 7.1
7.4 Inversion of alcohol stereochemistry

A versatile method employed generally for secondary alcohol inversion is the Mitsunobu reaction. This reaction involves the displacement of the hydroxyl group of the chiral alcohol by a nucleophile in a one-pot process with overall inversion of the stereochemistry. The generally accepted mechanism for the inversion of the configuration for chiral secondary alcohols is detailed below (Scheme 7.10).

The reaction proceeds by attack of triphenyl phosphine (PPh₃) on the weak N=N pi bond of the azo ester e.g. diethyl azodicarboxylate (DEAD) to give the anion 400 stabilised by resonance to the adjacent ester groups. The anion 400 subsequently abstracts a proton from the alcohol to form the alkoxide ion 401, which immediately attacks the positively charged phosphorus atom to give the species 402 and 403. The second basic nitrogen anion of 403 then abstracts the proton of the nucleophile to give the reduced azo diester 404 and the anion of the nucleophile. Finally, the nucleophile anion attacks the phosphorus derivative of the alcohol 402 in an S_N2 reaction at the carbon centre with triphenyl phosphine oxide 406 as the leaving group. The reaction gives the S_N2 product 405 together with the reduced azo diester 404 and triphenyl phosphine oxide 406. Nucleophiles that can participate in such reactions include carboxylic acids, thioacids, phenols, thiols, imides and sulfonamides.
Scheme 7.10

Initial efforts by Garbi et al to explore the Mitsunobu reaction to invert the stereochemistry at the C-7 position of the bicyclic alcohol 399, include the use of various combinations of Mitsunobu reagents for example PPh₃, acetic acid, disopropyl azodicarboxylate (DIAD); PPh₃, p-nitrobenzoic acid, DIAD were unsuccessful. Further efforts to vary the order of addition of reagents with a view to generating the betaine (PPh₃-DIAD adduct) were equally unsuccessful. Ultimately, it was thought that the alcohol group in 399 was too hindered for reaction with the betaine.
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In 2001, Wee reported an application of the combination of DEAD, PPh$_3$ and chloroacetic acid ($pK_a$ of 2.86 compared to acetic acid $pK_a$ 4.76) for the successful inversion of the configuration of the secondary alcohol 407 to give the chloroacetate derivative 408 in good yield (Scheme 7.11).$^5$

\[
\text{OH} \quad \text{ClH}_{2}\text{CO}_2\text{H}, \text{DEAD} \quad \text{PPh}_3, \text{THF} \rightarrow \quad \text{Cl} \quad \text{O} \quad \text{O} \\
\text{Cbz} \quad \text{407} \quad \text{408, 78%} \\
\]

**Scheme 7.11**

In view of this precedent, it was decided to investigate the conditions of Wee *et al* using the bicyclic alcohol 399. Thus the alcohol 399 was dissolved in THF followed by the successive addition of chloroacetic acid, PPh$_3$ and DEAD according to the literature procedure (Scheme 7.12).

\[
\text{OH} \quad \text{ClH}_{2}\text{CO}_2\text{H}, \text{DEAD} \quad \text{PPh}_3, \text{THF}, \text{rt, 12 h} \rightarrow \quad \text{Cl} \quad \text{O} \quad \text{O} \\
\text{399} \quad \text{409} \\
\]

**Scheme 7.12**

However, the reaction led to recovery of the starting material 399 with no trace of the chloroacetate derivative product 409 in the $^1$H NMR spectrum of the crude reaction mixture. Further efforts to change the bulky PPh$_3$ and azo ester DEAD led to the use of the less hindered tributyl phosphine (TBP) in combination with azodicarboxyldipiperidine (ADDP) which is a new ‘redox system’ developed by Ito *et al* and subsequently exploited for the conversion of 410 into 411 in good yield (81%) (Scheme 7.13).$^6$
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Scheme 7.13

However, attempts to apply this protocol to the alcohol 399 proved unsuccessful. As efforts at performing inversion at the C-7 position using the Mitsunobu reagents were unsuccessful, an alternative approach was then explored. It was considered that converting the alcohol into a good leaving group \((i.e \text{ mesylate or tosylate})\) followed by an \(S_N2\) reaction on the formed sulfonate might lead to the inverted product. Although Garbi had prepared the mesylate derivative from a related bicyclic alcohol, attempts to perform the subsequent \(S_N2\) inversion was unsuccessful.\(^1\) Reasoning that the mesylate derivative was more stable than anticipated, it was decided to convert the alcohol 399 into a better leaving group. Thus, the bicyclic alcohol 399 was dissolved in DCM and treated with trifluoromethane sulfonic anhydride in the presence of 2,6-lutidine (Scheme 7.14).\(^1\)

Scheme 7.14

Following chromatography, the triflate derivative 412 was isolated in good yield (78%). Evidence for the formation of 412 was obtained from the IR spectrum which showed a signal at 1413 cm\(^{-1}\) corresponding to the sulfonate \((\text{OSO}_2)\) functional group and the absence of the characteristic signal at 3670-2950 cm\(^{-1}\) corresponding to the alcohol moiety. The \(^{13}\)C NMR spectrum showed the appearance of a signal at 118.6 ppm attributed to the trifluoromethane carbon \((\text{CF}_3)\) and the \(^{19}\)F NMR spectrum confirmed the formation of 412 with the appearance of a signal at -74.8 ppm corresponding to the fluorine atoms.
It is worth noting that the triflate 412 is highly unstable at room temperature due to rapid decomposition. The stability could be marginally enhanced, for 24 hours upon storage under inert atmosphere. Storage at or below 0 °C could preserve it for no more than 48 hours.

The triflate derivative 412 was subjected to a nucleophilic displacement reaction using potassium hydroxide and 18-Crown-6 in refluxing dimethyl formamide (DMF). After 16 hours, analysis of the $^1$H NMR spectrum of the crude reaction mixture indicated the presence of two isomers in a ratio of 3:1 (Scheme 7.15).

![Scheme 7.15](image)

The isomeric products were identified using spectroscopic data to be the inverted alcohol 413 and its epimer 414. The epimeric mixture 413 and 414 were obtained in a combined yield of 63% following flash column chromatography, however, the epimers could not be separated. The formation of the latter isomer 414 is attributed to concomitant hydrolysis of the triflate derivative 413 during the course of the reaction.

As the alcohols 413 and 414 proved difficult to separate by column chromatography. Efforts were directed at derivatising the inverted alcohol 413 without affecting the epimer 414, in order to aid their separation. It was hoped that alcohol 413 would be more reactive than the epimer 414 as it was considered that the hydroxyl group was less sterically encumbered. Therefore, the epimeric mixture 413 and 414 was dissolved in DCM and treated with a combination of tert-butyldimethylsilyl chloride (TBDMSCl) and triethylamine (Et$_3$N). However, this condition was unsuccessful and gave only recovered starting material. Further efforts involved treating the alcohol mixture 413 and 414 with the more reactive tert-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) and 2,6-lutidine in DCM. Happily,
the silylated inverted alcohol 415 was isolated in 68% yield following chromatography and the alcohol 414 was obtained as an impure mixture (Scheme 7.16).

Evidence obtained for the formation of the silylated alcohol 415 was obtained from the IR and $^1\text{H}$ NMR spectra. Whilst the IR spectrum showed the disappearance of the broad signal at 3620-3170 cm$^{-1}$ attributed to the hydroxyl group, the $^1\text{H}$ NMR spectrum confirmed the formation of 415 with the appearance of the signals at 0.91 ppm, 0.10 ppm and 0.07 ppm corresponding respectively to the 9 protons of the $t$-butyl, and 3 protons each for the two methyls on the silicon atom. Additional data obtained was satisfactory.

With the TBDMS derivative 415 in hand, attention turned towards deprotecting the silyl group. Treatment of the silyl derivative 415 with tetrabutylammonium fluoride (TBAF) in THF at room temperature proceeded to afford the pure inverted alcohol 413 in an overall yield of 86% (Scheme 7.17).

Satisfactory evidence for the isolated alcohol 413 was obtained from analytical and spectroscopic data. The stereochemistry of the C-7 hydroxyl group, which confirmed that the isolated product 413 was the inverted alcohol, was determined from NOESY experiment. The
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NOESY spectrum showed a strong correlation between the 7-H proton and axial 3-H proton, indicating that both protons are on the same side of the molecule (Figure 7.2).

![Figure 7.2](image)

Further evidence to support the inversion of stereochemistry in 413 can be seen from a stackplot of the $^1$H NMR spectra of both alcohol epimers, which showed an upfield shift of the triplet corresponding to the axial 3-$H$ proton, from 3.83 ppm in 414 to 3.39 ppm in 413 (Figure 7.3).

![Figure 7.3](image)

With the pure inverted alcohol in hand, attention turned to explore the reductive cleavage reaction.
7.4.1 Titanium tetrachloride mediated reductive cleavage

The reductive cleavage of the inverted alcohol 413 proceeded successfully. To a cooled solution of the alcohol 413 was added in succession triethylsilane (Et₃SiH) and a 1M solution of titanium tetrachloride (TiCl₄) (Scheme 7.18).

Following work-up, two diastereoisomeric oxepanes 416 and 417 in a selectivity of 86:14 were observed in the ¹H NMR spectrum of the crude reaction mixture (Figure 7.4).

![Scheme 7.18](image)

![Figure 7.4](image)
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The isomers were obtained in near quantitative yield (99%) and could not be separated by flash column chromatography. As before, evidence obtained for the formation of the major oxepane isomer 416 from analytical and spectroscopic data of the mixtures, was satisfactory. In particular, the $^{13}$C NMR spectrum showed an upfield shift of the signal attributed to the carbon at C-1 from 106.3 ppm to 82.4 ppm corresponding to a shift from quartenary to a tertiary carbon. The $^1$H NMR spectrum confirmed the formation of 416 with the appearance of the signal at 3.81 ppm corresponding to the proton at the tertiary carbon (C-1). The data for the minor isomer 417 are not reported as the signals observed in the acquired $^1$H NMR spectrum were too weak to be accurately discerned.

The stereochemistry observed for the major isomer 416 as determined from 2D NMR experiments, in particular the NOESY (Figure 7.5), supports the conformational and stereochemical assignments shown (Scheme 7.19).

![Scheme 7.19](image)
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The NOESY showed a strong correlation between the 5-\(H\) and both the 4-\(H\) and 6-\(H\) (broken wedge) protons (cf 419). A strong correlation was also observed between the 7-\(H\) and the 6-\(H\) (normal wedge) protons (cf 419). The formation of 416 indicates that the transient oxocarbenium ion 419 adopts the preferred chair conformation as depicted (Scheme 7.19). Further support for this conformation is provided by Boggs *et al* following a study of the conformation of some cycloalkenes.\(^7\) In their study they reported that, whilst the possible conformations of the seven-membered ring, cycloheptene which exist as a pseudo six-membered ring may be relatively close in energy, it is the chair conformer that is the most stable. The intermediate 419 was formed from a complexation between the Lewis acid, TiCl\(_4\) and the 7-OH/8-O groups in 418. Attack of the nucleophile on the proposed oxocarbenium ion intermediate 419 via path ‘b’ results in the observed major isomer 416 while attack via path ‘a’ is proposed to lead to the minor isomer 417 and is disfavoured due to interactions between the approaching nucleophile and the 6-\(H\)/benzyl protons.

The desire to obtain crystallisable solids suitable for X-ray analysis, which would provide further evidence to confirm absolute stereochemistry, prompted renewed efforts to derivatise the oxepane isomers 416 and 417. Therefore, the acetate derivatives 420 and 421 were prepared (Scheme 7.20).

![Scheme 7.20](image-url)
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The bisacetate derivatives 420 and 421 were inseparable by column chromatography and isolated in moderate yield (55%) as a mixture of diastereoisomers. Evidence for the formation of the major bisacetate derivative 420 obtained from analytical and spectroscopic data of the mixture was satisfactory. Data for the minor derivative 421 are not reported as the signals were too weak. Disappointingly, the bisacetate derivatives were obtained as an oily mixture.

Further efforts led to the formation of the benzoates by protecting the alcohol mixture with 4-bromobenzoyl chloride. However, due to the limited amounts of alcohols 416 and 417 available, it was decided to deprotect the bisacetate derivatives 420 and 421 in order to recover additional quantity. Thus, the bisacetates 420 and 421 were treated with sodium methoxide before acidifying with an ion-exchange resin (Scheme 7.21).

Unfortunately, the deprotection of the bisacetates was incomplete leading to the monoacetate mixtures 422 and 423 which proved difficult to separate by column chromatography. Satisfactory analytical and spectroscopic evidence, acquired on the mixtures, was obtained for the major monoacetate isomer 422. The data for the minor isomer 423 are not reported due to weak signals.

In an attempt to maximise the isolation of the monoacetate mixtures 422 and 423, it was decided to derivatise the free hydroxyl groups as the benzoates anticipating that the products might be solid. Thus, the mixtures 422 and 423 were treated successively with triethylamine (Et₃N) and 4-bromobenzoyl chloride in the presence of dimethylaminopyridine (DMAP) to yield the monoacetate-monobenzoate mixtures 424 and 425 in 60% yield (Scheme 7.22).
Satisfactory analytical and spectroscopic data obtained on the mixture, were satisfactory for the major isomer 424. As before, data for the minor isomer 425 are not reported as signals in the $^1$H NMR spectrum acquired were too weak. Unfortunately, the isolated mixtures 424 and 425 were sticky solids and could not be recrystallised. Additional effort targeted at obtaining solids led to the preparation of the bisbenzoate derivatives of the alcohol mixtures. Thus, adding triethylamine (Et$_3$N), dimethylaminopyridine (DMAP) and 4-bromobenzoyl chloride successively to the alcohols 416 and 417 in DCM gave the bisbenzoate derivative mixtures 426 and 427 in 68% yield (Scheme 7.23).

The mixture of diastereoisomers proved difficult to separate by column chromatography. Evidence for the formation of the major bisbenzoate isomer 426 obtained from analytical and spectroscopic data of the mixture were satisfactory. In particular, the IR spectrum showed the presence of the signal at 1713 cm$^{-1}$ corresponding to the carbonyl of the ester group. As before, data for the minor bisbenzoate isomer 427 are not reported as the signals were too weak. More importantly, the bisbenzoate mixtures 426 and 427 were obtained as solids. However, efforts to grow crystals suitable for X-ray analysis have proven to be unsuccessful and
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challenging, largely attributable to only a small amount of material available. Fresh effort to reproduce the entire synthetic protocol that leads to the bisbenzoate derivatives, with a view to obtain enough material to enable easier recrystallisation was not concluded due to time constraints.

Although the oxepanes were successfully synthesised in good yield and selectivity, it was thought that the reaction sequence was cumbersome and poses problems of practicability. Reflecting this, it was therefore decided to explore alternative protocols that will enable easier access to this class of molecules. The following section will describe efforts toward achieving this objective.

7.5 Reductive cleavage mediated by samarium (II) iodide

Samarium (II) iodide (SmI₂) is a powerful one-electron reducing agent, which has found widespread applications. For example, this reagent has been utilised for the reduction of carbonyl compounds and the ring opening of cyclic ethers. In 2003, Kakiuchi et al highlighted the usefulness of samarium (II) iodide in regioselective radical ring-opening of bicyclo[4.2.0]octan-2-ones (Scheme 7.24).  

\[
\text{R} \quad \xrightarrow{(a)} \quad \text{NC} + \text{O} \\
\text{428} \quad 430, 2\% \quad 431, 81\%
\]

\[
\text{R} \quad \xrightarrow{(a)} \quad \text{NC} + \text{O} \\
\text{429, 79-99\%} \\
\text{R= alkyl}
\]

(a) SmI₂, tBuOH, HMPA, THF, rt

Scheme 7.24
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The reaction of 428 bearing various alkyl groups at the C-6 position resulted in the fission of the C1-C8 bond to give the cyclohexanone derivatives 429 in good yields. In contrast, a mixture of cyclooctanone 430 and bicyclo[3.3.1]nonanone 431 were obtained from the cleavage of the C1-C6 bond when a cyano group was placed at the C-6 position. Interestingly, the use of excess SmI₂ reagent led to a near quantitative conversion of 430 into 431.

Considering this, it was decided to explore the use of the SmI₂ reagent in the reductive cleavage of the bicyclic ketone 398. However, the success of this investigation was dependent on the preparation of fresh solutions of SmI₂ reagent as the commercially available material decomposed readily during an attempt to syringe an aliquot. Therefore, a solution of freshly prepared SmI₂ and hexamethylphosphoramide (HMPA) was stirred together to give a purple solution that was subsequently added into a solution of the ketone 398 at room temperature (Scheme 7.25).

Following work-up and analysis of the ¹H NMR spectrum of the crude reaction mixture, two diastereoisomers 432 and 433 were observed in a ratio of 7:3. The mixture of isomers were subsequently isolated in good yield (67%) but proved difficult to separate by column chromatography. The ¹H NMR spectrum and GCMS data obtained on the purified mixtures are shown in Figure 7.6 and 7.7 (A,B and C) respectively.
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Figure 7.6

Figure 7.7A
Figure 7.7B

<table>
<thead>
<tr>
<th>peak R.T.</th>
<th>first max last PK peak corre.</th>
<th>corr. % of</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>min scan scan scan TY height area</td>
<td>% max.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.129</td>
<td>1340 1356 1361 BV</td>
<td>6219031</td>
</tr>
<tr>
<td>2</td>
<td>8.215</td>
<td>1361 1371 1452 VB</td>
<td>12319729</td>
</tr>
</tbody>
</table>

Figure 7.7C
Chapter VII: Oxepane Synthesis

Analysis of the 2D NMR experiments supported the assignment of the isomers 432 and 433 as oxepanone derivatives with signals at 1.34 ppm and 1.27 ppm respectively corresponding to the 2-CH₃ groups as shown in Figure 6. The GCMS analysis showed two peaks with retention times of 8.13 mins and 8.22 mins having m/z of 234 which corresponds to the molecular mass of C₁₄H₁₇O₃ (Figure 7.7). Additional evidence obtained was in agreement and also satisfactory. It is important to note that the use of a dilute solution (low concentration) of SmI₂ reagent and also the addition of HMPA are both necessary for the reaction to be efficient. For example, an attempt to prepare higher concentrations of SmI₂ was unsuccessful due to the limiting solubility of samarium. While the use of a freshly prepared 0.1 M solution of SmI₂ without the addition of HMPA led to a complex mixture of products which proved difficult to identify. Furthermore, attempts to accelerate the reaction by the addition of trimethylsilylchloride (Me₃SiCl) led to the mixture of silylated derivatives 434 and 435 in 18% yield (ratio 7:3) together with the unsilylated derivatives 432 and 433 (21%, ratio 7:3) and starting material 398 was recovered in 21% yield (Scheme 7.26).

![Scheme 7.26](image_url)

The silylated 434, 435 / unsilylated 432, 433 derivatives were obtained in a combined yield of 39% as a 1:1 ratio. Evidence for the formation of the major silylated derivative 434 obtained from analytical and spectroscopic data was satisfactory. As before, data for the minor silylated derivative 435 are not reported due to the observed weak signals in the ¹H NMR spectrum. Evidence obtained for the unsilylated derivatives 432, 433 were in agreement with that...
Chapter VII: Oxepane Synthesis

acquired previously. Unfortunately, the anticipated acceleration was only marginal. The recovered starting material was attributed to the use of less active SmI\(_2\) reagent prepared a few days earlier. Therefore, it is imperative that the reagent be used within 48 hours of preparation to prevent its gradual decomposition at room temperature.

7.5.1 Preparation of suitable bicyclic ketones

With a view to examine the robustness of the SmI\(_2\) mediated reductive cleavage on bicyclic ketone acetals, it was decided to explore the reaction in the synthesis of oxepanone derivatives by varying the substitution pattern around the acetal ring. Towards this objective, the bicyclic ketone 436 bearing a phenyl ring and an ethyl group at the C-4 and C-6 positions respectively was targeted. It was anticipated that the ketone 436 could be prepared in two steps from the vinyldiazoketone 279 (earlier synthesised in section 5.2.3.1.1) by a Rh (II) catalysed diazo decomposition followed by selective reduction of the ethenyl group in compound 283 (Scheme 7.27).

Thus, the vinyldiazoketone 279 was stirred with Rh\(_2\)(hfb)\(_4\) according to the procedure earlier described (section 5.2.4) to give 283. Subsequent reduction of the alkene bond using hydrogen gas with palladium on carbon catalyst led to the isolation of bicyclic ketone 436 in an overall yield of 40%. Evidence for the formation of ketone 436 was obtained from the IR and \(^1\)H NMR spectra. The IR showed the disappearance of the signal at 2082 cm\(^{-1}\) attributed to the diazo functionality and the \(^1\)H NMR spectrum confirmed the reduction of the alkene with the appearance of the signals at 1.58 ppm, 1.00 ppm and 0.48 ppm corresponding to the protons of the ethyl group at the C-6 position. Additional analytical and spectroscopic data obtained was satisfactory. The stereochemistry at the C-6 position was determined by 2D NMR experiments.

\[ \text{N}_2 \quad \text{Rh}_2(\text{hfb})_4 \quad \text{C}_6\text{H}_6, \text{rt} \quad \text{279} \quad \text{283} \quad \text{H}_2, \text{Pd/C} \quad \text{EtOH} \quad \text{436}, 40\% \]

Scheme 7.27
in particular the NOESY experiment which showed correlation between the 6-CH$_2$CH$_3$ proton and the axial 3-$H$ proton, suggesting that these protons are on the same side of the molecule (Figure 7.8).

![Figure 7.8](image)

Similarly, the vinyldiazoketone 280 was successfully converted into the bicyclic ketone 437 in an overall yield of 37% (Scheme 7.28).

![Scheme 7.28](image)

Satisfactory analytical and spectroscopic evidence was obtained for the bicyclic ketone 437. Importantly, the formation of ketone 437 indicates that the palladium catalysed reaction was reproducible.

However, attempts to extend this methodology to vinyldiazoketone acetals 281 and 282 bearing a phenyl ring at the C-2’ position resulted in the formation of the spiro acetals 440 and 441 respectively (Scheme 7.29).
Evidence obtained for the formation of the spiro acetals 440 and 441 from analytical and spectroscopic data were satisfactory. In particular the $^1$H NMR spectrum showed a reduction in number of the protons from five to four corresponding to the aromatic signals. The formation of the spiro acetals 440 and 441 is attributed to the prior formation of the intermediates 438 and 439 from the initial Rh(II) catalysed step suggesting that the reaction of vinyldiazoketones 281 and 282 respectively proceeded via exclusive insertion into the hydrogen of the aromatic ring.

7.5.2 SmI$_2$ mediated cleavage of the bicyclic ketone 437

Having prepared the bicyclic ketones, attention turned towards examining the scope of the reductive cleavage reaction using SmI$_2$ reagent. The ketone 437 was submitted to cleavage following the same procedure earlier described in section 7.5 (Scheme 7.30).
Gratifyingly, the oxepanones 442 and 443 were isolated in good yield (85%) in a ratio of 6:4. However, the isomeric mixture was not separable by column chromatography. Analytical and spectroscopic evidence for the formation of the oxepanone isomers 442 and 443 was obtained on the mixtures and are reported. The marginal decrease in selectivity of 6:4 compared to 7:3 observed from the cleavage of ketone 398 is attributable to the ethyl substituent of bicyclic ketone 437.

A plausible mechanistic rationale for the formation of the oxepanones 442 and 443 is shown below (Scheme 7.31).

A one electron transfer from SmI$_2$ to bicyclic ketone 444 generates the bicyclooctanyl radical 445 which subsequently rearranges to the cycloheptenol radical 446 by a single electron donation from O-8 thereby resulting in the fission of the C1-O8 bond. Another one electron transfer followed by protonation of the organosamarium 447 leads to the observed product 448. Interestingly, it is not obvious why the C1-O8 bond would cleave in preference to the C1-O2 bond although conformational requirements may be a contributing factor. Despite SmI$_2$ having been used for the reduction of carbonyl compounds, there was no strong evidence to indicate further reduction of the observed oxepanones to the oxepanols or the open chain analogues.
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However, the potential use of this methodology to access penta substituted 7-membered-ring oxepane derivatives cannot be overemphasised as these motifs are generally difficult to prepare by conventional methods. Further development of this methodology would certainly complement existing methods.
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7.6 Conclusions

The preparation of 2,3,5,6-tetra and 2,3,4,5,6 pentasubstituted oxepanes by the reductive cleavage reactions of bicyclic acetals mediated by a titanium tetrachloride-triethylsilane combination and samarium (II) iodide was achieved in good yields.

The stereochemistry of the bicyclic alcohol was successful inverted and as anticipated, the inverted alcohol controlled the regioselectivity of the reductive cleavage reaction via chelation to give the desired oxepanes in good selectivity.

Attempts to derivatise the oxepanes, in an effort to obtain solids suitable for X-ray crystallography studies were successful. However, the recrystallisation has proved challenging due to the limited amount of sample available.

Further efforts intended to reduce the sequence of steps that leads to the oxepanes resulted in the preparation and investigation of samarium (II) iodide as an efficient reagent for reductive cleavage. Happily, the SmI$_2$ reagent also delivered a mixture of products in moderate selectivity. These products are believed to be oxepane derivatives.

Having successfully synthesised the oxepanes from the bicyclic acetals via two potent routes, the next chapter will aim to draw a general conclusion of all the studies conducted and attempt to project realistically, possible future work.
Chapter VII: Oxepane Synthesis

7.7 References


Chapter VIII: Conclusions and Future Work

8.1 General conclusions

The research presented in this thesis has involved the development of a methodology for the chemoselective synthesis of bicyclic acetal core structures, which served as useful intermediates for the stereo- and regioselective synthesis of highly functionalised tetrahydrofurans and oxepanes.

The functionalised oxepanes were synthesised via two independent reductive cleavage routes. 2,3-trans-3,5-cis-5,6-trans-oxepanes were obtained in good yield by regioselective reductive cleavage of bicyclic alcohol acetals upon treatment with titanium tetrachloride-triethylsilane combination. High stereoselectivity was observed in this case. However, the titanium tetrachloride-triethylsilane strategy involves a sequence of steps which was considered a substantial hindrance to its application by a synthetic chemist. Therefore, an alternative reductive cleavage protocol was explored. Happily, the regioselective reductive cleavage of bicyclic ketone acetals mediated by samarium (II) iodide gave 2,3,4,5,6-pentasubstituted oxepanes which were isolated in good yields. The stereoselectivity observed were moderate and reproducible.

2,3,4,5-tetrasubstituted tetrahydrofurans were obtained in high yield by regioselective reductive cleavage of bicyclic alcohol acetals initiated by titanium tetrachloride-triethylsilane combination. The stereoselectivities observed were however modest.

The bicyclic alcohol acetals were obtained from the bicyclic ketone acetals prepared chemoselectively by diazodecomposition of the corresponding diazo ketone acetals upon treatment with achiral rhodium (II) heptafluorobutyramide at room temperature. A similar sequence of steps involving the use of chiral rhodium (II) catalysts resulted in a high enantioselective synthesis of the bicyclic alcohol acetals. In all cases involving both catalyst systems the carbenoid intermediate regioselectively inserted into the C-H bond α to the oxygen heteroatom. A variety of bicyclic alcohols were prepared in respectable and reproducible yields from the bicyclic ketones which were not isolated as they proved extremely unstable to both acid and basic media including silica gel and basic alumina.

Initial efforts aimed at forcing the diazo ketones to undergo C-H insertion at elevated temperatures resulted in an unprecedented rearrangement of the acetal skeletal framework providing a novel synthesis of Barceloneic lactones previously isolated from a fungus of the genus Phoma during a screen for protein-farnesyl tranferase (PFT-ase) inhibitor.
Chapter VIII: Conclusions and Future Work

The diazo ketone acetals were prepared to represent the three recognised classes of carbenoids. The diazo ketones representing the acceptor substituted carbenoids were prepared following an established procedure within the group. The diazoacetoacetates, representing the acceptor-acceptor substituted carbenoids were obtained in good yields from diazo ketols following an oxidation sequence involving iodoxybenzoic acid. The diazo ketols were prepared as a racemic mixture in good yield via an aldol type condensation reaction between aldehyde acetals and ethyldiazoacetate in the presence of 1,8-diazabicyclo(5.4.0)-undec-7-ene. The vinyldiazo ketones, representing the donor-acceptor substituted carbenoids were obtained from mixture of ketones in good yield following a successful diazo transfer reaction involving p-acetamidobenzenesulfonyl azide. The mixtures of ketones were obtained from the pyridinium dichromate oxidation of allyl alcohol efficiently prepared from a reaction between allylmagnesium bromide and aldehyde acetals.

The aldehyde acetals required for the transformations were obtained in very good yields from the alcohol acetals by employing the Swern oxidation protocol. The alcohol acetals were prepared in excellent yields following the diisobutylaluminium hydride reduction of the ester acetals prepared by ketalisation of 2-substitutedpropan-1,3-diols with 2-substitutedmethylpyruvate. Anomeric control provided preferential formation of compounds with the ester group in the axial position.

8.2 Future work

This methodology holds great promise for the future due to the flexibility of the procedure. It could potentially be applied to the synthesis of a range of highly substituted 5-membered-ring heterocycles (Scheme 8.1).

\[
\begin{align*}
X &= Y: \text{O, N, S} \\
R_1, R_2, R_3, R_4 &= \text{alkyl, aryl}
\end{align*}
\]

Scheme 8.1
Chapter VIII: Conclusions and Future Work

By preparing O,O-, N,N- or S,S-diazo ketones or mixed acetals and varying the R groups, synthesis of functionalised 5-membered heterocycles could be achieved. This could be elaborated into natural products with biological properties. Equally, other bulky nucleophiles could be used to trap the intermediate oxocarbenium ion as this might lead to the stereospecific formation of heterocycles.

It is also worth noting that the samarium iodide mediated reductive cleavage could be similarly exploited for the synthesis of 7-membered heterocycles (Scheme 8.2).

\[
\begin{align*}
\text{Y} & \quad \text{X} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_4
\end{align*}
\]

2,3,4,5,6-pentasubstituted heterocycle

Scheme 8.2

Importantly, it would be interesting to study the effect other additives would have on the samarium iodide reaction.

In terms of the asymmetric catalytic studies, further efforts should be made to expand the scope of the catalyst screened or preferably a new chiral catalyst could be designed and synthesised following the standard procedure.
9.1 General procedure

All solvents were obtained dried from Innovative Technology Solvent Purification System (SPS) as per standard procedures within the department and stored under nitrogen before use. Petroleum ether (Petrol) was distilled and fractions collected corresponding to a boiling point of 40-60 °C. Triethylamine was distilled over 4Å molecular sieves and dried over potassium hydroxide pellets. All sensitive reactions were performed in oven-dried glassware under an inert atmosphere.

Melting point

Melting points were determined using a Thermo Scientific 9100.

Optical rotation

Optical rotations were acquired on a Jasco P-1020 polarimeter.

Microwave

Microwave reactions were performed in septum-containing, crimp-capped, sealed vials in an Emrys™ Optimizer (Personal Chemistry). The wattage was automatically adjusted to maintain the desired temperature for the desired period of time.

Chromatography

All reactions were monitored using thin layer chromatography (TLC) using normal phase silica plates which were revealed by UV (254 nm) for components with an active chromophore or visualised by sprays or stains (e.g.: phosphomolybdic acid in ethanol) and revealed by heating with a heat gun. Gas Chromatography (GC) was carried out on a Hewlett-Packard 5890 series II gas chromatograph fitted with a 25 cm column and connected to a flame ionisation detector.
Purification of the products was performed by flash column chromatography with normal phase silica gel (Kieselger 40-60 µm silica) or alumina using an appropriate choice of eluent (or solvent system).

**IR spectroscopy**

Infrared spectra were recorded either as a solution in chloroform via transmission IR cells for liquids or using a diamond ATR (attenuated total reflection) accessory (Golden Gate) for solids on a Perkin Elmer Paragon 1000 FT-IR Spectrometer. Absorption maxima are reported in wavenumbers (cm\(^{-1}\)).

**NMR spectroscopy**

\(^1\)H and \(^{13}\)C NMR spectra were acquired in CDCl\(_3\), unless otherwise stated, on a Varian Mercury-200 (\(^1\)H at 199.975 MHz, \(^{13}\)C at 50.289 MHz, \(^{19}\)F at 282.2 MHz), Varian Mercury-400 (\(^1\)H at 399.968 MHz, \(^{13}\)C at 75.412 MHz, \(^{19}\)F at 376.3 MHz), Bruker Avance-400 (\(^1\)H at 399.968 MHz, \(^{13}\)C at 75.412 MHz), Varian Inova-500 (\(^1\)H at 499.771 MHz, \(^{13}\)C at 125.681 MHz) or Varian VNMRS-700 (\(^1\)H at 699.735 MHz, \(^{13}\)C at 175.948 MHz) and reported as follows: chemical shift \(\delta\) (ppm) (number of protons, multiplicity, coupling constant \(J\) (Hz), assignment). The residual protic solvent was used as the internal reference: CHCl\(_3\) \(\delta_H = 7.26\) ppm; \(\delta_C = 77.0\) ppm: CH\(_3\)OH \(\delta_H = 3.41\) ppm, 1.09 ppm; \(\delta_C = 49.9\) ppm. Assignment and determination of stereochemistry were realised using DEPT, COSY, HSQC, HMBC and NOESY experiments.

**Mass spectrometry**

Low Resolution Mass Spectra were obtained on a Waters Micromass LCT Mass Spectrometer. Gas-Chromatography Mass Spectra (GC-MS : EI, CI) were taken using a Thermo-Finnigan Trace with a 25 cm column connected to a VG Mass Lab Trio 1000. Electrospray Mass Spectra (ES) were obtained on a Micromass LCT Mass Spectrometer. High Resolution Mass Spectra (HRMS) were performed on a Thermo-Finnigan LTQFT Mass Spectrometer or Xevo QToF Mass Spectrometer (Waters UK, Ltd) by Durham University Mass Spectrometry service.
Chapter IX: Experimental Procedure

9.2 Experimental details

2-Phenylpropane-1,3-diol (141):
A cooled suspension of lithium aluminium hydride (8.03 g, 211 mmol) in Et₂O (240 ml) at 0 °C was treated dropwise with a solution of phenyl diethyl malonate (9.10 ml, 42.3 mmol) in Et₂O (50.0 ml). After stirring for 3 h at room temperature, the reaction mixture was cooled in an external ice bath and treated successively by the dropwise addition of 8.00 ml of H₂O, 8.00 ml of aqueous NaOH 15% and 24.0 ml of H₂O. The mixture was then filtered through Celite®, washed with EtOAc and the filtrate concentrated in vacuo. The crude residue was then purified by flash column chromatography on silica gel (cyclohexane/EtOAc : 1:1) to give alcohol 141 as a white solid (3.77 g, 60%).

mp.: 53-54 °C (lit.¹ 53 °C). ν max (ATR) : 3440-2990 (OH br), 1260, 1037, 744, 699 cm⁻¹. δH (500 MHz; CDCl₃) : 7.54-7.51 (2H, m, Ar-H), 7.47-7.44 (1H, m, Ar-H), 7.42-7.40 (2H, m, Ar-H), 3.98 (2H, dd, J 7.6, 2.7, 1-Hα, 3-Hα), 3.91 (2H, dd, J 7.6, 5.4, 1-Hβ, 3-Hβ), 3.30-3.25 (1H, m, 2-H), 2.64 (2H, bs, 2 × OH). δC (125 MHz; CDCl₃) : 128.8 (Ar-C), 121.2 (Ar-C), 66.0 (C-1, C-3), 49.7 (C-2). m/z (EI) : 121 (M⁺-CH₂OH, 50%), 103 (M⁺-CH₂OH-OH, 100), 91 (M⁺-2 × CH₂OH, 50), 77 (C₆H₅⁺, 80).

2-Benzylpropane-1,3-diol (143):
A cooled suspension of lithium aluminium hydride (10.0 g, 264 mmol) in Et₂O (250 ml) at 0 °C was treated dropwise with a solution of benzyl diethyl malonate (15.5 ml, 66.0 mmol) in Et₂O (80.0 ml). After stirring for 3 h at room temperature, the reaction mixture was cooled in an external ice bath and treated successively by the dropwise addition of 10.0 ml of H₂O, 10.0 ml of aqueous NaOH 15% and 30.0 ml of H₂O. The mixture was then filtered through Celite®, washed copiously with EtOAc and the filtrate concentrated in vacuo. The crude residue was then purified by flash column chromatography on silica gel (cyclohexane/EtOAc : 1:1) to give alcohol 143 as a pale brown solid (8.70 g, 79%).
mp.: 65-68 °C (lit. 2 67 °C). \( \nu_{\text{max}} \) (ATR) : 3440-2980 (OH br), 1260, 1037, 744, 699 cm\(^{-1}\). \( \delta_H \) (400 MHz; CDCl\(_3\)) : 7.35-7.25 (2H, m, Ar-H), 7.25-7.20 (3H, m, Ar-H), 3.87 (2H, dd, \( J \) 10.5, 3.5, 1-H\(_a\), 3-H\(_b\)), 2.70 (2H, d, \( J \) 7.8, 2-CH\(_2\)Ph), 2.31 (2H, bs, 2 × OH), 2.15 (1H, m, 2-H). \( \delta_C \) (100.5 MHz; CDCl\(_3\)) : 140.0 (C-1'), 129.1 (Ar-C), 128.6 (Ar-C), 126.3 (Ar-C), 65.7 (C-1, C-3), 44.0 (C-2), 34.4 (2-CH\(_2\)Ph). m/z (ES\(^+\)) : 189.1 ([M+Na]\(^+\), 100%). \(^1\)H NMR spectra data for 2 was consistent with that previously reported\(^2\).

**Typical procedure for ester acetal synthesis from methyl pyruvate (A1):**

Methyl pyruvate (2 eq.) and boron trifluoride diethyletherate, BF\(_3\).OEt\(_2\) (2 eq.) were added dropwise to a solution of diol (1 eq.) in dry CH\(_3\)CN at room temperature and the reaction mixture was stirred at room temperature overnight. A saturated solution of sodium bicarbonate (NaHCO\(_3\)) was then added and the resulting mixture was left to stir for an additional 30 min. The mixture was concentrated *in vacuo* to 1/3 of its initial volume and extracted with DCM. The organic extract was then dried over MgSO\(_4\), filtered and concentrated *in vacuo*. The crude NMR shows the presence of two isomers. The residue was then purified by flash column chromatography on silica gel.

**Methyl-2-methyl-5-phenyl-1,3-dioxane-2-carboxylate (145, 146):**

Similar to procedure A1, methyl pyruvate (6.00 ml, 66.0 mmol) and boron trifluoride diethyletherate (BF\(_3\).OEt\(_2\), 8.10 ml, 66.0 mmol) were combined with 2-phenylpropane-1,3-diol 141 (5.00 g, 33.0 mmol) to afford a 8:2 mixture of isomeric ester acetals. Separation by flash column chromatography (cyclohexane/EtOAc : 9/1) afforded the major title ester acetal 145 (Ph in equatorial position) as a white crystalline solid (5.16 g, 83%) and the minor ester acetal 146 (Ph in axial position) as a white crystalline solid (1.00 g, 6%) after recrystallisation from cyclohexane.
Chapter IX: Experimental Procedure

Major isomer 145:

![Chemical structure](image)

mp.: 65-67 °C. ν\text{max} (ATR): 2923-2845, 1742 (C=O), 1103, 1078, 724, 659 cm\(^{-1}\). δ\text{H} (400 MHz; CDCl\(_3\)): 7.35-7.25 (3H, m, Ar-H), 7.15-7.10 (2H, m, Ar-H), 4.10 (2H, dd, J 11.7, 4.8, 4-H\text{eq}, 6-H\text{eq}), 3.95 (3H, s, OCH\(_3\)), 3.95 (2H, t, J 11.7, 4-H\text{ax}, 6-H\text{ax}), 3.30-3.20 (1H, m, 5-H), 1.60 (3H, s, 2-CH\(_3\)). δ\text{C} (100.5 MHz; CDCl\(_3\)) : 171.0 (C=O), 137.1 (C-1'), 128.7 (Ar-C), 127.5 (Ar-C), 98.1 (C-2), 68.1 (C-4, C-6), 52.6 (CH\(_3\)O), 39.9 (C-5), 26.0 (2-CH\(_3\)). m/z (ES\(^+\)) : 259 ([M+Na]+, 100%). Anal. [Found: C, 66.1; H, 6.9. C\(_{13}\)H\(_{16}\)O\(_4\) requires C, 66.1; H 6.8%].

Minor isomer 146:

![Chemical structure](image)

mp.: 55-57 °C. δ\text{H} (400 MHz; CDCl\(_3\)): 7.45-7.40 (2H, m, Ar-H), 7.35-7.20 (3H, m, Ar-H), 4.25 (2H, dd, J 12.1, 3.3, 4-H\text{eq}, 6-H\text{eq}), 4.10 (2H, dd, J 12.1, 2.0, 4-H\text{ax}, 6-H\text{ax}), 3.80 (3H, s, OCH\(_3\)), 2.80-2.70 (1H, m, 5-H), 1.60 (3H, s, 2-CH\(_3\)). δ\text{C} (100.5 MHz; CDCl\(_3\)): 170.3 (C=O), 141.1 (C-1'), 127.9 (Ar-C), 127.5 (Ar-C), 126.2 (Ar-C), 97.6 (C-2), 66.3 (C-4, C-6), 52.1 (CH\(_3\)O), 37.9 (C-5), 24.1 (2-CH\(_3\)). m/z (ES\(^+\)) : 291 ([M+Na+MeOH]+, 22%), 259 ([M+Na]+, 100%). Anal. [Found: C, 66.0; H, 6.9. C\(_{13}\)H\(_{16}\)O\(_4\) requires C, 66.1; H 6.8%].

Methyl-2-methyl-5-benzyl-1,3-dioxane-2-carboxylate (147, 148):

Similar to procedure A1, methyl pyruvate (6.80 ml, 75.0 mmol) and boron trifluoride diethyletherate (BF\(_3\).OEt\(_2\), 9.20 ml, 75.0 mmol) were combined with 2-benzylpropane-1,3-diol 143 (6.20 g, 37.0 mmol) to afford a 7:3 mixture of isomeric ester acetals. Flash column
chromatography (cyclohexane/EtOAc : 95/5 then 9/1) afforded the title ester acetals 147 and 148 as an inseparable mixture (7:3 ratio, 7.90 g, 85%).

However, a very small pure sample of each isomer was obtained and used for analysis.

**Major isomer 147**:

![Structure of Major Isomer 147](image1)

$\nu_{\text{max}}$ (ATR) : 3030-2853, 1741 (C=O), 1261, 1216, 1187, 1139, 1113, 1033, 760, 735, 699, 675 cm$^{-1}$. $\delta_H$ (400 MHz; CDCl$_3$) : 7.35-7.20 (3H, Ar-H), 7.10 (2H, d, $J$ 7.4, Ar-H), 3.83 (3H, s, OCH$_3$), 3.80 (2H, dd, $J$ 11.5, 4.4, 4-H$_{\text{eq}}$, 6-H$_{\text{eq}}$), 3.50 (2H, t, $J$ 11.5, 4-H$_{\text{ax}}$, 6-H$_{\text{ax}}$), 2.40-2.30 (3H, m, 5-H, 5-CH$_2$Ph), 1.50 (3H, s, 2-CH$_3$). $\delta_C$ (100.5 MHz; CDCl$_3$) : 171.2 (C=O), 138.0 (C-1'), 128.8 (Ar-C), 128.7 (Ar-C), 126.6 (Ar-C), 98.4 (C-2), 68.2 (C-4, C-6), 52.7 (CH$_3$O), 35.1 (C-5), 34.8 (5-CH$_2$Ph), 26.1 (2-CH$_3$). m/z (EI) : 251 (M$^+$+H+, 2%), 235 (M$^+$-Me, 6), 191 (M$^+$-COOMe, 90), 131 (100), 117 (46), 91 (PhCH$_2^+$, 94), 65 (40). m/z (ES$^+$) : 305 ([M+Na+MeOH]$^+$, 11%), 273 ([M+Na]$^+$, 100). HRMS (ES$^+$) found: 273.1077 (C$_{14}$H$_{18}$O$_4$Na requires [M+Na]$^+$ 273.1097).

**Minor isomer 148**:

![Structure of Minor Isomer 148](image2)

$\delta_H$ (400 MHz; CDCl$_3$) : 7.35-7.20 (5H, m, Ar-H), 3.95-3.90 (2H, m, 4-H$_{\text{eq}}$, 6-H$_{\text{eq}}$), 3.81 (3H, s, OCH$_3$), 3.78 (2H, d, $J$ 11.0, 4-H$_{\text{ax}}$, 6-H$_{\text{ax}}$), 3.00 (2H, d, $J$ 8.0, 5-CH$_2$Ph), 1.70-1.60 (1H, m, 5-H), 1.57 (3H, s, 2-CH$_3$). $\delta_C$ (100.5 MHz; CDCl$_3$) : 171.3 (CO), 140.2 (C-1'), 129.4 (Ar-C), 129.4 (Ar-C), 126.3 (Ar-C), 98.7 (C-2), 66.0 (C-4, C-6), 52.7 (CH$_3$O), 35.4 (C-5), 35.3 (5-CH$_2$Ph), 26.0 (2-CH$_3$). m/z (EI) : 235 (M$^+$-Me, 6%), 191 (M$^+$-COOMe, 88), 131 (100), 117
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(30), 91 (PhCH$_2^+$, 90), 65 (28). HRMS (ES$^+$) found: 273.1095 (C$_{14}$H$_{18}$O$_4$Na requires [M+Na]$^+$ 273.1097).

**Methyl-2,5-dimethyl-5-nitro-1,3-dioxane-2-carboxylate (149, 150):**

Similar to procedure A1, methyl pyruvate (6.70 ml, 74.1 mmol) and boron trifluoride diethyletherate (BF$_3$.OEt$_2$, 9.40 ml, 74.1 mmol) were combined with 2-methyl-2-nitropropane-1,3-diol (5.00 g, 37.1 mmol) to afford an 8.6:1 mixture of C-5 diastereoisomeric ester acetals. Separation by flash column chromatography (cyclohexane/EtOAc : 9/1 then 7/3) afforded the major *trans* ester acetal 149 (nitro in axial position) as a white solid (7.05 g, 87%) and the minor *cis* ester acetal 150 (nitro in equatorial position) as a white solid (0.83 g, 10%).

**Major isomer 149:**

\[
\begin{align*}
\text{MeO} & \quad \text{Me} \\
\text{H$_3$C} & \quad \text{O} \\
\text{O} & \quad \text{NO$_2$}
\end{align*}
\]

mp.: 80-81 °C. $\nu_{\text{max}}$ (ATR) : 2882, 1738 (C=O), 1550+1349 (NO$_2$), 1270, 1213, 1184, 1122, 1077, 1048, 880, 803, 665, 572 cm$^{-1}$. $\delta_{\text{H}}$ (700 MHz; CDCl$_3$) : 4.70 (2H, d, $J_{\text{13.3}}$, 4-$H_{\text{eq}}$, 6-$H_{\text{eq}}$), 3.85 (2H, d, $J_{\text{13.3}}$, 4-$H_{\text{ax}}$, 6-$H_{\text{ax}}$), 3.84 (3H, s, OCH$_3$), 1.50 (3H, s, 2-C$_3$H$_3$), 1.35 (3H, s, 5-C$_3$H$_3$). $\delta_{\text{C}}$ (175 MHz; CDCl$_3$) : 169.7 (C=O), 98.3 (C-2), 82.2 (C-5), 67.4 (C-4, C-6), 52.8 (CH$_3$O), 25.2 (2-C$_3$H$_3$), 19.5 (5-C$_3$H$_3$). $m/z$ (ES$^+$) : 242 ([M+Na]$^+$, 100%), 220 ([M+H]$^+$, 50).

Anal. [Found: C, 43.9; H, 6.0; N, 6.1. C$_8$H$_{13}$O$_6$N requires C, 43.8; H, 6.0; N, 6.4%].

**Minor isomer 150:**

\[
\begin{align*}
\text{MeO} & \quad \text{O$_2$N} \\
\text{O} & \quad \text{CH$_3$}
\end{align*}
\]

mp.: 80-81 °C. $\nu_{\text{max}}$ (ATR) : 2955, 1738 (C=O), 1534+1353 (NO$_2$), 1281, 1227, 1189, 1127, 1081, 1051, 967, 889, 807, 750 cm$^{-1}$. $\delta_{\text{H}}$ (700 MHz; CDCl$_3$) : 4.15 (2H, d, $J_{\text{11.7}}$, 4-$H_{\text{eq}}$, 6-$H_{\text{eq}}$), 4.05 (2H, d, $J_{\text{11.7}}$, 4-$H_{\text{ax}}$, 6-$H_{\text{ax}}$), 3.84 (3H, s, OCH$_3$), 1.84 (3H, s, 5-C$_3$H$_3$), 1.57 (3H, s, 2-
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\[ \text{CH}_3 \]. \( \delta_C \) (175 MHz; CDCl\_3) : 169.3 (C=O), 98.5 (C-2), 79.1 (C-5), 67.6 (C-4, C-6), 53.0 (CH\_3O), 24.5 (2-CH\_3), 21.5 (5-CH\_3). \( m/z \) (ES\(^+\)) : 283 ([M+Na+CH\_2CN]\(^+\), 90%), 242 ([M+Na]\(^+\), 30). Anal. [Found: C, 43.9; H, 6.0; N, 6.3]. C\(_8\)H\(_{13}\)O\(_6\)N requires C, 43.8; H, 6.0; N, 6.4%.

Typical procedure for ester acetal synthesis from methyl benzoylformate (A2):

Methyl benzoylformate (2 eq.) and BF\(_3\).OEt\(_2\) (2 eq.) were added dropwise to a solution of diol (1 eq.) in dry CH\_3CN at room temperature and the reaction mixture was stirred at room temperature overnight. A saturated solution of sodium bicarbonate (NaHCO\(_3\)) was then added and the resulting mixture was left to stir for an additional 30 min. Thereafter the mixture was concentrated *in vacuo* to 1/3 of its initial volume and extracted with DCM. The organic extract was then dried over MgSO\(_4\), filtered and concentrated *in vacuo*. The crude reaction mixture which contained two isomers as obtained from the \(^1\)H NMR spectrum was then purified by flash column chromatography.

Methyl-2,5-diphenyl-1,3-dioxane-2-carboxylate (151, 152):

Similar to procedure A2, methyl benzoylformate (3.10 ml, 22.1 mmol) and boron trifluoride diethyletherate (BF\(_3\).OEt\(_2\), 2.80 ml, 22.1 mmol) were combined with 2-phenylpropane-1,3-diol 141 (1.68 g, 11.1 mmol) to afford an 8:2 mixture of isomeric ester acetals. Separation by flash column chromatography (petroleum ether/EtOAc : 9/1) afforded the major title ester acetal 151 (Ph in equatorial position), which upon recrystallization from petroleum ether afforded a white crystalline solid (2.89 g, 88%) and the other fraction when recrystallized gave the minor ester acetal 152 (Ph in axial position) as a white crystalline solid (0.33 g, 10%).

Major isomer 151:

![Structure of Methyl-2,5-diphenyl-1,3-dioxane-2-carboxylate 151](image)

mp.: 115-116 °C. \( \nu_{\text{max}} \) (ATR) : 2995-2865, 1737 (C=O), 1452, 1237, 1092, 810, 724, 610 cm\(^{-1}\). \( \delta_H \) (500 MHz; CDCl\_3) : 7.71-7.69 (2H, m, Ar-\( H \)), 7.42-7.37 (3H, m, Ar-\( H \)), 7.36-7.33 (2H, m, Ar-\( H \)), 7.30-7.27 (1H, m, Ar-\( H \)), 7.19 (2H, d, \( J \) 7.6, Ar-\( H \)), 4.31 (2H, dd, \( J \) 11.6, 4.8, 4-\( H \)\(_{\text{eq}}\), 6-
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$H_{eq}$, 4.10 (2H, t, $J$ 11.6, $4H_{ax}$, 6-$H_{ax}$), 3.82 (3H, s, OCH$_3$), 3.37-3.31 (1H, m, 5-$H$). $\delta$C (125 MHz; CDCl$_3$) : 169.9 (C=O), 138.1 (Ar-C), 137.3 (Ar-C) 129.2 (Ar-C), 128.8 (Ar-C), 128.3 (Ar-C), 127.6 (Ar-C), 127.6 (Ar-C), 125.5 (Ar-C), 98.6 (C-2), 68.4 (C-4, C-6), 52.9 (CH$_3$O), 40.1 (C-5). m/z (ES$^+$) : 362 ([M+Na+CH$_3$CN]$^+$, 80%), 321 ([M+Na]$^+$, 100). Anal. [Found: C, 72.6; H, 6.1. C$_{18}$H$_{18}$O$_4$ requires C, 72.5; H, 6.1%].

Minor isomer 152:

\[
\text{MeO} \quad \begin{array}{c}
\text{O} \\
\text{H} \quad \begin{array}{c}
\text{O} \\
\text{H} \quad \begin{array}{c}
\text{MeO} \quad \begin{array}{c}
\text{O} \\
\text{Bn}
\end{array}
\end{array}
\end{array}
\end{array}
\]

mp.: 106-107 °C. $\nu_{max}$ (ATR) : 2864, 1737 (C=O), 1495, 1227, 1054, 942, 810, 745, 696, 664 cm$^{-1}$. $\delta$H (500 MHz; CDCl$_3$) : 7.69 (2H, d, $J$ 6.9, Ar-$H$), 7.49-7.42 (3H, m, Ar-$H$), 7.28-7.21 (3H, m, Ar-$H$), 7.11 (2H, d, $J$ 7.0, Ar-$H$), 4.25 (2H, dd, $J$ 11.8, 4.5, 4-$H_{ax}$, 6-$H_{ax}$), 4.05 (2H, t, $J$ 11.8, 4-$H_{eq}$, 6-$H_{eq}$), 3.78 (3H, s, OCH$_3$), 3.27-3.22 (1H, m, 5-$H$). $\delta$C (125 MHz; CDCl$_3$) : 168.8 (C=O), 138.2 (Ar-$C$), 135.2 (Ar-$C$) 129.3 (Ar-$C$), 128.9 (Ar-$C$), 128.6 (Ar-$C$), 127.6 (Ar-$C$), 127.4 (Ar-$C$), 127.3 (Ar-$C$), 98.4 (C-2), 66.6 (C-4, C-6), 53.2 (CH$_3$O), 40.1 (C-5). m/z (ES$^+$) : 619 ([2M+Na]$^+$, 100%), 362 ([M+Na+CH$_3$CN]$^+$, 10). Anal. [Found: C, 72.6; H, 6.1. C$_{18}$H$_{18}$O$_4$ requires C, 72.5; H, 6.1%].

Methyl-5-benzyl-2-phenyl-1,3-dioxane-2-carboxylate (153, 154):

Similar to procedure A2, methyl benzoyleformate (3.70 ml, 26.3 mmol) and boron trifluoride diethyl etherate (BF$_3$.OEt$_2$, 3.30 ml, 26.3 mmol) were combined with 2-benzylpropane-1,3-diol 143 (2.18 g, 13.1 mmol) to afford a 1.5:1 mixture of isomeric ester acetals. Separation by flash column chromatography (petroleum ether/EtOAc : 95/5 then 9/1) afforded the major title ester acetal 153 (Bn in equatorial position), which upon recrystallization from petroleum ether afforded a white crystalline solid (2.28 g, 56%) and the other fraction when recrystallized gave the minor ester acetal 154 (Bn in axial position) as a white crystalline solid (1.50 g, 37%).
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Major isomer 153:

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{Ar} & \quad \text{Ar}
\end{align*}
\]

mp.: 105-106 °C. \(\nu_{\text{max}}\) (ATR) : 2879, 1734 (C=O), 1496, 1452, 1243, 1188, 1135, 1020, 980, 808, 725, 678 cm\(^{-1}\). \(\delta_H\) (500 MHz; CDCl\(_3\)) : 7.60 (2H, d, J 7.9, Ar-H), 7.36-7.32 (3H, m, Ar-H), 7.29-7.24 (2H, m, Ar-H), 7.20 (1H, t, J 7.2, Ar-H), 7.13 (2H, d, J 7.2, Ar-H), 4.07 (2H, dd, J 11.5, 4.4, 4-H\(_{\text{ax}}\), 6-H\(_{\text{ax}}\)), 3.75 (3H, s, OCH\(_3\)), 3.69 (2H, t, J 11.5, 4-H\(_{\text{ax}}\), 6-H\(_{\text{ax}}\)), 2.50 (2H, d, J 7.7, 5-CH\(_2\)Ph), 2.25-2.34 (1H, m, 5-H). \(\delta_C\) (125 MHz; CDCl\(_3\)) : 169.8 (C=O), 138.1 (Ar-C), 137.8 (Ar-C) 129.1 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 128.3 (Ar-C), 126.4 (Ar-C), 125.7 (Ar-C), 98.8 (C-2), 67.9 (C-4, C-6), 52.9 (CH\(_3\)O), 35.2 (C-5), 34.8 (5-CH\(_2\)Ph). m/z (ES\(^+\)) : 313 ([M+H]\(^+\), 100%). Anal. [Found: C, 73.0; H, 6.5. C\(_{19}\)H\(_20\)O\(_4\) requires C, 73.1; H, 6.5%].

Minor isomer 154:

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{Ar} & \quad \text{Ar}
\end{align*}
\]

\(\nu_{\text{max}}\) (ATR) : 2865, 1741 (C=O), 1493, 1451, 1247, 1182, 1128, 1021, 916, 807, 747, 697 cm\(^{-1}\). \(\delta_H\) (700 MHz; CDCl\(_3\)) : 7.64 (2H, d, J 7.8, Ar-H), 7.42 (2H, t, J 7.8, Ar-H), 7.39 (1H, t, J 7.8, Ar-H), 7.28 (2H, t, J 7.5, Ar-H), 7.20 (1H, t, J 7.5, Ar-H), 7.14 (2H, d, J 7.5, Ar-H), 4.05 (2H, dd, J 11.9, 5.8, 4-H\(_{\text{ax}}\), 6-H\(_{\text{ax}}\)), 3.78 (2H, dd, J 11.9, 5.8, 4-H\(_{\text{ax}}\), 6-H\(_{\text{ax}}\)), 3.73 (3H, s, OCH\(_3\)), 2.67 (2H, d, J 7.8, 5-CH\(_2\)Ph), 2.08 (1H, m, 5-H). \(\delta_C\) (175 MHz; CDCl\(_3\)) : 169.4 (C=O), 139.0 (Ar-C), 136.8 (Ar-C) 129.2 (Ar-C), 128.9 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 126.6 (Ar-C), 126.3 (Ar-C), 98.9 (C-2), 66.4 (C-4, C-6), 52.9 (CH\(_3\)O), 35.5 (C-5), 35.0 (5-CH\(_2\)Ph). m/z (ES\(^+\)) : 647 ([2M+Na]\(^+\), 10%), 376 ([M+Na+CH\(_3\)CN]\(^+\), 60), 313 ([M+H]\(^+\), 90), 105 (100). HRMS (ES\(^+\)) found: 313.1434 (C\(_{19}\)H\(_23\)O\(_4\) requires [M+H]\(^+\) 313.1434).
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Typical procedure for nitrination of ester acetal (A3):

Trifluoroacetic anhydride (4 eq) was added dropwise to a solution of ester acetal (1 eq) and ammonium nitrate (1 eq) in anhydrous chloroform. The mixture was stirred for 2 h at 0 °C then allowed to warm to room temperature and stirred overnight. Once the reaction was complete, it was poured into ice-water mixture and extracted with chloroform twice. The combined organic extracts were dried over MgSO₄ and solvent was evaporated in vacuo. The residue was then purified by flash column chromatography on silica gel.

Methyl-2-methyl-5-(4’-nitrophenyl)-1,3-dioxane-2-carboxylate (159, 161) and Methyl-2-methyl-5-(2’-nitrophenyl)-1,3-dioxane-2-carboxylate (160, 162):

Similar to procedure A3, trifluoroacetic anhydride (11.9 ml, 84.4 mmol) was added to a solution of ester acetal 145 (4.98 g, 21.1 mmol) and ammonium nitrate (1.86 g, 23.2 mmol) in CHCl₃ (60.0 ml). The NMR of the crude reaction mixture showed the presence of two isomeric products 159 and 160 in ratio 12:1. Separation by flash column chromatography (petroleum ether/EtOAc : 9/1, then 8/2) afforded the title nitro ester acetals 159 (nitro in para position) as a yellow solid (5.30 g, 89%) and 160 (nitro in ortho position) as a yellow solid (0.39 g, 7%).

Major isomer 159:

![Methyl-2-methyl-5-(4’-nitrophenyl)-1,3-dioxane-2-carboxylate](image)

mp.: 119-121 °C. νmax (ATR) : 2930, 2928, 2853, 1743 (C=O), 1514+1350 (NO₂), 1142, 1053, 906, 726 cm⁻¹. δH (400 MHz; CDCl₃) : 8.10 (2H, d, J 8.5, 3’-H), 7.30 (2H, d, J 8.5, 2’-H), 4.10 (2H, dd, J 11.2, 4.6, 4-Hax, 6-Hax), 3.90 (2H, t, J 11.2, 4-Hax, 6-Hax), 3.85 (3H, s, OCH₃), 3.40 (1H, dd, J 11.2, 4.6, 5-H), 1.60 (3H, s, 2-CH₃). δC (100.5 MHz; CDCl₃) : 170.5 (C=O), 148.0 (C-1’), 145.0 (C-4’), 128.7 (C-2’), 124.2 (C-3’), 98.1 (C-2), 67.9 (C-4, C-6), 53.2 (CH₃O), 40.1 (C-5), 26.0 (2-CH₃). m/z (ES⁺) : 304 ([M+Na]⁺, 100%). Anal. [Found: C, 55.5; H, 5.4; N, 4.9. C₁₃H₁₅NO₆ requires C, 55.5; H, 5.4; N, 5.0%].
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Isomer 160:

\[
\text{mp.: } 161-162 \, ^\circ \text{C. } \nu_{\text{max}} \text{(ATR)} : 2872, 2377, 1978, 1734 (\text{C}=\text{O}), 1524+1350 (\text{NO}_2), 1269, 1216, 1131, 1043, 975, 886, 795, 726 \text{ cm}^{-1}. \delta_H \text{(700 MHz; CDCl}_3 \text{): 7.79 (1H, d, } J = 8.0, 3'-H), 7.54 (1H, t, } J = 8.0, 5'-H), 7.40 (1H, d, } J = 8.0, 4'-H), 7.29 (1H, d, } J = 8.0, 6'-H), 4.14 (2H, dd, } J = 11.7, 4.6, 4'-H_{\text{eq}}, 6'-H_{\text{eq}}), 3.96 (2H, t, } J = 11.7, 4'-H_{\text{ax}}, 6'-H_{\text{ax}}), 3.89 (3H, s, OCH_3), 3.75-3.70 (1H, m, 5-H), 1.59 (3H, s, 2-CH_3). \delta_C \text{(175 MHz; CDCl}_3 \text{): 170.8 (C=O), 150.9 (C-2'), 132.6 (C-5'), 131.4 (C-1'), 128.4 (C-6'), 128.2 (C-4'), 124.7 (C-3'), 98.2 (C-2), 67.2 (C-4, C-6), 52.7 (CH_3O), 35.0 (C-5), 25.6 (2-CH_3). m/z \text{(ES}^+) : 345 ([M+Na+CH_3CN]^+, 20%), 287 (30), 246 (70), 180 (100). \text{Anal. [Found: C, 55.6; H, 5.5; N, 4.9. C}_{13}H_{15}NO_6 \text{ requires C, 55.5; H, 5.4; N, 5.0%].} \]

Minor isomer 161:

Similar to procedure A3, trifluoroacetic anhydride (1.70 ml, 12.0 mmol) was added to a solution of ester acetal 146 (0.71 g, 3.01 mmol) and ammonium nitrate (0.26 g, 3.31 mmol) in CHCl_3 (10.0 ml). The NMR of the crude reaction mixture showed the presence of two isomeric products 161 and 162 in ratio 10:1. Separation by flash column chromatography (cyclohexane/EtOAc : 9/1, then 7/3) afforded the title nitro ester acetals 161 (nitro in para position) as a yellow solid (0.72 g, 86%) and 162 (nitro in ortho position) as a yellow solid (0.07 g, 8%).
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mp.: 78-80 °C. \( \nu_{\text{max}} \) (ATR) : 2940, 2932, 2860, 1742 (C=O), 1516+1346 (NO\(_2\)), 1127, 1031, 909, 727 cm\(^{-1}\). \( \delta_H \) (400 MHz; CDCl\(_3\)) : 8.12 (2H, d, J 8.8, 3′-H), 7.65 (2H, d, J 8.8, 2′-H), 4.28 (2H, dd, J 12.4, 3.5, 4′-H\(_{ax}\), 6′-H\(_{ax}\)), 4.07 (2H, m, 4′-H\(_{eq}\), 6′-H\(_{eq}\)), 3.85 (3H, s, OCH\(_3\)), 2.78 (1H, m, 5-H), 1.58 (3H, s, 2-CH\(_3\)). \( \delta_C \) (100.5 MHz; CDCl\(_3\)) : 170.6 (C=O), 150.1 (C-1′), 146.9 (C-4′), 129.8 (C-2′), 124.0 (C-3′), 98.3 (C-2), 66.5 (C-4, C-6), 53.1 (CH\(_3\)O), 38.2 (C-5), 26.0 (2-CH\(_3\)). m/z (ES\(^+\)) : 304 ([M+Na]\(^+\), 100%). HRMS (ES\(^+\)) found: 304.0788 (C\(_{13}\)H\(_{15}\)NO\(_6\)Na requires [M+Na]\(^+\) 304.0792).

Isomer 162:

![Structural diagram](image)

mp.: 99-100 °C. \( \nu_{\text{max}} \) (ATR) : 2999, 2949, 2878, 1740 (C=O), 1609, 1511+1339 (NO\(_2\)), 1258, 1187, 1122, 1027, 970, 853, 743, 635 cm\(^{-1}\). \( \delta_H \) (700 MHz; CDCl\(_3\)) : 8.30 (1H, d, J 8.0, 6′-H), 7.89 (1H, d, J 8.0, 3′-H), 7.64 (1H, t, J 8.0, 5′-H), 7.43 (1H, t, J 8.0, 4′-H), 4.34 (2H, dd, J 12.6, 3.8, 4′-H\(_{eq}\), 6′-H\(_{eq}\)), 4.16 (2H, dd, J 12.6, 1.2, 4′-H\(_{ax}\), 6′-H\(_{ax}\)), 3.83 (3H, s, OCH\(_3\)), 3.23-3.22 (1H, m, 5-H), 1.61 (3H, s, 2-CH\(_3\)). \( \delta_C \) (175 MHz; CDCl\(_3\)) : 170.6 (C=O), 149.3 (C-2′), 137.0 (C-1′), 133.2 (C-5′), 130.8 (C-6′), 127.7 (C-4′), 124.5 (C-3′), 98.5 (C-2), 66.5 (C-4, C-6), 52.7 (CH\(_3\)O), 32.9 (C-5), 25.8 (2-CH\(_3\)). m/z (ES\(^+\)) : 345 ([M+Na+CH\(_3\)CN]\(^+\), 100%), 180 (10). Anal. [Found: C, 54.8; H, 5.4; N, 4.9. C\(_{13}\)H\(_{15}\)NO\(_6\) requires C, 55.5; H, 5.4; N, 5.0%].

**Typical procedure for carbinol acetal synthesis (A4):**

A solution of ester acetal (1 eq) in THF was cooled to -78 °C and DIBAL (3 eq, 1.0 M solution in toluene) was added. Upon complete addition, the reaction was maintained at this temperature for 2 h, then at room temperature for 1 h. It was then recooled to -78 °C, methanol was added and the resultant solution stirred at room temperature for 1 h. Water was subsequently added and the resultant gelatinous precipitate stirred with Celite® until a granular solid was obtained. After filtration through a bed of Celite® and washing of the filter-cake with
ethyl acetate, the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography.

\textbf{(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)methanol (166, 167):}

Major isomer 166:

Similar to procedure A4, DIBAL (19.9 ml of a 1.0 M solution in toluene, 19.9 mmol) was added to a solution of 145 (1.56 g, 6.62 mmol) in THF (40.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal 166 (1.30 g, 95%) as a white solid.

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\text{mp.: 94-95 °C. } \nu_{\text{max}} \text{(ATR): 3390 (OH), 1175, 1130, 1050, 1021, 853, 670 cm}^{-1}. \ \delta_H \text{(500 MHz; CDCl}_3) : 7.29-7.24 (4H, m, Ar-H), 7.22-7.18 (1H, m, Ar-H), 4.09 (2H, dd, J 12.0, 4.7, 4'-H_{eq}, 6'-H_{eq}), 3.96 (2H, dd, J 12.0, 7.9, 4'-H_{ax}, 6'-H_{ax}), 3.73 (2H, d, J 6.1, 1-H_2), 3.01-2.96 (1H, m, 5'-H), 1.83 (1H, t, J 6.1, OH), 1.43 (3H, s, 2'-CH_3). \ \delta_C \text{(125 MHz; CDCl}_3) : 139.7 (C-1''), 128.7 (Ar-C), 127.7 (Ar-C), 127.1 (Ar-C), 98.2 (C-2''), 64.9 (C-4', C-6'), 63.0 (C-1), 40.1 (C-5'), 21.2 (2'-CH_3). m/z \text{ (ES}^+) : 272 ([M+Na+CH_3CN]^+, 100%), 209 ([M+H]^+, 40). Anal. [Found: C, 69.3; H, 7.8. C_{12}H_{16}O_3 requires C, 69.2; H, 7.7%].

Minor isomer 167:

Similar to procedure A4, DIBAL (6.40 ml of a 1.0 M solution in toluene, 6.40 mmol) was added to a solution of 146 (0.50 g, 2.12 mmol) in THF (15.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal 167 (0.43 g, 98%) as a white solid.
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mp.: 74-76 °C. νmax (ATR) : 3460 (OH), 1259, 1152, 1119, 1020, 948, 850, 764, 678 cm⁻¹. δH (500 MHz; CDCl₃) : 7.29-7.26 (3H, m, Ar-H), 7.16-7.14 (2H, m, Ar-H), 4.03 (2H, t, J 12.1, 4'-H$_{eq}$, 6'-H$_{eq}$), 3.94 (2H, dd, J 12.1, 5.4, 4'-H$_{ax}$, 6'-H$_{ax}$), 3.52 (2H, d, J 5.9, 1-H$_{2}$), 3.17-3.11 (1H, m, 5'-H), 2.23 (1H, t, J 5.9, OH), 1.48 (3H, s, 2'-CH$_{3}$). δC (125 MHz; CDCl₃) : 137.9 (C-1’’), 128.6 (Ar-C), 127.6 (Ar-C), 27.4 (Ar-C), 97.9 (C-2’’), 69.0 (C-1), 65.0 (C-4’, C-6’), 41.2 (C-5’), 15.3 (2'-CH$_{3}$). m/z (ES+) : 272 ([M+Na+CH$_{3}$CN]$^{+}$, 100%), 209 ([M+H]$^{+}$, 20). Anal. [Found: C, 69.3; H, 7.8. C$_{12}$H$_{16}$O$_{3}$ requires C, 69.2; H, 7.7%].

(2’,5’-diphenyl-1’,3’-dioxan-2’-yl)methanol (168, 169):

Major isomer 168:

Similar to procedure A4, DIBAL (25.2 ml of a 1.0 M solution in toluene, 25.2 mmol) was added to a solution of 151 (2.50 g, 8.39 mmol) in THF (64.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal 168 (2.27 g, 100%) as a white solid.

min: 112-114 °C. νmax (ATR) : 3567 (OH), 1407, 1439, 1345, 1243, 1162, 1006, 742, 695, 659 cm⁻¹. δH (500 MHz; CDCl₃) : 7.53 (2H, d, J 7.4, Ar-H), 7.40 (2H, d, J 8.2, Ar-H), 7.35 (2H, t, J 8.2, Ar-H), 7.30-7.27 (3H, m, Ar-H), 7.19-7.15 (1H, t, J 7.4, Ar-H), 4.17 (2H, dd, J 11.2, 3.6, 4'-H$_{eq}$, 6'-H$_{eq}$), 4.02 (2H, t, J 11.2, 4'-H$_{ax}$, 6'-H$_{ax}$), 3.49 (2H, d, J 6.7, 1-H$_{2}$), 2.47 (1H, m, 5'-H), 2.01 (1H, t, J 6.7, OH). δC (125 MHz; CDCl₃) : 142.6 (Ar-C), 136.8 (Ar-C) 128.8 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 127.7 (Ar-C), 126.6 (Ar-C), 101.1 (C-2’), 70.5 (C-1), 65.2 (C-4’, C-6’), 38.7 (C-5’). m/z (ES+) : 334 ([M+Na+CH$_{3}$CN]$^{+}$, 70%), 293 ([M+Na]$^{+}$, 100), 288 ([M+H$_{2}$O]$^{+}$, 40). Anal. [Found: C, 75.5; H, 6.7. C$_{17}$H$_{18}$O$_{3}$ requires C, 75.5; H, 6.7%].

Minor isomer 169:

Similar to procedure A4, DIBAL (3.50 ml of a 1.0 M solution in toluene, 3.52 mmol) was added to a solution of 152 (0.35 g, 1.17 mmol) in THF (10.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal 169 (0.32 g, 100%) as a white solid.
(5'-benzyl-2'-phenyl-1',3'-dioxane-2'-yl) methanol (170, 171):

Major isomer 170:

Similar to procedure A4, DIBAL (35.8 ml of a 1.0 M solution in toluene, 35.8 mmol) was added to a solution of 153 (3.72 g, 11.9 mmol) in THF (60.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal 170 (3.11 g, 92%) as a white solid.

mp.: 98-100 °C. νmax (ATR): 3465 (OH), 1407, 1439, 1345, 1243, 1162, 1046, 742, 695, 659 cm⁻¹. δH (500 MHz; CDCl₃): 7.56-7.54 (2H, m, Ar-H), 7.50 (2H, t, J 7.7, Ar-H), 7.45-7.42 (1H, m, Ar-H), 7.30-7.22 (3H, m, Ar-H), 7.03 (2H, d, J 7.2, Ar-H), 4.10 (2H, dd, J 11.6, 4.7, 4'-Hax, 6'-Hax), 3.96 (2H, t, J 11.6, 4'-Heq, 6'-Heq), 3.64 (2H, d, J 6.6, 1-H₂), 3.43-3.36 (1H, m, 5'-H), 2.30 (1H, t, J 6.6, OH). δC (125 MHz; CDCl₃): 137.6 (Ar-C), 136.8 (Ar-C) 129.0 (Ar-C), 128.66 (Ar-C), 128.65 (Ar-C), 127.68 (Ar-C), 127.5 (Ar-C), 127.4 (Ar-C), 100.9 (C-2'), 70.6 (C-1), 66.2 (C-4', C-6'). m/z (ES⁺): 334 ([M+Na+CH₃CN]⁺, 100%), 271 ([M+H]⁺, 10). Anal. [Found: C, 75.5; H, 6.7. C₁₇H₁₈O₃ requires C, 75.5; H, 6.7%].
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C), 101.2 (C-2’), 70.8 (C-1), 63.9 (C-4’, C-6’), 35.9 (C-5’), 35.7 (5’-CH2Ph). m/z (ES+) : 348 ([M+Na+CH3CN]⁺, 10%), 307 ([M+Na]⁺, 65), 137 (100). HRMS (ES⁺) found: 285.1486 (C18H21O3 requires [M+H]⁺ 285.1485). Anal. [Found: C, 75.8; H, 7.0. C18H20O3 requires C, 76.0; H, 7.1%].

Minor isomer 171:

Similar to procedure A4, DIBAL (12.2 ml of a 1.0 M solution in toluene, 12.1 mmol) was added to a solution of 154 (1.26 g, 4.04 mmol) in THF (20.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal 171 (1.05 g, 92%) as a white solid.

mp.: 106-107 °C. νmax (ATR) : 3472 (OH), 1491, 1446, 1395, 1268, 1167, 1025, 758, 699, 610 cm⁻¹. δH (700 MHz; CDCl3) : 7.45-7.42 (4H, m, Ar-H), 7.38-7.36 (1H, m, Ar-H), 7.25 (2H, t, J 7.2, Ar-H), 7.18 (1H, t, J 7.2, Ar-H), 7.05 (2H, d, J 7.2, Ar-H), 3.85 (2H, dd, J 11.7, 4.4, 4’-Heq, 6’-Heq), 3.51-3.48 (4H, m, 4’-Hax, 6’-Hax,1-H2), 2.45-2.38 (1H, m, 5’-H), 2.22 (2H, d, J 7.6, 5’-CH2Ph), 2.01 (1H, bs, OH). δC (175 MHz; CDCl3) : 138.1 (Ar-C), 137.0 (Ar-C) 128.8 (Ar-C), 128.6 (Ar-C), 128.52 (Ar-C), 128.50 (Ar-C), 127.7 (Ar-C), 126.4 (Ar-C), 101.0 (C-2’), 70.6 (C-1), 66.3 (C-4’, C-6’), 36.0 (C-5’), 34.6 (5’-CH2Ph). m/z (ES⁺) : 592 ([M+Na]⁺, 10%), 348 ([M+Na+CH3CN]⁺, 40), 285 ([M+H]⁺, 100). HRMS (ES⁺) found: 285.1485 (C18H21O3 requires [M+H]⁺ 285.1485).

[2’-methyl-5’-(4’’-nitrophenyl)-1’,3’-dioxan-2’-yl)methanol (172, 173):

Major isomer 172:

Similar to procedure A4, DIBAL (13.7 ml of a 1.0 M solution in hexane, 13.7 mmol) was added to a solution of 159 (1.28 g, 4.56 mmol) in THF (16.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal 172 (1.13 g, 98%) as a yellow solid.
mp.: 120-121 °C. ν max (ATR) : 3470 (OH), 2905, 1601, 1513+1345 (NO2), 1261, 1171, 1111, 1055, 1010, 920, 843, 696 cm⁻¹. δ H (700 MHz; CDCl3) : 8.19 (2H, d, J 8.7, 3''-H), 7.63 (2H, d, J 8.7, 2''-H), 4.34 (2H, dd, J 12.1, 4.2, 4'-H eq, 6'-H eq), 4.02 (2H, dd, J 12.1, 4.5, 4'-H ax, 6'-H ax), 3.67 (2H, d, J 6.5, 1-H2), 2.99-2.97 (1H, m, 5'-H), 1.84 (1H, t, J 6.5, OH), 1.52 (3H, s, 2'-CH3). δ C (175 MHz; CDCl3) : 149.0 (C-1'''), 147.0 (C-4'''), 128.9 (C-3'''), 123.7 (C-2'''), 98.6 (C-2'), 66.2 (C-1), 63.9 (C-4', C-6'), 39.6 (C-5'), 17.8 (2'-CH3). m/z (ES⁺) : 317 ([M+Na+CH3CN]⁺, 100%), 276 ([M+Na]⁺, 40), 254 ([M+H]⁺, 80). Anal. [Found: C, 56.9; H, 6.0; N, 5.5. C12H15O3N requires C, 56.9; H, 6.0; N, 5.5%].

Minor isomer 173 : Similar to procedure A4, DIBAL (7.90 ml of a 1.0 M solution in hexane, 7.90 mmol) was added to a solution of 161 (0.74 g, 2.63 mmol) in THF (10.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal 173 (0.63 g, 95%) as a yellow solid.

mp.: 58-59 °C. ν max (ATR) : 3520-3310 (OH), 2872, 1737, 1601, 1513+1344 (NO2), 1236, 1151, 1111, 1060, 938, 844, 744, 695 cm⁻¹. δ H (700 MHz; CDCl3) : 8.21 (2H, d, J 8.7, 3''-H), 7.41 (2H, d, J 8.7, 2''-H), 4.09 (2H, t, J 11.7, 4'-H eq, 6'-H eq), 4.06 (2H, dd, J 11.7, 5.4, 4'-H ax, 6'-H ax), 3.61 (2H, d, J 6.6, 1-H2), 3.33-3.29 (1H, m, 5'-H), 2.00 (1H, t, J 6.6, OH), 1.55 (3H, s, 2'-CH3). δ C (175 MHz; CDCl3) : 147.3 (C-4'''), 145.8 (C-1'''), 128.6 (C-2'''), 124.0 (C-3'''), 98.2 (C-2'), 68.4 (C-1), 64.4 (C-4', C-6'), 41.2 (C-5'), 15.8 (2'-CH3). m/z (ES⁺) : 317 ([M+Na+CH3CN]⁺, 100%), 276 ([M+Na]⁺, 60). Anal. [Found: C, 56.6; H, 6.2; N, 5.1. C12H15O3N requires C, 56.9; H, 6.0; N, 5.5%].
(2',5'-dimethyl-5'-nitro-1',3'-dioxan-2'-yl)methanol (174, 175):

Major trans isomer 174:
Similar to procedure A4, DIBAL (77.8 ml of a 1.0 M solution in hexane, 77.8 mmol) was added to a solution of 149 (4.68 g, 25.9 mmol) in THF (80.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal 174 (4.01 g, 81%) as a white solid.

Minor cis isomer 175:
Similar to procedure A4, DIBAL (44.5 ml of a 1.0 M solution in hexane, 44.5 mmol) was added to a solution of 150 (3.25 g, 14.8 mmol) in THF (56.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal 175 (2.34 g, 83%) as a white solid.
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68.3 (C-1), 64.9 (C-4’, C-6’), 19.8 (5’-CH₃), 14.7 (2’-CH₃). \( m/z \) (ES⁺) : 255 ([M+Na+CH₃CN]⁺, 100%). Anal. [Found: C, 43.9; H, 6.8; N, 7.2. \( C_{7}H_{13}O_{5}N \) requires C, 44.0; H, 6.9; N, 7.3%].

*Typical procedure for aldehyde acetal synthesis (A5):*

To a stirred solution of oxalyl chloride (1.2 eq) in DCM maintained at -78 °C was added dimethylsulphoxide (2.4 eq) and the resultant solution was stirred at this temperature for 10 min. Then a solution of carbinol acetal (1 eq) in DCM was added dropwise and the reaction stirred at -78 °C for an additional 20 min. Triethylamine (4.7 eq) was then added and the reaction allowed to attain ambient temperature. The reaction mixture was diluted with ether, quenched by addition of brine and then extracted with ether (3 x 20.0 ml). The combined organic extracts were then washed with brine, dried using \( \text{MgSO}_4 \), filtered and concentrated in vacuo.

*2-methyl-5-phenyl-1,3-dioxane-2-carbaldehyde (176, 177):*

Major isomer 176:

Similar to procedure A5, dimethylsulphoxide (0.90 ml, 12.7 mmol) was added to a solution of oxalyl chloride (0.55 ml, 6.35 mmol) in DCM (20.0 ml), thenafter a solution of 166 (1.10 g, 5.29 mmol) in DCM (5.00 ml) was added before finally adding triethylamine (3.50 ml, 24.9 mmol). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title aldehyde acetal 176 (1.04 g, 95%) as a yellow solid.

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\text{mp.: 41-42 °C. } v_{\text{max}} \text{ (ATR)} : 1744 (\text{CHO}), 1604, 1515, 1218, 1133, 1049, 918, 795, 671 \text{ cm}^{-1}. \\
\delta_H (500 MHz; \text{CDCl}_3) : 9.63 (1H, s, \text{CHO}), 7.28-7.24 (2H, m, Ar-H), 7.22-7.19 (1H, m, Ar-H), 7.08-7.05 (2H, m, Ar-H), 4.05 (2H, dd, \text{J} 12.0, 4.7, 4-H_{\text{eq}}, 6-H_{\text{eq}}), 3.88 (2H, t, \text{J} 12.0, 4-H_{\text{ax}}, 6-H_{\text{ax}}), 3.24-3.17 (1H, m, 5-H), 1.38 (3H, s, 2-CH₃). \\
\delta_C (125 MHz; \text{CDCl}_3) : 201.4 (\text{CHO}), 137.3 (\text{C-1’}), 129.1 (\text{Ar-C}), 127.9 (\text{Ar-C}), 127.8 (\text{Ar-C}), 99.8 (\text{C-2}), 68.3 (\text{C-4}, \text{C-6}), 41.0 (\text{C-5}), 22.3 (\text{2-CH₃}). \\
\text{m/z} (\text{ES}^+) : 453 ([2M+CH₃CN]⁺, 100%), 437 (65), 261 (15), 217 (30), 104 (25). \\
m/z
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(EI) : 177 (M⁺-CHO, 30 %), 117 (60), 77 (Ph⁺, 30), 43 (100). Anal. [Found: C, 69.4; H, 6.8. C₁₂H₁₄O₃ requires C, 69.8; H, 6.8%].

Minor isomer 177:
Similar to procedure A5, dimethylsulphoxide (0.25 ml, 3.46 mmol) was added to a solution of oxalyl chloride (0.15 ml, 1.73 mmol) in DCM (5.00 ml), then after a solution of 167 (0.30 g, 1.44 mmol) in DCM (3.00 ml) was added before finally adding triethylamine (0.95 ml, 6.77 mmol). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title aldehyde acetal 177 (0.28 g, 94%) as a yellow oil.

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\text{H} & \quad \text{O} \\
\text{O} & \quad \text{H} \\
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\(\nu_{\text{max}}\) (ATR) : 1747 (CHO), 1604, 1453, 1374, 1051, 994, 865, 631 cm\(^{-1}\). \(\delta_H\) (500 MHz; CDCl\(_3\)) : 9.55 (1H, s, CHO), 7.42-7.40 (2H, m, Ar-H), 7.37-7.33 (2H, m, Ar-H), 7.31-7.27 (1H, m, Ar-H), 4.21 (2H, dd, \(J=12.0, 4.8\), 4-\(H_{\text{eq}}\), 6-\(H_{\text{eq}}\)), 4.14 (2H, dd, \(J=12.0, 4.8\), 4-\(H_{\text{ax}}\), 6-\(H_{\text{ax}}\)), 2.94-2.90 (1H, m, 5-H), 1.49 (3H, s, 2-\(CH_3\)), \(\delta_C\) (125 MHz; CDCl\(_3\)) : 199.2 (CHO), 140.5 (C-1’), 128.9 (Ar-C), 128.2 (Ar-C), 127.4 (Ar-C), 98.8 (C-2), 66.6 (C-4, C-6), 39.8 (C-5), 18.9 (2-\(CH_3\)). \(m/z\) (ES\(^+\)) : 453 ([2M+CH\(_3\)CN]+, 30%), 425 (100), 257 (25). \(m/z\) (EI) : 177 (M⁺-CHO, 10%), 117 (15), 77 (Ph⁺, 30), 43 (100).

2,5-diphenyl-1,3-dioxane-2-carbaldehyde (178, 179):
Major isomer 178:
Similar to procedure A5, dimethylsulphoxide (0.55 ml, 7.56 mmol) was added to a solution of oxalyl chloride (0.30 ml, 3.78 mmol) in DCM (12.0 ml), then after a solution of 168 (0.85 g, 3.15 mmol) in DCM (5.00 ml) was added before finally adding triethylamine (2.10 ml, 14.8 mmol). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title aldehyde acetal 178 (0.80 g, 95%) as a white solid.
mp.: 66-70 °C. \( \nu_{\text{max}} \) (ATR) : 1729 (CHO), 1603, 1496, 1450, 1250, 1147, 1025, 854, 657 cm\(^{-1}\). 
\( \delta_H \) (500 MHz; CDCl\(_3\)) : 9.54 (1H, s, CHO), 7.65 (2H, d, J 7.6, Ar-H), 7.45-7.38 (3H, m, Ar-H), 7.35-7.32 (2H, m, Ar-H), 7.29-7.25 (1H, m, Ar-H), 7.21 (2H, d, J 7.5, Ar-H), 4.30 (2H, dd, J 11.7, 4.6, 4-H\(_{\text{eq}}\), 6-H\(_{\text{eq}}\)), 4.17 (2H, t, J 11.7, 4-H\(_{\text{ax}}\), 6-H\(_{\text{ax}}\)), 3.31-3.25 (1H, m, 5-H).

Minor isomer 179 :
Similar to procedure A5, dimethylsulphoxide (0.19 ml, 2.67 mmol) was added to a solution of oxalyl chloride (0.12 ml, 1.33 mmol) in DCM (5.00 ml), then after a solution of 169 (0.30 g, 1.11 mmol) in DCM (2.00 ml) was added before finally adding triethylamine (0.73 ml, 5.22 mmol). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title aldehyde acetal 179 (0.29 g, 98%) as a yellow oil.

mp.: 83-86. \( \nu_{\text{max}} \) (ATR) : 1727 (CHO), 1600, 1494, 1453, 1272, 1134, 1025, 915, 698 cm\(^{-1}\). 
\( \delta_H \) (500 MHz; CDCl\(_3\)) : 9.35 (1H, s, CHO), 7.62-7.56 (2H, m, Ar-H), 7.54-7.37 (3H, m, Ar-H), 7.33-7.20 (3H, m, Ar-H), 7.08-6.96 (2H, m, Ar-H), 4.21 (1H, dd, J 11.5, 4.6, 4-H\(_{\text{ax}}\)), 4.16-4.10 (1H, m, 6-H\(_{\text{ax}}\)), 4.05 (1H, t, J 11.5, 4-H\(_{\text{eq}}\)), 3.97-3.83 (1H, m, 6-H\(_{\text{eq}}\)), 3.43-3.34 (1H, m, 5-H).
\( \delta_C \) (125 MHz; CDCl\(_3\)) : 192.3 (CHO), 137.4 (Ar-C), 132.5 (Ar-C) 129.6 (Ar-C), 129.4 (Ar-C), 128.7 (Ar-C), 128.4 (Ar-C), 128.0 (Ar-C), 127.4 (Ar-C), 99.5 (C-2), 66.4 (C-4), 66.3 (C-6), 66.1 (C-6), 66.0 (C-6).
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40.8 (C-5). m/z (EI): 239 (M⁺-CHO, 100), 117 (40), 91 (PhCH₂⁺, 5), 77 (Ph⁺, 15). HRMS (ASAP⁺) found: 269.1168 (C₁₇H₁₇O₃ requires [M+H]⁺ 269.1172).

5-benzyl-2-phenyl-1,3-dioxane-2-carbaldehyde (180, 181):
Major isomer 180:
Similar to procedure A5, dimethylsulphoxide (1.86 ml, 26.3 mmol) was added to a solution of oxalyl chloride (1.15 ml, 13.1 mmol) in DCM (31.0 ml), then after a solution of 170 (3.11 g, 11.0 mmol) in DCM (20.0 ml) was added before finally adding triethylamine (7.18 ml, 51.5 mmol). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title aldehyde acetal 180 (2.80 g, 91%) as a clear oil.

Minor isomer 181:
Similar to procedure A5, dimethylsulphoxide (0.58 ml, 8.03 mmol) was added to a solution of oxalyl chloride (0.36 ml, 4.01 mmol) in DCM (9.00 ml), then after a solution of 171 (0.95 g, 3.35 mmol) in DCM (9.00 ml) was added before finally adding triethylamine (2.20 ml, 15.7 mmol). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title aldehyde acetal 181 (0.89 g, 94%) as a clear oil.

\[
\begin{align*}
\nu_{\text{max}} (\text{ATR}) & : 1736 (\text{CHO}), 1451, 1253, 1145, 1028, 751, 698, 660 \text{ cm}^{-1}. \\delta_H (700 \text{ MHz}; \text{CDCl}_3) : 9.42 (1H, s, \text{CHO}), 7.54 (2H, d, J 7.4, \text{Ar-H}), 7.41 (2H, t, J 7.4, \text{Ar-H}), 7.38 (1H, t, J 7.4, \text{Ar-H}), 7.30 (2H, t, J 7.3, \text{Ar-H}), 7.22 (1H, t, J 7.3, \text{Ar-H}), 7.16 (2H, d, J 7.3, \text{Ar-H}), 4.08 (2H, dd, J 11.7, 4.0, 4-\text{H}_{eq}, 6-\text{H}_{eq}), 3.79 (2H, dd, J 11.7, 7.7, 4-\text{H}_{as}, 6-\text{H}_{as}), 2.67 (2H, d, J 7.7, 5-\text{CH}_2\text{Ph}), 2.17-2.12 (1H, m, 5-H). \\delta_C (175 \text{ MHz}; \text{CDCl}_3) : 196.0 (\text{CHO}), 138.5 (\text{Ar-C}), 134.1 (\text{Ar-C}), 129.5 (\text{Ar-C}), 128.88 (\text{Ar-C}), 128.87 (\text{Ar-C}), 128.6 (\text{Ar-C}), 126.9 (\text{Ar-C}), 126.4 (\text{Ar-C}), 100.2 (\text{C-2}, 66.7 (\text{C-4}, \text{C-6}), 36.0 (\text{C-5}), 34.9 (5-\text{CH}_2\text{Ph}). m/z (\text{ES}⁺) : 305 ([\text{M+Na}]⁺, 10%), 283 ([\text{M+H}]⁺, 100). HRMS (\text{ES}⁺) found: 283.1331 (C₁₃H₁₉O₃ requires [M+H]⁺ 283.1332).
\end{align*}
\]
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\[ \text{CHO} \]  
\[ \text{CH}_{2}
\]

\[ \nu_{\text{max}} \text{(ATR)} : 1733 \text{ (CHO), 1371, 1231, 1134, 1027, 751, 701, 633 cm}^{-1}. \delta_{\text{H}} (700 \text{ MHz; CDCl}_3) : 9.30 (1H, s, CHO), 7.54 (2H, d, J 7.1, Ar-H), 7.47 (2H, t, J 7.1, Ar-H), 6.72 (2H, d, J 7.1, Ar-H), 7.28 (2H, t, J 7.1, Ar-H), 7.21 (1H, t, J 7.1, Ar-H), 7.10 (2H, d, J 7.1, Ar-H), 4.01 (2H, dd, J 11.5, 4.1, 4-H\textsubscript{ax}, 6-H\textsubscript{ax}), 3.69 (2H, t, J 11.5, 4-H\textsubscript{eq}, 6-H\textsubscript{eq}), 2.47 (2H, d, J 7.8, 5-CH\textsubscript{2}Ph), 2.34-2.23 (1H, m, 5-H). \delta_{\text{C}} (175 \text{ MHz; CDCl}_3) : 193.6 (CHO), 138.3 (Ar-C), 133.3 (Ar-C) 129.5 (Ar-C), 129.2 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 127.7 (Ar-C), 126.4 (Ar-C), 99.9 (C-2), 66.2 (C-4, C-6), 36.0 (C-5), 34.7 (5-CH\textsubscript{2}Ph). m/z (ES\textsuperscript{+}) : 346 ([M+Na+CH\textsubscript{2}CN]\textsuperscript{+}, 10%), 283 ([M+H]\textsuperscript{+}, 100). HRMS (ES\textsuperscript{+}) found: 283.1329 (C\textsubscript{18}H\textsubscript{19}O\textsubscript{3} requires [M+H]\textsuperscript{+} 283.1329).

2-methyl-5-(4’-nitrophenyl)-1,3-dioxane-2-carbaldehyde (182, 183):

Major isomer 182:

Similar to procedure A5, dimethylsulphoxide (1.15 ml, 16.1 mmol) was added to a solution of oxalyl chloride (0.70 ml, 8.06 mmol) in DCM (19.0 ml), thenafter a solution of 172 (1.70 g, 6.72 mmol) in DCM (19.0 ml) was added before finally adding triethylamine (4.40 ml, 31.6 mmol). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title aldehyde acetal 182 (1.48 g, 88%) as a yellow solid.

\[ \text{CHO} \]  
\[ \text{CH}_{2}\]

mp.: 98-99 °C. \( \nu_{\text{max}} \text{(ATR)} : 2857, 1737 \text{ (CHO), 1602, 1511+1343 (NO}_2\text{), 1195, 1129, 1050, 1021, 919, 844, 769, 691 \text{ cm}^{-1}. \delta_{\text{H}} (700 \text{ MHz; CDCl}_3) : 9.63 (1H, s, CHO), 8.15 (2H, d, J 8.6, 3'-H), 7.30 (2H, d, J 8.6, 2'-H), 4.11 (2H, dd, J 11.9, 4.7, 4-H\textsubscript{eq}, 6-H\textsubscript{eq}), 3.94 (2H, t, J 11.9, 4-H\textsubscript{ax}, 6-H\textsubscript{ax}), 3.38-3.34 (1H, m, 5-H), 1.43 (3H, s, 2-CH\textsubscript{3}). \delta_{\text{C}} (175 \text{ MHz; CDCl}_3) : 200.2 (CHO), 147.3 (C-4’), 144.6 (C-1’), 128.5 (C-2’), 124.0 (C-3’), 99.4 (C-2), 67.2 (C-4, C-6), 40.7 (C-5), 21.7 (2-CH\textsubscript{3}). m/z (ES\textsuperscript{+}) : 543 ([2M+CH\textsubscript{3}CN]\textsuperscript{+}, 40%), 333 (100), 315
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([M+Na+CH$_3$CN]$^+$, 30). Anal. [Found: C, 57.3; H, 5.2; N, 5.5. C$_{12}$H$_{13}$O$_3$N requires C, 57.4; H, 5.2; N, 5.6%].

Minor isomer 183:
Similar to procedure A5, dimethylsulphoxide (0.36 ml, 5.03 mmol) was added to a solution of oxalyl chloride (0.20 ml, 2.51 mmol) in DCM (6.00 ml), then after a solution of 173 (0.53 g, 2.09 mmol) in DCM (3.00 ml) was added before finally adding triethylamine (1.37 ml, 9.85 mmol). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title aldehyde acetal 183 (0.42 g, 80%) as a yellow oil.

![Image of chemical structure]

$\nu_{\text{max}}$ (ATR) : 2948, 1741 (CHO), 1601, 1514+1343 (NO$_2$), 1245, 1153, 1100, 1036, 919, 846, 770, 744, 696 cm$^{-1}$, $\delta_H$ (700 MHz; CDCl$_3$) : 9.61 (1H, s, CHO), 8.22 (2H, d, $J$ 8.9, 2'-H), 7.68 (2H, d, $J$ 8.9, 3'-H), 4.31 (2H, dd, $J$ 12.4, 3.7, 4-$H_{\text{eq}}$, 6-$H_{\text{eq}}$), 4.14 (2H, dd, $J$ 12.4, 2.6, 4-$H_{\text{ax}}$, 6-$H_{\text{ax}}$), 2.89-2.87 (1H, m, 5-H), 1.45 (3H, s, 2-CH$_3$). $\delta_C$ (175 MHz; CDCl$_3$) : 199.5 (CHO), 148.8 (C-1’), 147.0 (C-4’), 129.1 (C-2’), 123.7 (C-3’), 99.5 (C-2), 66.2 (C-4, C-6), 38.9 (C-5), 20.7 (2-CH$_3$). m/z (EI) : 236 (M$^+$-Me, 6%), 222 (M$^+$-CHO, 100), 207 (M$^+$-Me-CHO, 5), 116 (70), 91 (PhCH$_3$+, 6), 77 (Ph+, 15). m/z (ES$^+$) : 543 ([2M+CH$_3$CN]$^+$, 100%), 252 ([M+H]$^+$, 20). HRMS (ES$^+$) found: 252.0872 (C$_{12}$H$_{14}$O$_3$N requires [M+H]$^+$ 252.0869).

2,5-dimethyl-5-nitro-1,3-dioxane-2-carbaldehyde (184, 185):
Major isomer 184:
Similar to procedure A5, dimethylsulphoxide (3.00 ml, 42.2 mmol) was added to a solution of oxalyl chloride (1.85 ml, 21.1 mmol) in DCM (50.0 ml), then a solution of 174 (3.36 g, 17.6 mmol) in DCM (50.0 ml) was added before finally adding triethylamine (11.6 ml, 82.7 mmol). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title aldehyde acetal 184 (2.64 g, 79%) as a white solid.
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mp.: 47-48 °C. ν\text{max} (ATR) : 2838, 1741 (\textit{CHO}), 1543+1348 (NO_2), 1445, 1301, 1199, 1127, 1074, 1041, 900, 766, 628, 571 cm\(^{-1}\). δ\text{H} (700 MHz; CDCl_3) : 9.52 (1H, s, \textit{CHO}), 4.72 (2H, d, J 12.9, 4-\textit{H}_\text{eq}, 6-\textit{H}_\text{ax}), 3.83 (2H, d, J 12.9, 4-\textit{H}_\text{ax}, 6-\textit{H}_\text{ax}), 1.35 (3H, s, 2-\textit{CH}_3), 1.34 (3H, s, 5-\textit{CH}_3). δ\text{C} (175 MHz; CDCl_3) : 198.6 (\textit{CHO}), 99.5 (C-2), 82.4 (C-5), 67.2 (C-4, C-6), 21.3 (2-\textit{CH}_3), 19.3 (5-\textit{CH}_3). \text{m/z} (ES\textsuperscript{+}) : 533 (50%), 242 (100), 232 (30), 173 (60). Anal. [Found: C, 44.2; H,5.8; N, 7.3. C\textsubscript{7}H\textsubscript{11}O\textsubscript{5}N requires C, 44.5; H, 5.9; N, 7.4%].

Minor isomer 185:
Similar to procedure A5, dimethylsulphoxide (2.10 ml, 29.4 mmol) was added to a solution of oxalyl chloride (1.30 ml, 14.7 mmol) in DCM (35.0 ml), then after a solution of 175 (2.34 g, 12.3 mmol) in DCM (35.0 ml) was added before finally adding triethylamine (8.10 ml, 57.6 mmol). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title aldehyde acetal 185 (2.00 g, 86%) as a snow white solid.

mp.: 49-50 °C. ν\text{max} (ATR) : 2837, 1759 (\textit{CHO}), 1541+1352 (NO\textsubscript{2}), 1459, 1378, 1164, 1112, 1066, 1041, 990, 849, 759, 681 cm\(^{-1}\). δ\text{H} (700 MHz; CDCl_3) : 9.40 (1H, s, \textit{CHO}), 4.35 (2H, d, J 12.3, 4-\textit{H}_\text{eq}, 6-\textit{H}_\text{ax}), 4.06 (2H, d, J 12.3, 4-\textit{H}_\text{ax}, 6-\textit{H}_\text{ax}), 1.71 (3H, s, 5-\textit{CH}_3), 1.44 (3H, s, 2-\textit{CH}_3). δ\text{C} (175 MHz; CDCl_3) : 196.7 (\textit{CHO}), 98.8 (C-2), 80.6 (C-5), 66.6 (C-4, C-6), 20.8 (5-\textit{CH}_3), 18.2 (2-\textit{CH}_3). \text{m/z} (ES\textsuperscript{+}) : 419 ([2M+CH\textsubscript{3}CN]\textsuperscript{+}, 100%), 401 ([2M+Na]\textsuperscript{+}, 30), 190 ([M+H]\textsuperscript{+}, 10). Anal. [Found: C, 44.0; H,6.2; N, 7.0. C\textsubscript{7}H\textsubscript{11}O\textsubscript{5}N requires C, 44.5; H, 5.9; N, 7.4%].
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**Typical procedure for diazoketol synthesis (A6):**

To a solution of ethyl diazoacetate (12 eq) in anhydrous CH$_3$CN at room temperature under nitrogen, was added successively a solution of 1,8-diazabicyclo(5.4.0)-undec-7-ene (DBU) (1 eq) in anhydrous CH$_3$CN and aldehyde acetal (10 eq) in anhydrous CH$_3$CN via cannular. After stirring at room temperature for 15 h, the reaction was quenched with saturated aqueous NaHCO$_3$ and then extracted with DCM (3 × 20.0 ml). The solvent was removed by evaporation under reduced pressure and the crude product was purified by flash column chromatography on silica gel.

**Ethyl-2-diazo-3-hydroxy-3-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)propanoate (194, 195):**

Major isomer 194:

Similar to procedure A6, DBU (0.08 ml, 0.52 mmol) in anhydrous CH$_3$CN (6.00 ml) and 176 (1.06 g, 5.15 mmol) in CH$_3$CN (12.0 ml) were added successively to a solution of ethyl diazoacetate (0.65 ml, 6.17 mmol) in anhydrous CH$_3$CN (12.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 194 (1.37 g, 86%) as a shiny yellow oil.

\[
\begin{align*}
\text{EtO} & \quad \text{N} \quad 2 \\
\text{H} & \quad 3 \\
\text{OH} & \quad \text{O} \\
\text{N}_2 & \quad \text{OH}
\end{align*}
\]

$\nu_{\text{max}}$ (ATR) : 3520-3410 (OH br), 2980, 2875, 2096 (C=O), 1683 (C=N), 1496, 1394, 1107, 1050, 870, 701 cm$^{-1}$. $\delta_H$ (500 MHz; CDCl$_3$) : 7.41 (2H, d, J 7.6, Ar-H), 7.35 (2H, t, J 7.6, Ar-H), 4.85 (1H, bs, 3-H), 4.27 (2H, q, J 7.0, OCH$_2$CH$_3$), 4.25-4.19 (2H, m, 4'-H$_{eq}$, 6'-H$_{eq}$), 4.15 (2H, dd, J 11.7, 5.4, 4'-H$_{ax}$, 6'-H$_{ax}$), 2.94-2.90 (1H, m, 5'-H), 2.84 (1H, bs, OH), 1.50 (3H, s, 2'-CH$_3$), 1.28 (3H, t, J 7.0, OCH$_2$CH$_3$). $\delta_C$ (125 MHz; CDCl$_3$) : 166.4 (C-1), 140.0 (C-1''), 128.9 (Ar-C), 127.8 (Ar-C), 126.9 (Ar-C), 100.4 (C-2''), 67.8 (C-3), 65.1 (C-4''), 64.2 (C-6''), 60.8 (OCH$_2$CH$_3$), 57.9 (C-2), 39.1 (C-5''), 17.6 (2'-CH$_3$), 14.4 (OCH$_2$CH$_3$). $m/z$ (ES$^+$) : 663 ([2M+Na]$^+$, 35%), 417 (100), 343 ([M+Na]$^+$, 60). HRMS (ES$^+$) found: 343.1262 (C$_{16}$H$_{20}$O$_5$N$_2$Na requires [M+Na]$^+$ 343.1264).

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Minor isomer 195:
Similar to procedure A6, DBU (0.01 ml, 0.06 mmol) in anhydrous CH$_3$CN (1.00 ml) and 177 (0.13 g, 0.63 mmol) in CH$_3$CN (2.00 ml) were added successively to a solution of ethyl diazoacetate (0.08 ml, 0.76 mmol) in anhydrous CH$_3$CN (2.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 195 (0.16 g, 79%) as a shiny yellow oil.

![Chemical structure](image)

$\nu_{\text{max}}$ (ATR) : 3620-3390 (OH br), 2981, 2875, 2103 (C=O), 1682 (C=O), 1496, 1394, 1126, 1056, 877, 701, 621 cm$^{-1}$. $\delta_H$ (500 MHz; CDCl$_3$) : 7.34 (2H, t, J 7.5, Ar-H), 7.30-7.26 (2H, m, Ar-H), 7.20 (1H, t, J 7.5, Ar-H), 4.56 (1H, d, J 4.2, 3-H), 4.30-4.21 (2H, q, J 7.2, OCH$_2$CH$_3$), 4.12-4.06 (2H, m, 4'-H$_{\text{eq}}$, 6'-H$_{\text{eq}}$), 4.04-3.99 (2H, m, 4'-H$_{\text{ax}}$, 6'-H$_{\text{ax}}$), 3.24-3.16 (1H, m, 5'-H), 3.07 (1H, bs, O=H), 1.61 (3H, s, 2'-CH$_3$), 1.29 (3H, t, J 7.2, OCH$_2$CH$_3$). $\delta_C$ (125 MHz; CDCl$_3$) : 166.7 (C-1), 137.4 (C-1’), 128.9 (Ar-C), 127.58 (Ar-C), 127.57 (Ar-C), 99.8 (C-2’), 71.3 (C-3), 65.2 (C-4’), 65.0 (C-6’), 60.9 (OCH$_2$CH$_3$), 57.3 (C-2), 40.9 (C-5’), 15.3 (2'-CH$_3$), 14.5 (OCH$_2$CH$_3$). m/z (ES$^+$) : 663 ([2M+Na]$^+$, 45%), 384 ([M+Na+CH$_3$CN]$^+$, 100). HRMS (ES$^+$) found: 343.1261 (C$_{16}$H$_{20}$O$_5$N$_2$Na requires [M+Na]$^+$ 343.1264).

**Ethyl-2-diazo-3-(2',5'-diphenyl-1',3'-dioxan-2'-yl)-3-hydroxypropanoate (196, 197):**
Major isomer 196:
Similar to procedure A6, DBU (0.05 ml, 0.30 mmol) in anhydrous CH$_3$CN (4.00 ml) and 178 (0.80 g, 2.99 mmol) in CH$_3$CN (7.00 ml) were added successively to a solution of ethyl diazoacetate (0.38 ml, 3.58 mmol) in anhydrous CH$_3$CN (7.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 196 (0.91 g, 80%) as a yellow solid.
Minor isomer 197:

Similar to procedure A6, DBU (0.01 ml, 0.03 mmol) in anhydrous CH$_3$CN (0.50 ml) and 179 (0.08 g, 0.30 mmol) in CH$_3$CN (1.00 ml) were added successively to a solution of ethyl diazoacetate (0.04 ml, 0.36 mmol) in anhydrous CH$_3$CN (1.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 197 (0.09 g, 79%) as a shiny yellow oil that turns solid upon standing at room temperature.

mp.: 103-105 °C. $\nu$$_{max}$ (ATR) : 3493-3413 (OH br), 2980, 2960, 2870, 2103 (C=N$_2$), 1682 (C=O), 1493, 1396, 1269, 1141, 1000, 918, 878, 702, 609 cm$^{-1}$. $\delta$$_H$ (500 MHz; CDCl$_3$) : 7.51 (2H, d, Ar-$H$), 7.44 (2H, t, J 7.7, Ar-$H$), 7.41-7.39 (1H, m, Ar-$H$), 7.23-7.20 (3H, m, Ar-
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H), 6.98 (2H, t, J 7.0, Ar-H), 4.58 (1H, s, 3-H), 4.08 (2H, d, J 12.1, 4'-H_eq, 6'-H_eq), 4.01 (2H, bs, OCH\textsubscript{2}CH\textsubscript{3}), 3.94-3.88 (2H, m, 4'-H\textsubscript{ax}, 6'-H\textsubscript{ax}), 3.36-3.34 (1H, m, 5'-H), 3.11 (1H, s, OH), 1.11 (3H, bs, OCH\textsubscript{2}CH\textsubscript{3}). \(\delta\text{C} (125\text{ MHz; CDCl}_3) : 166.0\text{ (C-1), 137.3 (Ar-C), 131.8 (Ar-C)}\) 129.0 (Ar-C), 128.8 (Ar-C), 128.7 (2 \times Ar-C), 128.1 (Ar-C), 127.5 (Ar-C), 102.4 (C-2'), 72.7 (C-3), 66.3 (C-4'), 66.3 (C-6'), 60.6 (OCH\textsubscript{2}CH\textsubscript{3}), 56.0 (C-2), 40.9 (C-5'), 14.3 (OCH\textsubscript{2}CH\textsubscript{3}).

\(m/\ell\) (ES\textsuperscript{+}) : 787 ([M+Na]\textsuperscript{+}, 100%), 446 ([M+Na+CH\textsubscript{3}CN]\textsuperscript{+}, 20), 405 ([M+Na]\textsuperscript{+}, 10). HRMS (ES\textsuperscript{+}) found: 787.2953 (C\textsubscript{42}H\textsubscript{44}O\textsubscript{10}N\textsubscript{2}Na requires [M+Na]\textsuperscript{+} 787.2950).

**Ethyl-3-(5'-benzyl-2'-phenyl-1',3'-dioxan-2'-yl)-2-diazo-3-hydroxypropanoate (198)**:

Similar to procedure A6, DBU (0.02 ml, 0.11 mmol) in anhydrous CH\textsubscript{3}CN (2.00 ml) and 180 (0.30 g, 1.06 mmol) in CH\textsubscript{3}CN (4.00 ml) were added successively to a solution of ethyl diazoacetate (0.13 ml, 1.28 mmol) in anhydrous CH\textsubscript{3}CN (6.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 198 (0.27 g, 64%) as a yellow solid.

\(\nu_{\text{max}}\text{(ATR)} : 3434\text{ (OH)}, 2871, 2098\text{ (C=N\textsubscript{2})}, 1679\text{ (C=O)}, 1451, 1371, 1290, 1136, 1041, 958, 740, 701, 663\text{ cm}^{-1}.\ \delta\text{H} (700\text{ MHz; CDCl}_3) : 7.47\text{ (2H, d, J 7.4, 2b''-H)}, 7.42\text{ (2H, t, J 7.4, 3b''-H)}, 7.37\text{ (1H, t, J 7.4, 4b''-H)}, 7.33\text{ (2H, t, J 7.7, 3a''-H)}, 7.24\text{ (3H, m, 2a''-H, 4a''-H)}, 4.54\text{ (1H, s, 3-H)}, 4.13\text{ (2H, bq, J 7.1, OCH\textsubscript{2}CH\textsubscript{3})}, 3.92\text{ (2H, d, J 11.3, 4'-H\textsubscript{eq}, 6'-H\textsubscript{eq})}, 3.76\text{ (2H, d, J 11.3, 4'-H\textsubscript{ax}, 6'-H\textsubscript{ax})}, 3.30\text{ (1H, bs, OH)}, 3.14\text{ (1H, dd, J 13.6, 8.3, 5'-CHHPh)}, 3.10\text{ (1H, dd, J 13.6, 8.3, 5'-CHHPh)}, 1.53\text{(1H, t, J 8.3, 5'-H)}, 1.20\text{ (3H, bt, J 7.1, OCH\textsubscript{2}CH\textsubscript{3})}. \(\delta\text{C} (175\text{ MHz; CDCl}_3) : 166.0\text{ (C-1), 139.9 (C-1a''), 135.6 (C-1b''), 129.2 (C-2a''), 128.7 (C-4b''), 128.6 (C-3b''), 128.4 (C-3a''), 127.9 (C-2b''), 126.1 (C-4a''), 102.8 (C-2'), 72.8 (C-3), 64.0 (C-4'), 63.7 (C-6'), 60.5 (OCH\textsubscript{2}CH\textsubscript{3}), 57.1 (C-2), 35.7 (C-5'), 35.6 (5'-CH\textsubscript{2}Ph), 14.3 (OCH\textsubscript{2}CH\textsubscript{3}). \(m/\ell\) (ES\textsuperscript{+}) : 419 ([M+Na]\textsuperscript{+}, 40%), 387 (50), 351 (100). HRMS (ES\textsuperscript{+}) found: 419.1574 (C\textsubscript{22}H\textsubscript{24}O\textsubscript{5}N\textsubscript{2}Na requires [M+Na]\textsuperscript{+} 419.1577).
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Ethyl-2-diazo-3-hydroxy-3-(2’-methyl-5’-(4’’-nitrophenyl)-1’,3’-dioxan-2’-yl)propanoate (199):
Similar to procedure A6, DBU (0.02 ml, 0.12 mmol) in anhydrous CH$_3$CN (2.00 ml) and 182 (0.30 g, 1.20 mmol) in CH$_3$CN (4.00 ml) were added successively to a solution of ethyl diazoacetate (0.15 ml, 1.43 mmol) in anhydrous CH$_3$CN (5.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 199 (0.41 g, 94%) as a shiny yellow oil.

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{EtO} \quad \text{CO} \\
\text{N}_2 & \quad \text{OH} & \text{H} & \text{O}_2\text{N} & \text{EtO} & \text{N}_2
\end{align*}
\]

$\nu_{\text{max}}$ (ATR) : 3458-3410 (OH br), 2982, 2880, 2099 (C=N), 1678 (C=O), 1517+1343 (NO$_2$), 1268, 1047, 849, 742 cm$^{-1}$. $\delta_H$ (700 MHz; CDCl$_3$) : 8.20 (2H, d, $J$ 8.7, Ar-H), 7.66 (2H, d, $J$ 8.7, Ar-H), 4.66 (1H, bs, 3-H), 4.40 (2H, dd, $J$ 12.2, 3.5, 4’-H$_{\text{ax}}$, 6’-H$_{\text{ax}}$), 4.25 (2H, q, $J$ 7.0, OCH$_2$CH$_3$), 4.13 (2H, ddd, $J$ 12.2, 2.8, 2.0, 4’-H$_{\text{eq}}$, 6’-H$_{\text{eq}}$), 2.92 (1H, tt, $J$ 3.5, 2.8, 5’-H), 1.56 (3H, s, 2’-CH$_3$), 1.29 (3H, t, $J$ 7.0, OCH$_2$CH$_3$). $\delta_C$ (175 MHz; CDCl$_3$) : 166.4 (C-1), 149.0 (C-4’’), 146.9 (C-1’’), 128.9 (C-2’’), 123.7 (C-3’’), 100.9 (C-2’), 70.0 (C-3), 64.4 (C-4’), 63.4 (C-6’), 61.0 (C-2), 60.4 (OCH$_2$CH$_3$), 38.9 (C-5’), 16.0 (2’-CH$_3$), 14.5 (OCH$_2$CH$_3$). $m/z$ (ES$^+$) : 222 (100%), 429 ([M+Na+CH$_3$CN]$^+$, 15%).

Ethyl-2-diazo-3-(2’,5’-dimethyl-5-nitro-1’,3’-dioxan-2’-yl)-3-hydroxypropanoate (200):
Similar to procedure A6, DBU (0.04 ml, 0.28 mmol) in anhydrous CH$_3$CN (4.00 ml) and 184 (0.52 g, 2.75 mmol) in CH$_3$CN (7.00 ml) were added successively to a solution of ethyl diazoacetate (0.35 ml, 3.30 mmol) in anhydrous CH$_3$CN (9.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 200 (0.80 g, 96%) as a yellow solid.

\[
\begin{align*}
\text{EtO} & \quad \text{O} \\
\text{N}_2 & \quad \text{OH} & \text{H}_3\text{C} & \text{O} & \text{N}_2
\end{align*}
\]
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mp.: 73-74 °C. $\nu_{\text{max}}$ (ATR) : 3397 (OH), 2987, 2107 (C=N$_2$), 1650 (C=O), 1544+1303 (NO$_2$), 1180, 1156, 1049, 867, 848, 776, 753 cm$^{-1}$. $\delta_H$ (700 MHz; CDCl$_3$) : 4.76 (1H, s, 3-$H$), 4.42 (2H, d, J 12.3, 4'-$H_{\text{ac}}$, 6'-$H_{\text{aq}}$), 4.25 (2H, q, J 7.8, OCH$_2$CH$_3$), 4.12 (1H, d, J 12.3, 4'-$H_{\text{eq}}$), 4.04 (1H, d, J 12.3, 6'-$H_{\text{eq}}$), 2.83 (1H, bs, OH), 1.68 (3H, s, 5'-$CH_3$), 1.43 (3H, s, 2'-$CH_3$), 1.29 (3H, t, J 7.8, OCH$_2$CH$_3$). $\delta_C$ (175 MHz; CDCl$_3$) : 166.2 (C-1), 101.2 (C-2'), 81.4 (C-5'), 68.4 (C-2), 67.2 (C-3), 65.4 (C-4'), 65.1 (C-6'), 61.1 (OCH$_2$CH$_3$), 21.3 (5'-CH$_3$), 16.9 (2'-CH$_3$), 14.4 (OCH$_2$CH$_3$). m/z (ES$^+$) : 629 ([M+Na]$^+$, 20%), 326 ([M+Na]$^+$, 60%), 304 ([M+H]$^+$, 100%). Anal. [Found: C, 43.6; H,5.7; N, 13.1. C$_{11}$H$_7$O$_3$N$_3$ requires C, 43.6; H, 5.7; N, 13.9%].

**Ethyl-2-diazo-3-hydroxy-4-methylhexanoate (220)**

Similar to procedure A6, DBU (0.09 ml, 0.58 mmol) in anhydrous CH$_3$CN (6.00 ml) and 2-methylbutanal 214 (0.50 g, 5.81 mmol) in CH$_3$CN (12.0 ml) were added successively to a solution of ethyl diazoacetate (0.73 ml, 6.97 mmol) in anhydrous CH$_3$CN (12.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 220 (1.10 g, 95%) as a shiny yellow oil.

\[
\begin{align*}
\text{OH} & \quad \text{N}_2 \\
\text{OEt} & \quad \text{Et}
\end{align*}
\]

$\nu_{\text{max}}$ (ATR) : 3520-3410 (OH br), 2965, 2089 (C=N$_2$), 1663 (C=O), 1461, 1373, 1286, 1012, 914, 744 cm$^{-1}$. $\delta_H$ (500 MHz; CDCl$_3$) : 4.38 (1H, d, J 7.5, 3-$H$), 4.24 (2H, q, J 7.2, OCH$_2$CH$_3$), 2.50 (1H, bs, OH), 1.76-1.61 (1H, m, 4-$H$), 1.54-1.50 (1H, m, 5-$HH$), 1.28 (3H, t, J 7.2, OCH$_2$CH$_3$), 1.26-1.10 (1H, m, 5-$HH$), 1.03 (3H, d, J 6.7, 4-CH$_3$), 0.95-0.91 (3H, m, 6-$H_3$). $\delta_C$ (125 MHz; CDCl$_3$) : 166.8 (C-1), 71.1 (C-2), 70.7 (C-3), 60.9 (OCH$_2$CH$_3$), 39.2 (C-4), 25.7 (C-5), 14.9 (4- CH$_3$), 14.4 (OCH$_2$CH$_3$), 11.3 (C-6). m/z (ES$^+$) : 433 (70%), 423 ([2M+Na]$^+$, 80), 405 (100), 321 (60).

**Ethyl-2-diazo-3-hydroxy-3-(4'-trifluoromethylphenyl)propanoate (221)**

Similar to procedure A6, DBU (0.04 ml, 0.29 mmol) in anhydrous CH$_3$CN (2.00 ml) and 4-(trifluoromethyl)benzaldehyde 215 (0.39 ml, 2.87 mmol) in CH$_3$CN (4.00 ml) were added successively to a solution of ethyl diazoacetate (0.36 ml, 3.45 mmol) in anhydrous CH$_3$CN
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(4.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 221 (0.77 g, 93%) as a yellow solid.

![Chemical structure of 221](image)

mp.: 51-53 °C. ν\text{max} (ATR) : 3520-3367 (OH br), 2989, 2092 (C=O), 1653 (C=O), 1402, 1310, 1111, 1013, 807, 706, 599 cm\(^{-1}\). δ\text{H} (500 MHz; CDCl\(_3\)) : 7.66 (2H, d, J 8.3, Ar-H), 7.57 (2H, d, J 8.3, Ar-H), 5.97 (1H, d, J 3.6, 3-H), 4.29 (2H, q, J 7.1, OCH\(_2\)CH\(_3\)), 2.90 (1H, d, J 3.6, OH), 1.31 (3H, t, J 7.1, OCH\(_2\)CH\(_3\)).

δ\text{F} (376.3 MHz; CDCl\(_3\)) : -63.03.

δ\text{C} (125 MHz; CDCl\(_3\)) : 166.0 (C-1), 142.7 (Ar-C), 130.4 (t, J 32.5, CF\(_3\)), 126.2 (Ar-C), 125.78 (Ar-C), 125.75 (Ar-C), 77.21 (C-2), 68.3 (C-3), 61.4 (OCH\(_2\)CH\(_3\)), 14.5 (OCH\(_2\)CH\(_3\)). m/z (ES\(^{+}\)) : 921 (100%), 577 ([2M+H]\(^{+}\), 95), 521 (40), 469 (25), 311 ([M+Na]\(^{+}\), 10). Anal. [Found: C, 50.2; H, 3.9; N, 9.6. C\(_{12}\)H\(_{11}\)O\(_3\)N\(_2\)F\(_3\) requires C, 50.0; H, 3.9; N, 9.7%].

**Ethyl-2-diazo-3-hydroxy-3-(4'-methoxyphenyl)propanoate (222):**

Similar to procedure A6, DBU (0.05 ml, 0.37 mmol) in anhydrous CH\(_3\)CN (4.00 ml) and 4-methoxybenzaldehyde 216 (0.45 ml, 3.67 mmol) in CH\(_3\)CN (7.00 ml) were added successively to a solution of ethyl diazoacetate (0.46 ml, 4.41 mmol) in anhydrous CH\(_3\)CN (7.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 222 (0.30 g, 32%) as a yellow oil.

![Chemical structure of 222](image)

ν\text{max} (ATR) : 3680-3443 (OH br), 2980, 2091 (C=O), 1665 (C=O), 1511, 1244, 1103, 1025, 780, 568, 525 cm\(^{-1}\). δ\text{H} (500 MHz; CDCl\(_3\)) : 7.35 (2H, d, J 8.7, Ar-H), 6.91 (2H, d, J 8.7, Ar-H), 5.87 (1H, d, J 3.3, 3-H), 4.27 (2H, q, J 7.1, OCH\(_2\)CH\(_3\)), 3.81 (3H, s, OCH\(_3\)), 2.96 (1H, bs, OH), 1.30 (3H, t, J 7.1, OCH\(_2\)CH\(_3\)). δ\text{C} (125 MHz; CDCl\(_3\)) : 166.4 (C-1), 159.5 (C=N), 130.79 (Ar-C), 130.78 (Ar-C), 127.0 (Ar-C), 114.1 (Ar-C), 68.5 (C-3), 62.5 (C-2), 61.1 (OCH\(_2\)CH\(_3\)), 52.1 (OCH\(_2\)CH\(_3\)).
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55.3 (OCH₃), 14.5 (OCH₂CH₃). \( m/z \) (ES⁺) : 505 (100%), 477 (40), 445 (100), 371 (10), 309 (10), 285 (5), 245 (10), 229 (5).

**Ethyl-2-diazo-3-hydroxy-3-phenylpropanoate (223)**:

Similar to procedure A6, DBU (0.07 ml, 0.47 mmol) in anhydrous CH₃CN (4.00 ml) and benzaldehyde 217 (0.48 ml, 4.71 mmol) in CH₃CN (6.00 ml) were added successively to a solution of ethyl diazoacetate (0.59 ml, 5.65 mmol) in anhydrous CH₃CN (6.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 223 (0.84 g, 81%) as a yellow oil.

\[ \text{EtO} \quad \begin{array}{c} \text{OH} \\ \text{N} \end{array} \quad \text{OEt} \]

\( \nu_{\text{max}} \) (ATR) : 3643-3317 (OH br), 2093 (C=N), 1665 (C=O), 1451, 1373, 1289, 1107, 1018, 721, 533 cm⁻¹. \( \delta_H \) (500 MHz; CDCl₃) : 7.43 (2H, d, J 7.4, Ar-H), 7.39 (2H, t, J 7.4, Ar-H), 7.33 (1H, t, J 7.4, Ar-H), 5.92 (1H, d, J 3.4, 3-H), 4.28 (2H, q, J 7.2, OCH₂CH₃), 2.96 (1H, bs, OH), 1.30 (3H, t, J 7.2, OCH₂CH₃). \( \delta_C \) (125 MHz; CDCl₃) : 166.3 (C-1), 138.7 (Ar-C), 128.8 (Ar-C), 128.4 (Ar-C), 125.7 (Ar-C), 68.8 (C-3), 66.4 (C-2), 61.2 (OCH₂CH₃), 14.5 (OCH₂CH₃). \( m/z \) (ES⁺) : 645 (40%), 519 (75), 453 (35), 415 (100), 317 (30), 284 ([M+Na+CH₃CN]+, 5), 255 (10), 215 (10), 105 (30), 64 (20).

**Ethyl-2-diazo-3-hydroxy-4-phenylbutanoate (224)**:

Similar to procedure A6, DBU (0.06 ml, 0.42 mmol) in anhydrous CH₃CN (4.00 ml) and 2-phenylacetaldehyde 218 (0.47 ml, 4.17 mmol) in CH₃CN (6.00 ml) were added successively to a solution of ethyl diazoacetate (0.53 ml, 5.00 mmol) in anhydrous CH₃CN (6.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol 224 (0.65 g, 67%) as a yellow oil.

\[ \text{O} \quad \begin{array}{c} \text{N} \end{array} \quad \text{EtO} \quad \text{OH} \]
\( v_{\text{max}} \) (ATR) : 3601-3311 (OH br), 2091 (C=N), 1666 (C=O), 1451, 1373, 1289, 1109, 1021, 741, 698 cm\(^{-1}\). \( \delta_H \) (500 MHz; CDCl\(_3\)) : 7.33 (2H, t, \( J 7.7 \), Ar-H), 7.28-7.23 (3H, m, Ar-H), 4.89 (1H, dt, \( J 6.9 \), 4.4, 3-H), 4.23 (2H, q, \( J 7.2 \), OCH\(_2\)CH\(_3\)), 3.04 (1H, dd, \( J 13.7 \), 6.9, 4-H), 2.98 (1H, dd, \( J 13.7 \), 6.9, 4-H), 1.27 (3H, t, \( J 7.2 \), OCH\(_2\)CH\(_3\)).

\( \delta_C \) (125 MHz; CDCl\(_3\)) : 166.3 (C-1), 136.6 (Ar-C), 129.2 (Ar-C), 128.7 (Ar-C), 127.0 (Ar-C), 67.6 (C-3), 65.9 (C-2), 61.0 (OCH\(_2\)CH\(_3\)), 41.0 (C-4), 14.4 (OCH\(_2\)CH\(_3\)). m/z (ES\(^{+}\)) : 610 (25%), 575 (10), 539 (15), 479 (10), 395 (100), 363 (25), 323 (30), 280 (20), 239 (25).

**Typical procedure for diazodiketone synthesis:**

**MnO\(_2\) oxidation procedure (A7).** Following a modified Deng’s method\(^3\), activated MnO\(_2\) (10 eq) was added in 3 portions over 48 h to a stirred solution of diazoketol (1 eq) in DCM at room temperature. Upon complete addition, the manganese dioxide was removed by filtration through a bed of Celite\(^\circledR\). The filtrate was concentrated in vacuo and purified by flash column chromatography using silica gel.

**A typical procedure for iodoxybenzoic acid (IBX) oxidation (A8).** IBX (1.5 eq) was dissolved in DMSO over 20 min at room temperature. To this was added a solution of the diazoketol (1 eq) in DMSO via cannular and the reaction mixture was stirred for 4 h at room temperature. It was then quenched with aqueous NaHCO\(_3\) and then extracted with DCM (3 \( \times \) 20.0 ml), the combined organic layer was copiously washed with aqueous NaHCO\(_3\) (3 \( \times \) 10.0 ml) and finally with water, it was subsequently dried with MgSO\(_4\), filtered and concentrated in vacuo, the resulting crude product were essentially pure however further purification by flash column chromatography on silica gel resulted in the isolation of the diazodiketones.

**Ethyl-2-diazo-3-(2’-methyl-5’-phenyl-1’,3’-dioxan-2’-yl)-3-oxopropanoate (205, 210) :**

Major isomer 205 :

Similar to procedure A7, MnO\(_2\) (0.14 g, 1.56 mmol) was added to a solution of 194 (0.05 g, 0.16 mmol) in DCM (1.50 ml). Purification by flash column chromatography (DCM/EtOAc : 9/1) afforded the title diazodiketone 205 (0.04 g, 80%) as a light yellow solid.

Similar to procedure A8, to a solution of IBX (1.37 g, 4.88 mmol) in DMSO (15.0 ml) was added a solution of 194 (1.04 g, 3.25 mmol) in DMSO (7.00 ml). Purification by flash column...
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chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone 205 (0.93 g, 90%) as a clear oil.

Alternatively, to a stirred solution of oxalyl chloride (0.31 ml, 3.56 mmol, 1.2 eq) in DCM maintained at -78 °C was added dimethylsulphoxide (0.51 ml, 7.13 mmol, 2.4 eq) and the resultant solution was stirred at this temperature for 10 min. Then a solution of 194 (0.89 g, 2.97 mmol, 1 eq) in DCM was added dropwise and the reaction stirred at -78 °C for an additional 20 min. Triethylamine (2.00 ml, 14.0 mmol, 4.7 eq) was then added and the reaction allowed to attain ambient temperature. The reaction mixture was then diluted with ether, quenched by addition of brine and was extracted with ether (3 × 15.0 ml). Ether extracts were washed with brine, the combined organic layers were then dried using MgSO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (DCM/EtOAc : 9/1) gave the title diazodiketone 205 (0.67 g, 76%) as a yellow solid.

Minor isomer 210:
Similar to procedure A7, MnO₂ (0.15 g, 1.69 mmol) was added to a solution of 195 (0.05 g, 0.17 mmol) in DCM (1.50 ml). Purification by flash column chromatography (DCM/EtOAc : 9/1) afforded the title diazodiketone 210 (0.04 g, 75%) as a yellow oil.

mp.: 60-62 °C. νmax (ATR) : 2127 (C=N₂), 1732 (COC=N₂), 1666 (COOEt), 1305, 1186, 1015, 856, 702, 629 cm⁻¹. δH (500 MHz; CDCl₃) : 7.28-7.25 (2H, t, J 7.4, Ar-H), 7.23-7.19 (1H, t, J 7.4, Ar-H), 7.08 (2H, d, J 7.4, Ar-H), 4.31 (2H, q, J 7.4, OCH₂CH₃), 4.06 (2H, dd, J 11.9, 4.8, 4'-Heq, 6'-Heq), 3.91 (2H, t, J 11.9, 4'-Hax, 6'-Hax), 3.25-3.18 (1H, m, 5'-H), 1.53 (3H, s, 2'-CH₃), 1.31 (3H, t, J 7.4, OCH₂CH₃). δC (125 MHz; CDCl₃) : 188.6 (C-3), 161.2 (C-1), 136.7 (C-1''), 128.8 (Ar-C), 127.61 (Ar-C), 127.58 (Ar-C), 100.5 (C-2'), 70.0 (C-2), 67.8 (C-4', C-6'), 62.0 (OCH₂CH₃), 40.1 (C-5'), 25.0 (2'-CH₃), 14.3 (OCH₂CH₃). m/z (ES⁺) : 382 ([M+Na+CH₃CN]⁺, 20%), 341 ([M+Na]⁺, 100), 319 ([M+H]⁺, 30). Anal. [Found: C, 60.8; H, 5.7; N, 7.3. C₁₆H₁₈O₅N₂ requires C, 60.4; H, 5.7; N, 8.8%].
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Alternatively, to a stirred solution of oxalyl chloride (0.05 ml, 0.53 mmol, 1.2 eq) in DCM maintained at -78 °C was added dimethylsulphoxide (0.07 ml, 1.05 mmol, 2.4 eq) and the resultant solution was stirred at this temperature for 10 min. Then a solution of 195 (0.14 g, 0.44 mmol, 1 eq) in DCM was added dropwise and the reaction stirred at -78 °C for an additional 20 min. Triethylamine (0.29 ml, 2.06 mmol, 4.7 eq) was then added and the reaction allowed to attain ambient temperature. The reaction mixture was then diluted with ether, quenched by addition of brine and was extracted with ether (3 x 15.0 ml). Ether extracts were washed with brine, the combined organic layers were then dried using MgSO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (DCM/EtOAc : 9/1) gave the title diazodiketone 210 (0.09 g, 65%) as a yellow oil.

\[
\begin{align*}
\text{EtO} & \text{O} \\
\text{N}_2 & \text{C} \\
\text{H} & \text{O} \\
\end{align*}
\]

\( \nu_{\text{max}} \) (ATR) : 2130 (C=N), 1733 (CO-C=N), 1684 (COOEt), 1293, 1159, 1093, 1017, 918, 869, 748, 691 cm\(^{-1}\). \( \delta_H \) (500 MHz; CDCl₃) : 7.28-7.23 (3H, m, Ar-H), 7.20-7.15 (2H, m, Ar-H), 4.24 (2H, q, J 7.2, OCH₂CH₃), 4.12 (2H, dd, J 11.9, 5.5, 4'-H<sub>eq</sub>, 6'-H<sub>eq</sub>), 4.04 (2H, dd, J 11.9, 5.5, 4'-H<sub>ax</sub>, 6'-H<sub>ax</sub>), 2.88-2.84 (1H, m, 5'-H), 1.55 (3H, s, 2'-CH₃), 1.24 (3H, t, J 7.2, OCH₂CH₃).

\( \delta_C \) (125 MHz; CDCl₃) : 186.2 (C-3), 161.7 (C-1), 139.6 (C-1’’’), 128.7 (Ar-C), 127.8 (Ar-C), 127.3 (Ar-C), 100.4 (C-2’), 70.2 (C-2), 66.2 (C-4’, C-6’), 61.9 (OCH₂CH₃), 38.9 (C-5’’), 19.7 (2’-CH₃), 14.3 (OCH₂CH₃). \( m/z \) (ES⁺) : 382 ([M+Na+CH₃CN]⁺, 30%), 341 ([M+Na]⁺, 100), 319 ([M+H]⁺, 45). HRMS (ES⁺) found: 341.1109 (C₁₆H₁₈O₅N₂Na requires [M+Na]⁺ 341.1108).

**Ethyl-2-diazo-3-(2’,5’-diphenyl-1’,3’-dioxan-2’-yl)-3-oxopropanoate (206, 211):**

Major isomer 206:

Similar to procedure A7, MnO₂ (2.07 g, 23.8 mmol) was added to a solution of 196 (0.91 g, 2.38 mmol) in DCM (20.0 ml). Purification by flash column chromatography (DCM/EtOAc : 9/1) afforded the title diazodiketone 206 (0.60 g, 66%) as a yellow solid.
Similar to procedure A8, to a solution of IBX (0.29 g, 1.02 mmol) in DMSO (5.00 ml) was added a solution of 196 (0.26 g, 0.68 mmol) in DMSO (7.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone 206 (0.24 g, 93%) as a clear oil.

![Chemical structure](image1)

mp.: 138-140 °C. νmax (ATR) : 2922, 2130 (C=N₂), 1727 (COC=N₂), 1695, 1667 (COOEt), 1599, 1494, 1394, 1249, 1038, 892, 753, 704, 668, 618 cm⁻¹. δH (500 MHz; CDCl₃) : 7.61-7.59 (2H, m, Ar-H), 7.43-7.41 (2H, m, Ar-H), 7.35-7.32 (2H, m, Ar-H), 7.29-7.25 (2H, m, Ar-H), 7.18 (2H, d, J 8.0, Ar-H), 4.31-4.21 (6H, m, OCH₂CH₃, 4'-Hₑq, 6'-Hₑq, 4'-Hₐx, 6'-Hₐx), 3.39-3.33 (1H, m, 5'-H), 1.29 (3H, t, J 7.1, OCH₂CH₃). δC (125 MHz; CDCl₃) : 186.2 (C-3), 161.3 (C-1), 136.8 (Ar-C), 133.9 (Ar-C), 129.6 (Ar-C), 128.9 (Ar-C), 128.4 (Ar-C), 127.9 (Ar-C), 127.7 (Ar-C), 125.7 (Ar-C), 100.7 (C-2'), 66.5 (C-2), 68.3 (C-⁴', C-⁶'), 61.9 (OCH₂CH₃), 40.3 (C-⁵'), 14.2 (OCH₂CH₃). m/z (ES⁺) : 783 ([2M+Na]⁺, 90%), 381 ([M+H]⁺, 100). HRMS (ES⁺) found: 403.1262 (C₂₁H₂₀O₅N₂Na requires [M+Na]⁺ 403.1264).

Minor isomer 211:

Similar to procedure A7, MnO₂ (0.30 g, 3.40 mmol) was added to a solution of 197 (0.13 g, 0.34 mmol) in DCM (5.00 ml). Purification by flash column chromatography (DCM/EtOAc : 9/1) afforded the title diazodiketone 211 (0.08 g, 62%) as a yellow oil.

![Chemical structure](image2)
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$\nu_{\text{max}}$ (ATR) : 2980, 2131 (C=N$_2$), 1735 (COC=N$_2$), 1684 (COOEt), 1451, 1368, 1299, 1176, 1032, 889, 747, 700, 667 cm$^{-1}$. $\delta$H (500 MHz; CDCl$_3$) : 7.52 (2H, d, J 8.3, Ar-H), 7.48-7.41 (3H, m, Ar-H), 7.28-7.21 (3H, m, Ar-H), 7.12 (2H, d, J 7.3, Ar-H), 4.31-4.27 (4H, m, OCH$_3$CH$_3$, 4'-H$_{ax}$, 6'-H$_{eq}$), 4.10-4.05 (2H, m, 4'-H$_{ax}$, 6'-H$_{ax}$), 3.27-3.21 (1H, m, 5'-H), 1.30 (3H, t, J 7.1, OCH$_2$CH$_3$). $\delta$C (125 MHz; CDCl$_3$) : 183.6 (C-3), 162.0 (C-1), 138.2 (Ar-C), 134.0 (Ar-C), 129.4 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 127.62 (Ar-C), 127.61 (Ar-C), 127.5 (Ar-C), 101.9 (C-2'), 66.8 (C-4', C-6'), 66.0 (C-2'), 61.9 (OCH$_2$CH$_3$), 39.6 (C-5'), 14.3 (OCH$_2$CH$_3$). m/z (ES$^+$) : 783 ([2M+Na]$^+$, 100%). HRMS (ES$^+$) found: 403.1264 (C$_{21}$H$_{20}$O$_3$N$_2$Na requires [M+Na]$^+$ 403.1264).

Ethyl-3-(5'-benzyl-2'-phenyl-1',3'-dioxan-2'-yl)-2-diazo-3-oxopropanoate (207) :

Similar to procedure A8, to a solution of IBX (0.19 g, 0.68 mmol) in DMSO (5.00 ml) was added a solution of 198 (0.18 g, 0.45 mmol) in DMSO (7.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone 207 (0.18 g, 100%) as a clear oil.

$\nu_{\text{max}}$ (ATR) : 2978, 2127 (C=N$_2$), 1735 (COC=N$_2$), 1684 (COOEt), 1451, 1368, 1299, 1176, 1032, 889, 747, 700, 667 cm$^{-1}$. $\delta$H (500 MHz; CDCl$_3$) : 7.51 (2H, d, J 7.0, 2b''-H), 7.37 (3H, m, 3b''-H, 4b''-H), 7.29 (2H, t, J 7.7, 3a''), 7.22 (1H, t, J 7.7, 4a''-H), 7.12 (2H, d, J 7.7, 2a''-H), 4.27 (2H, q, J 7.2, OCH$_2$CH$_3$), 4.08 (2H, dd, J 12.3, 4.3, 4'-H$_{eq}$, 6'-H$_{eq}$), 3.84 (2H, t, J 12.3, 4'-H$_{ax}$, 6'-H$_{ax}$), 2.45 (2H, d, J 6.1, 5'-CH$_2$Ph), 2.42-2.40 (1H, m, 5'-H), 1.29 (3H, t, J 7.2, OCH$_2$CH$_3$). $\delta$C (125 MHz; CDCl$_3$) : 186.3 (C-3), 161.4 (C-1), 137.7 (C-1a''), 136.4 (C-1b''), 129.5 (C-4b''), 128.65 (C-3a''), 128.64 (C-2a''), 128.61 (C-3b''), 126.5 (C-4a''), 125.7 (C-2b''), 100.9 (C-2'), 68.1 (C-4', C-6'), 66.8 (C-2), 61.9 (OCH$_2$CH$_3$), 35.2 (C-5'), 34.6 (5'-CH$_2$Ph), 14.2 (OCH$_2$CH$_3$). m/z (ES$^+$) : 458 ([M+Na+CH$_3$CN]$^+$, 70%), 417 ([M+Na]$^+$, 40), 395 ([M+H]$^+$, 20), 253 (100). HRMS (ES$^+$) found: 395.1606 (C$_{22}$H$_{22}$O$_5$N$_2$ requires [M+H]$^+$ 395.1602).
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Ethyl-2-diazo-3-(2’-methyl-5’-(4”’-nitrophenyl-1’,3’-dioxan-2’-yl)-3-oxopropanoate (208):
Similar to procedure A8, to a solution of IBX (0.47 g, 1.68 mmol) in DMSO (10.0 ml) was added a solution of 199 (0.41 g, 1.12 mmol) in DMSO (7.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone 208 (0.41 g, 100%) as a yellow solid.

![Diazo-Ketone Structure](image)

mp.: 148-150 °C. νmax (ATR) : 2989, 2133 (C=N2), 1723 (COC=N2), 1654 (COOEt), 1513+1323 (NO2), 1188, 1134, 1019, 889, 849, 747, 650 cm⁻¹. δH (500 MHz; CDCl3) : 8.17 (2H, d, J 8.6, 3a”-H), 7.31 (2H, d, J 8.6, 2a”-H), 4.36 (2H, q, J 7.1, OCH2CH3), 4.13 (2H, dd, J 11.8, 4.5, 4’-H_eq, 6’-H_eq), 3.98 (2H, t, J 11.8, 4’-H_ax, 6’-H_ax), 3.42-3.36 (1H, m, 5’-H), 1.60 (3H, s, 2’-CH3), 1.36 (3H, t, J 7.1, OCH2CH3). δC (125 MHz; CDCl3) : 188.1 (C-3), 161.0 (C-1), 147.4 (C-4a”), 144.2 (C-1a”), 128.6 (C-2a”), 124.0 (C-3a”), 100.6 (C-2’), 68.9 (C-2), 67.2 (C-4’,C-6’), 62.1 (OCH2CH3), 40.2 (C-5’), 24.9 (2’-CH3), 14.3 (OCH2CH3). m/z (ES⁺) : 427 ([M+Na+CH3CN]⁺, 20%), 364 ([M+H]⁺, 10), 222 (100). HRMS (ES⁺) found: 386.0956 (C16H17O3N3Na requires [M+Na]⁺ 386.0959). Anal. [Found: C, 52.3; H, 4.7; N, 11.4. C16H17O3N3 requires C, 52.9; H, 4.7; N, 11.6%].

Ethyl-2-diazo-3-(2’,5’-dimethyl-5’-nitro-1’,3’-dioxan-2’-yl)-3-oxopropanoate (209):
Similar to procedure A8, to a solution of IBX (1.11 g, 3.96 mmol) in DMSO (15.0 ml) was added a solution of 200 (0.80 g, 2.64 mmol) in DMSO (10.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone 209 (0.68 g, 86%) as a yellow solid.

![Diazo-Ketone Structure](image)
mp.: 116-118 °C. νₚₑ₉ (ATR): 2993, 2132 (C=N₂), 1735 (COC=N₂), 1659 (COOEt), 1547+1447 (NO₂), 1306, 1187, 1134, 1071, 1011, 857, 757, 663 cm⁻¹. δₜ (500 MHz; CDCl₃): 4.74 (2H, d, J 13.3, 4'-Hₘₚ, 6'-Hₘₚ), 4.34 (2H, q, J 7.1, OCH₂CH₃), 3.90 (2H, d, J 13.3, 4'-Hₘₚ, 6'-Hₘₚ), 1.51 (3H, s, 2'-CH₃), 1.34 (3H, s, 5'-CH₃), 1.33 (3H, t, J 7.1, OCH₂CH₃). δC (125 MHz; CDCl₃): 186.8 (C-3), 160.6 (C-1), 100.6 (C-2'), 82.1 (C-5'), 70.2 (C-2), 67.1 (C-4',C-6'), 62.2 (OCH₂CH₃), 24.3 (2'-CH₃), 19.3 (5'-CH₃), 14.3 (OCH₂CH₃). m/z (ES⁺): 365 ([M+Na+CH₃CN]⁺, 100%), 342 ([M+CH₃CN]⁺, 30), 324 ([M+Na]⁺, 20). HRMS (ES⁺) found: 324.0800 (C₁₁H₁₅O₃N₃Na requires [M+Na]⁺ 324.0802). Anal. [Found: C, 43.8; H, 5.0; N, 13.8. C₁₁H₁₅O₃N₃ requires C, 43.9; H, 5.0; N, 13.9%].

**Ethyl-2-diazo-4-methyl-3-oxohexanoate (226)**:

Similar to procedure A8, to a solution of IBX (1.72 g, 6.15 mmol) in DMSO (15.0 ml) was added a solution of the alcohol 220 (0.82 g, 4.10 mmol) in DMSO (5.00 ml). Subsequent purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone 226 (0.65 g, 80%) as a shiny yellow oil.

![Ethyl-2-diazo-4-methyl-3-oxohexanoate](image)

νₚₑ₉ (ATR): 2970, 2130 (C=N₂), 1712 (COC=N₂), 1663 (COOEt), 1458, 1372, 1292, 1021, 977, 751 cm⁻¹. δₜ (500 MHz; CDCl₃): 4.26 (2H, q, J 7.2, OCH₂CH₃), 3.42 (1H, q, J 6.9, 4-H), 1.73-1.66 (1H, m, 5-HH), 1.39-1.32 (1H, m, 5-HH), 1.29 (3H, t, J 7.2, OCH₂CH₃), 1.06 (3H, d, J 6.9, 4-C₃H₃), 0.87 (3H, t, J 7.6, 6-H₃). δC (125 MHz; CDCl₃): 196.7 (C-3), 161.1 (C-1), 75.6 (C-2), 61.2 (OCH₂CH₃), 43.2 (C-4), 26.2 (C-5), 16.0 (4-C₃H₃), 14.2 (OCH₂CH₃), 11.5 (C-6). m/z (ES⁺): 418 ([2M+Na]⁺, 40%), 262 ([M+Na+CH₃CN]⁺, 85), 221 ([M+Na]⁺, 100). HRMS (ES⁺) found: 221.0898 (C₉H₁₄O₃N₃Na requires [M+Na]⁺ 221.0897).

**Ethyl-2-diazo-3-oxo-3-(4'-trifluoromethylphenyl)propanoate (227)**:

Similar to procedure A8, to a solution of IBX (0.55 g, 1.98 mmol) in DMSO (10.0 ml) was added a solution of the alcohol 221 (0.38 g, 1.32 mmol) in DMSO (5.00 ml). Subsequent purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone 227 (0.38 g, 100%) as a yellow oil.
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\[ \text{Ethy-2-diazo-3-(4'-methoxyphenyl)-3-oxopropanoate (228):} \]

Similar to procedure A8, to a solution of IBX (0.12 g, 0.42 mmol) in DMSO (10.0 ml) was added a solution of the alcohol 222 (0.07 g, 0.28 mmol) in DMSO (5.00 ml). Subsequent purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone 228 (65 mg, 93%) as a yellow oil.

\[ \text{\[M+Na\]}^+ \text{ requires [M+Na]}^+ \text{309.0458}. \]

\[ \nu_{\text{max}} \text{(ATR)} : 2980, 2840, 2139 (C=\text{N}_2), 1715 (\text{COCN}_2), 1598 (\text{COOEt}), 1460, 1367, 1249, 1107, 1018, 839, 757, 692, 613 \text{ cm}^{-1}. \delta_{\text{H}} \text{(500 MHz; CDCl}_3) : 7.66 (2\text{H, d, J 8.7, Ar-H}), 4.26 (2\text{H, q, J 7.1, OCH}_2\text{CH}_3), 3.85 (3\text{H, s, OCH}_3), 1.28 (3\text{H, t, J 7.1, OCH}_2\text{CH}_3). \delta_{\text{C}} \text{(125 MHz; CDCl}_3) : 185.3 \text{(C-3), 163.1 \text{(C-1), 161.3 (C-4'), 131.0 (C-1'), 129.3 (Ar-C), 113.1 (Ar-C), 75.6 (C-2), 61.5 (OCH}_2\text{CH}_3), 55.4 \text{(OCH}_3), 14.2 \text{(OCH}_2\text{CH}_3). m/z \text{(ES}^+) : 519 \text{([2M+Na]}^+, 100\%), 312 \text{([M+Na+CH}_3\text{CN]}^+, 55), 271 \text{([M+Na]}^+, 65). HRMS (ES}^+) \text{ found: 271.0692 (C}_{12}\text{H}_{12}\text{O}_4\text{N}_2\text{Na requires [M+Na]}^+ \text{271.0689}.} \]
Ethyl-2-diazo-3-oxo-3-phenylpropanoate (229):
Similar to procedure A8, to a solution of IBX (0.73 g, 2.59 mmol) in DMSO (18.0 ml) was added a solution of the alcohol 223 (0.38 g, 1.73 mmol) in DMSO (8.00 ml). Subsequent purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone 229 (0.36 g, 96%) as a yellow oil.

\[
\text{OEt} \quad \text{N}_2 \quad \text{OEt}
\]

\[\nu_{\text{max}} (\text{ATR}) : 2983, 2139 (C=\text{N}_2), 1717 (\text{COCN}_2), 1625 (\text{COOEt}), 1447, 1368, 1291, 1109, 1010, 931, 786, 744, 697, 536 \text{ cm}^{-1}. \delta_{\text{H}} (500 \text{ MHz; CDCl}_3) : 7.62 (2\text{H, d, J} 7.3, \text{Ar-H}), 7.52 (1\text{H, t, J} 7.3, \text{Ar-H}), 7.41 (2\text{H, t, J} 7.3, \text{Ar-H}), 4.24 (2\text{H, q, J} 7.0, \text{OCH}_2\text{CH}_3), 1.24 (3\text{H, t, J} 7.0, \text{OCH}_2\text{CH}_3). \delta_{\text{C}} (125 \text{ MHz; CDCl}_3) : 186.8 (\text{C-3}), 160.9 (\text{C-1}), 137.1 (\text{Ar-C}), 132.2 (\text{Ar-C}), 128.3 (\text{Ar-C}), 127.8 (\text{Ar-C}), 76.1 (\text{C-2}), 61.5 (\text{OCH}_2\text{CH}_3), 14.1 (\text{OCH}_2\text{CH}_3). m/z (\text{ES}^+) : 459 ([2\text{M+Na}]^+, 100%), 282 ([\text{M+Na+CH}_3\text{CN}]^+, 75), 241 ([\text{M+Na}]^+, 80). \text{HRMS (ES}^+) \text{ found: 241.0586 (C}_{11}\text{H}_{10}\text{O}_3\text{N}_2\text{Na requires [M+Na]}^+ 241.0584).}

Ethyl-2-diazo-3-oxo-4-phenylbutanoate (230):
Similar to procedure A8, to a solution of IBX (0.20 g, 0.71 mmol) in DMSO (10.0 ml) was added a solution of the alcohol 224 (0.11 g, 0.47 mmol) in DMSO (5.00 ml). Subsequent purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone 230 (0.07 g, 64%) as a yellow oil.

\[
\text{OEt} \quad \text{N}_2 \quad \text{O}
\]

\[\nu_{\text{max}} (\text{ATR}) : 2982, 2133 (C=\text{N}_2), 1709 (\text{COCN}_2), 1649 (\text{COOEt}), 1493, 1369, 1293, 1120, 1028, 854, 743, 711, 630, 532 \text{ cm}^{-1}. \delta_{\text{H}} (500 \text{ MHz; CDCl}_3) : 7.35-7.23 (5\text{H, m, Ar-H}), 4.33 (2\text{H, q, J} 7.2, \text{OCH}_2\text{CH}_3), 4.21 (2\text{H, s, 4-H_2}), 1.35 (3\text{H, t, J} 7.2, \text{OCH}_2\text{CH}_3). \delta_{\text{C}} (125 \text{ MHz; CDCl}_3) : 190.2 (\text{C-3}), 161.2 (\text{C-1}), 134.0 (\text{Ar-C}), 129.7 (\text{Ar-C}), 128.5 (\text{Ar-C}), 127.0 (\text{Ar-C}), 76.2 (\text{C-2}), 61.5 (\text{OCH}_2\text{CH}_3), 45.7 (\text{C-4}), 14.3 (\text{OCH}_2\text{CH}_3). m/z (\text{ES}^+) : 479 (100%), 296
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(E) Ethyl-2-diazo-3-oxo-5-phenylpent-4-enoate (231):
To a solution of ethyldiazoacetate (0.19 ml, 1.82 mmol) in DMSO (8.00 ml) at room temperature was added, in succession, DBU (0.02 ml, 0.15 mmol), cinnamaldehyde 219 (0.19 ml, 1.52 mmol) and a solution of IBX (0.85 g, 3.03 mmol) in DMSO (10.0 ml). The reaction mixture was then stirred at room temperature. After 10 h, the reaction was quenched with aqueous NaHCO3 (15.0 ml) and then extracted with DCM (3 × 20.0 ml). The combined organic layers were copiously washed with aqueous NaHCO3 (3 × 40.0 ml) and water, dried over MgSO4, filtered and concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 8/2) to afford the title diazodiketone 231 (0.22 g, 60%) as a yellow solid.

(Z)-ethyl-2-(1'-methyl-4'-phenyl-2',6',8'-trioxabicyclo[3.2.1]octan-7'-ylidene)acetate (235):
To a solution of rhodium (II) perfluorobutyrate catalyst, Rh2(CO2C3F7)4 (9.30 mg, 0.0088 mmol, 1 mmol/L, 5 mol%), in DCM (8.80 ml), was slowly added a solution of diazodiketone 205 (56 mg, 0.18 mmol, 100 mmol/L) in DCM (1.76 ml) at room temperature. The slow addition was achieved using a syringe pump with the reaction mixture stirred for 16 h. Upon
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complete addition, silica gel was added and the reaction mixture concentrated in vacuo. The residue was then immediately purified by flash column chromatography (petroleum ether/EtOAc : 8/2) affording the O-H insertion product 235 as an oil (20 mg, 39%)

\[
\begin{align*}
\text{EtO} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

\[\nu_{\text{max}}\ (\text{ATR}) : 1705 \ (\text{C}-\text{O}), 1656 \ (\text{COOEt}), 1495, 1304, 1113, 1019, 948, 823, 702, 617 \ \text{cm}^{-1} \]

\[\delta_{\text{H}} \ (500 \ \text{MHz}; \ \text{CDCl}_3) : 7.41 \ (2\text{H}, \text{d}, J \ 7.2, \text{Ar-H}), 7.35 \ (2\text{H}, \text{t}, J \ 7.2, \text{Ar-H}), 7.31 \ (1\text{H}, \text{d}, J \ 7.2, \text{Ar-H}), 6.00 \ (1\text{H}, \text{s}, 5'-\text{H}), 5.16 \ (1\text{H}, \text{s}, 2'-\text{H}), 4.33 \ (1\text{H}, \text{q}, J \ 7.2, \text{OCHHCH}_3), 4.25 \ (1\text{H}, \text{q}, J \ 7.2, \text{OCHHCH}_3), 4.08-4.00 \ (2\text{H}, \text{m}, 3'-\text{H}_{\text{ax}}, 3'-\text{H}_{\text{eq}}), 3.49-3.45 \ (1\text{H}, \text{m}, 4'-\text{H}), 1.67 \ (3\text{H}, \text{s}, 1'-\text{CH}_3), 1.36 \ (3\text{H}, \text{t}, J \ 7.2, \text{OCH}_2\text{CH}_3).
\]

\[\delta_{\text{C}} \ (125 \ \text{MHz}; \ \text{CDCl}_3) : 165.6 \ (\text{C}-1), 162.7 \ (\text{C}-7', \text{enol ether}), 135.0 \ (\text{C}-1'''), 128.8 \ (\text{Ar-C}), 128.7 \ (\text{Ar-C}), 128.0 \ (\text{Ar-C}), 106.3 \ (\text{C}-5''), 103.5 \ (\text{C}-1''), 88.5 \ (\text{C}-2), 66.6 \ (\text{C}-3''), 60.2 \ (\text{OCH}_2\text{CH}_3), 45.5 \ (\text{C}-4''), 20.0 \ (1'-\text{CH}_3), 14.3 \ (\text{OCH}_2\text{CH}_3). m/z \ (\text{ES}^+) : 354 ([\text{M+Na+CH}_3\text{CN}]^+, 20\% ), 313 ([\text{M+Na}]^+, 70\%), 291 ([\text{M+H}]^+, 100\%). \text{HRMS} \ (\text{ES}^+) \ \text{found:} \ 313.1044 \ (\text{C}_{16}\text{H}_{18}\text{O}_5\text{Na requires} \ [\text{M+Na}]^+ \ 313.1047).
\]

(Z)-ethyl-4-methyl-2-oxo-7-phenyl-2,6,7,8-tetrahydro-1,5-dioxocine-3-carboxylate (248) :

Rhodium (II) perfluorobutate, \( \text{Rh}_2(\text{CO}_2\text{C}_3\text{F}_7)_4 \) (5 mol%) solution in benzene (18.0 ml) was maintained at 75 °C and with the aid of a syringe pump, a solution of 205 (0.08 g, 0.25 mmol) in benzene (3.70 ml) was added over a period of 2 h. Upon complete addition, the reaction mixture was allowed to attain room temperature, silica gel was added and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8) to give the title lactone 248 as an oil (0.03 g, 40%).

Alternatively, rhodium (II) perfluorobutate, \( \text{Rh}_2(\text{CO}_2\text{C}_3\text{F}_7)_4 \) (5 mol%) solution in toluene (10.0 ml) placed in a microwave vial (20.0 ml) was argon flushed and maintained at 70 °C. After 2 min, a solution of diazoketone acetal 205 (0.08 g, 0.25 mmol) in toluene (5.00 ml) was added and the vial was immediately placed into the reactor at 70 °C for 15 min. The
reaction mixture was then allowed to attain room temperature, silica gel was added and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8) to give the title lactone \(248\) as an oil (0.03 g, 40%).

\[
\begin{align*}
\delta_{\text{H}} & (500 \text{ MHz; CDCl}_3) : \\
\delta_{\text{C}} & (125 \text{ MHz; CDCl}_3) : \\
m/z \text{ (El)} & : \\
\text{δC} & (125 MHz; CDCl3) : \\
m/z & (EI) : 290 (M^+ , 30%), 275 (M^+ -Me, 45), 244 (M^+ -OEt, 30), 218 (M^+ -CO_2Et, 5), 117 (100), 104 (70), 91 (PhCH}_2^+ ,40). \text{ HRMS (GCMS, El) found: 290.1146 (C}_{16}H_{18}O_5 \text{ requires M}^+ 290.1149).}
\end{align*}
\]

\(\text{(Z)-ethyl-2-oxo-4,7-diphenyl-2,6,7,8-tetrahydro-1,5-dioxocine-3-carboxylate (249)}:\)
Rhodium (II) perfluorobutyrinate, Rh\(_2\)(CO\(_2\)C\(_3\)F\(_7\))\(_4\) (5 mol\%) solution in toluene (10.0 ml) placed in a microwave vial (20.0 ml) was argon flushed and maintained at 70 °C. After 2 min, a solution of diazodiketone acetal \(206\) (0.07 g, 0.18 mmol) in toluene (5.00 ml) was added and the vial was immediately placed into the reactor at 70 °C for 15 min. The reaction mixture was then allowed to attain room temperature, silica gel was added and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8) to give the title lactone \(249\) as an oil (18 mg, 28%).
(Z)-ethyl-4-methyl-7-(4-nitrophenyl)-2-oxo-2,6,7,8-tetrahydro-1,5-dioxocine-3-carboxylate (250):

Rhodium (II) perfluorobutyrate, Rh₂(CO₂C₅F₇)₄ (5 mol%) solution in toluene (10.0 ml) placed in a microwave vial (20.0 ml) was argon flushed and was maintained at 70 °C. After 2 min, a solution of diazodiketone acetal 208 (0.16 g, 0.44 mmol) in toluene (5.00 ml) was added and the vial was immediately placed into the reactor at 70 °C for 15 min. The reaction mixture was then allowed to attain room temperature, silica gel was added and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8) to give the title lactone 250 as an oil (0.07 g, 47%).

υ<sub>max</sub> (ATR) : 2978, 1724 (C=O), 1608 (C=C), 1520+1350(NO₂), 1350, 1180, 1116, 1030, 946, 852, 812, 752, 706 cm⁻¹. δ<sub>H</sub> (400 MHz, CDCl₃) : 8.17 (2H, d, J 8.7, 3'-H), 7.57 (2H, d, J 8.7, 2'-H), 4.31 (2H, d, J 7.1, 8-H₂), 4.21 (2H, q, J 7.1, 3-CO₂CH₂CH₃), 4.03 (1H, dd, J 11.5, 2.2, 6-HH), 3.94 (1H, dd, J 11.5, 4.8, 6-HH), 3.28-3.23 (1H, m, 7-H), 2.43 (3H, s, 4-CH₃), 1.27 (3H, t, J 7.1, 3-CO₂CH₂CH₃). δ<sub>C</sub> (100 MHz; CDCl₃) : 168.7 (C-4, enol ether), 167.9 (C-2), 166.0 (3-CO₂CH₂CH₃), 147.7 (C-4'), 142.4 (C-1'), 129.0 (C-2'), 123.8 (C-3'), 100.2 (C-3), 68.2 (C-6), 68.0 (C-8), 60.3 (3-CO₂CH₂CH₃), 45.4 (C-7), 19.9 (4-CH₃), 14.3 (3-CO₂CH₂CH₃).
m/z (EI) : 335 (M+, 10%), 320 (M+-Me, 5), 290 (M+-OEt, 20), 262 (M+-CO2Et, 5), 149 (100), 104 (20). HRMS (ASAP+) found: 336.1071 (C16H18O7N requires [M+H]+ 336.1083).

(Z)-ethyl-4,7-dimethyl-7-nitro-2-oxo-2,6,7,8-tetrahydro-1,5-dioxocine-3-carboxylate (251):
Rhodium (II) perfluorobutyrate, Rh2(CO2C3F7)4 (5 mol%) solution in toluene (10.0 ml) placed in a microwave vial (20.0 ml) was argon flushed and maintained at 75 °C. After 2 min, a solution of diazodiketone acetal 209 (0.28 g, 0.93 mmol) in toluene (5.00 ml) was added and the vial was immediately placed into the reactor at 70 °C for 15 min. The reaction mixture was then allowed to attain room temperature, silica gel was added and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8) to give the title lactone 251 as an oil (0.08 g, 30%).

\[
\text{H}_2\text{C} = \text{O} \text{Et} \text{O} \text{N} \text{O} \text{C} \text{H}_3
\]

\(\nu_{\text{max}}\) (ATR) : 2985, 1720 (C=O), 1607 (C=C), 1549+1458 (NO2), 1380, 1299, 1244, 1155, 1067, 907, 864, 820, 766, 637 cm\(^{-1}\). \(\delta_H\) (700 MHz, CDCl3) : 4.91 (1H, d, J 12.9, 8-HH), 4.70 (1H, d, J 13.9, 6-HH), 4.45 (1H, d, J 12.9, 8-HH), 4.28 (1H, d, J 13.9, 6-HH), 4.21 (2H, q, J 7.1, 3-CO2CH2CH3), 2.21 (3H, s, 4-CH3), 1.68 (3H, s, 7-CH3), 1.27 (3H, t, J 7.1, 3-CO2CH2CH3). \(\delta_C\) (175 MHz; CDCl3) : 167.4 (C-4, enol ether), 165.9 (C-2), 165.4 (3-CO2CH2CH3), 101.0 (C-3), 87.4 (C-7), 68.3 (C-6), 67.1 (C-8), 61.9 (3-CO2CH2CH3), 21.2 (4-CH3), 20.2 (7-CH3), 13.9 (3-CO2CH2CH3). m/z (EI) : 273 (M+, 20%), 258 (M+-Me, 10), 228 (M+-OEt, 40), 160 (100), 129 (20), 100 (30), 69 (80). HRMS (GCMS, EI) found: 273.0845 (C11H15O5N requires M+ 273.0843).

(Z)-4-methyl-7-phenyl-3-ethenyl-7,8-dihydro-1,5-dioxocin-2(6H)-one (284):
Rhodium (II) perfluorobutyrate, Rh2(CO2C3F7)4 (5 mol%) solution in toluene (10.0 ml) placed in a microwave vial (20.0 ml) was argon flushed and maintained at 70 °C. After 2 min, a solution of vinyl Diazoketone acetal 279 (0.10 g, 0.37 mmol) in toluene (5.00 ml) was added and the vial was immediately placed into the reactor at 70 °C for 15 min. The reaction mixture was then allowed to attain room temperature, silica gel was added and the solvent was
evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8) to give the title lactone 284 as an oil (0.04 g, 45%).

$\nu_{max}$ (ATR) : 1714 ($C=O$), 1617 ($C=C$), 1494, 1390, 1302, 1258, 1173, 1012, 896, 764, 700, 616 cm$^{-1}$. $\delta_H$ (700 MHz, CDCl$_3$) : 7.37-7.35 (2H, m, Ar-$H$), 7.31-7.30 (3H, m, Ar-$H$), 6.43 (1H, dd, $J_{17.1, 11.1}$, $3'-CH=CH_2$), 5.27 (1H, d, $J_{17.1}$, CH=CH$H$H), 5.13 (1H, d, $J_{11.1}$, CH=CH$H$H), 4.53 (1H, dd, $J_{12.0, 7.2}$, 8-$H$H), 4.50 (1H, dd, $J_{12.0, 4.3}$, 8-$H$H), 4.37 (1H, dd, $J_{13.5, 3.4}$, 6-$H$H), 4.24 (1H, dd, $J_{13.5, 6.8}$, 6-$H$H), 3.35-3.31 (1H, m, 7-$H$), 2.11 (3H, s, 4-$CH_3$). $\delta_C$ (175 MHz; CDCl$_3$) : 169.7 ($C=2$), 157.4 ($C=4$, enol ether), 137.6 ($C=1'$), 131.0 ($3'-CH=CH_2$), 128.9 (Ar-$C$), 128.1 (Ar-$C$), 127.8 (Ar-$C$), 114.2 (3'-CH=CH$_2$), 105.3 (C-3), 68.0 (C-8), 67.4 (C-6), 47.2 (C-7), 19.0 (4-$CH_3$). m/z (ES$^+$) : 308 ([M+Na+CH$_3$CN]$^+$, 20%), 267 ([M+Na]$^+$, 20), 245 ([M+H]$^+$, 60). HRMS (ES$^+$) found: 267.0993 (C$_{15}$H$_{16}$O$_3$Na requires [M+Na]$^+$, 267.0992).

1-ethyl-3-methyl-2-(2',5'-dimethyl-5'-nitro-1',3'-dioxan-2'-yl)malonate (258) :
Rhodium (II) perfluorobutyrate, Rh$_2$(CO$_2$C$_3$F$_7$)$_4$ (5 mol%) solution in a mixture of toluene (5.00 ml) and methanol (5.00 ml) placed in a microwave vial (20.0 ml) was argon flushed and maintained at 70 °C. After 2 min, a solution of vinylidiazoketone 209 (0.11 g, 0.35 mmol) in toluene (5.00 ml) was added and the vial was immediately placed into the reactor at 70 °C for 15 min. The reaction mixture was then allowed to attain room temperature, silica gel was added and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8) to give the title compound 258 as an oil (0.02 g, 18%) together with trace amount of lactone 251.
Chapter IX: Experimental Procedure

\[ \nu_{\text{max}} \text{(ATR)} : 2987, 2953, 1756+1731 \text{ (C=O)}, 1547+1454 \text{ (NO}_2\text{)}, 1383, 1295, 1245, 1112, 1036, 878, 754, 618 \text{ cm}^{-1}. \delta_{\text{H}} \text{ (500 MHz; CDCl}_3\text{)} : 4.54 \text{ (2H, d, J 13.0, 4'-H}_{\text{ax}},6'-H}_{\text{ax}}\text{),} 4.24 \text{ (1H, s, 2-H)}, 4.21 \text{ (3H, q, J 7.1, OCH}_2\text{CH}_3\text{)}, 3.97 \text{ (2H, d, J 13.0, 4'-H}_{\text{eq}},6'-H}_{\text{eq}}\text{),} 3.75 \text{ (3H, s, OCH}_3\text{),} 1.65 \text{ (3H, s, 5'-CH}_3\text{)}, 1.56 \text{ (3H, s, 2'-CH}_3\text{),} 1.27 \text{ (3H, t, J 7.1, OCH}_2\text{CH}_3\text{).} \delta_{\text{C}} \text{ (125 MHz; CDCl}_3\text{)} : 165.9 \text{ (C-3),} 165.3 \text{ (C-1),} 99.1 \text{ (C-2'),} 82.2 \text{ (C-5'),} 64.7 \text{ (C-4',C-6'),} 61.8 \text{ (OCH}_2\text{CH}_3\text{),} 54.1 \text{ (C-2),} 52.7 \text{ (OCH}_3\text{),} 20.8 \text{ (5'-CH}_3\text{),} 20.7 \text{ (2'-CH}_3\text{),} 14.0 \text{ (OCH}_2\text{CH}_3\text{).} m/z \text{ (ASAP}^+\text{)} : 306 \text{ ([M+H]$,^+$, 20%),} 290 \text{ ([M+H-CH}_4\text{]$^+$, 20),} 173 \text{ (15),} 160 \text{ (100). HRMS (ASAP}^+\text{) found: 306.1187 \text{ (C}_{12}\text{H}_{20}\text{O}_3\text{N requires [M+H]}^+$, 100.1%].}

5-benzyl-2-methyl-1,3-dioxane-2-carboxylic acid (390, 391):

To a solution of an isomeric mixture of 147 and 148 (7:3 ratio) (8.50 g, 36.0 mmol) in THF/H$_2$O (1:1, 75.0 ml) was added sodium hydroxide (6.40 g, 0.16 mmol). The reaction was left to stir at room temperature overnight, then it was cooled to 0 °C and treated using a cold 5 M solution of aqueous HCl to pH 1, it was then quickly extracted with EtOAc, the combined organic extracts were dried with MgSO$_4$, filtered and concentrated in vacuo. After purification by flash column chromatography, the two isomers were inseperable and the title acid acetals 390 and 391 (6.04 g, 80%, 7:3) were obtained as a white solid. Recrystallization from petroleum ether afforded the major isomer 390 (3.55 g, 59%).

Major isomer 390:

```
\[
\begin{array}{c}
\text{HO} \\
\text{O} \\
\text{H} \\
\text{O}
\end{array}
\]
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mp.: 99-101 °C. \( \nu_{\text{max}} \text{(ATR)} : 3200-2700 \text{ (COOH),} 1718 \text{ (C=O)}, 1142, 1032, 750, 672 \text{ cm}^{-1}. \delta_{\text{H}} \text{ (400 MHz; CDCl}_3\text{)} : 8.10 \text{ (1H, s, COOH),} 7.30-7.23 \text{ (2H, m, Ar-H)}, 7.23-7.20 \text{ (1H, m, Ar-H)}, 7.20-7.05 \text{ (2H, m, Ar-H),} 3.98 \text{ (2H, dd, J 11.5, 4.2, 4-H}_{\text{eq}},6-H}_{\text{eq}}\text{),} 3.58 \text{ (2H, dd, J 11.5, 10.8, 4-H}_{\text{ax}},6-H}_{\text{ax}}\text{),} 2.40-2.30 \text{ (3H, m, 5-H, 5-CH}_2\text{Ph),} 1.60 \text{ (3H, s, 2-CH}_3\text{).} \delta_{\text{C}} \text{ (100.5 MHz; CDCl}_3\text{)} : 174.0 \text{ (CO),} 137.9 \text{ (C-1'),} 129.2 \text{ (Ar-C),} 128.8 \text{ (Ar-C),} 126.7 \text{ (Ar-C),} 98.2 \text{ (C-2),} 68.3 \text{ (C-4, C-6),} 35.1 \text{ (C-5),} 34.8 \text{ (5-CH}_2\text{Ph),} 25.9 \text{ (2-CH}_3\text{).} m/z \text{ (ES}^+\text{)} : 259.1 \text{ ([M+Na]$,^+$, 100 %). Anal. [Found: C, 66.0; H, 6.8. C}_{13}\text{H}_{16}\text{O}_4 \text{ requires C, 66.1; H, 6.8%].}
```
Minor isomer 391: (as a mixture with the major isomer)

\[
\begin{align*}
\delta_H (400 \text{ MHz; CDCl}_3) & : 7.95 (1\text{H, s, COOH}), 7.40-7.30 (2\text{H, m, Ar-H}), 7.30-7.20 (2\text{H, m, Ar-H}), 7.15-7.05 (1\text{H, m, Ar-H}), 4.04 (2\text{H, dd, } J = 12.2, 2.8, 4-H_{eq}, 6-H_{eq}), 3.84 (2\text{H, dd, } J = 12.2, 2.6, 4-H_{ax}, 6-H_{ax}), 3.05 (2\text{H, d, } J = 7.8, 5-C\text{H}_2\text{Ph}), 1.70-1.60 (1\text{H, m, } 5-H), 1.68 (3\text{H, s, 2-CH}_3). \\
\delta_C (100.5 \text{ MHz; CDCl}_3) & : 175.2 (\text{C-1}), 139.9 (\text{C-1'}, 129.3 (\text{Ar-C}), 128.6 (\text{Ar-C}), 126.6 (\text{Ar-C}), 98.4 (\text{C-2}), 66.0 (\text{C-4, C-6}), 35.2 (\text{C-5}), 35.1 (5-\text{CH}_2\text{Ph}), 25.6 (2-\text{CH}_3). m/z (\text{ES}^+) : 259.1 ([M+Na]^+, 100 \%). \text{ HRMS (ES}^+) \text{ found: 259.0937 (C}_{13}\text{H}_{16}\text{O}_4\text{Na requires [M+Na]^+ 259.0946).}
\end{align*}
\]

**Diazald® (p-Tolylsulfonylmethylnitrosamide) (394) preparation:**

![Diazald® reaction scheme](image)

A total of 20.00 g (105 mmol) of p-toluenesulfonyl chloride 392 was divided into 3 portions of 11.9, 5.60 and 2.50 g. A 25 M solution of NaOH (4.40 g) was prepared by dissolving the amount in 4.40 ml H\text{2O} with cooling. The first portion (11.9 g) was added over 5 min to 10.9 ml of 40% solution of methylamine 393. The temperature was kept at 80-90 °C in order to maintain the sulfonylmethylamine (m.p. 78 °C) in molten condition. The reaction mixture was stirred for a while.
Once the mixture had become acidic, indicated by taking the pH using an indicator paper, 3.10 ml of the alkali solution was added, followed by the immediate addition of the second portion (5.60 g) of the \( p \)-toluenesulfonyl chloride 392. Once the solution had become acidic again, 1.60 ml of the alkali was added followed by the final portion of the \( p \)-toluenesulfonyl chloride 392. When the reaction mixture became acidic, the remainder amount of NaOH was added.

The walls of the reaction flask were rinsed with 5.00 ml of H\(_2\)O and the mixture was heated at 100 °C for 15 min. The hot mixture was carefully poured into 94.0 ml of glacial acetic acid and the original flask was rinsed with 15.6 ml of acetic acid.

The resultant solution was cooled to 7 °C and a solution of 7.75 g of NaNO\(_2\) dissolved in 15.6 ml of H\(_2\)O was added slowly via a dropping funnel over 45 min. Temperature was kept below 10 °C. The reaction mixture was stirred for another 15 min after addition was complete. The nitroso compound separates as yellow crystalline product.

62.5 ml of H\(_2\)O was added to the mixture and the product was separated by suction filtration and washed with 31.0 ml H\(_2\)O. The product 394 was washed again till complete absence of acetic acid odour and dried under vacuum (19.5 g, 87%).

**Diazomethane (395) – non-ethanolic preparation**:\(^5\)

\[
\text{H}_3\text{C}-\text{SO}_3\text{N}^+\text{CH}_3 + \text{ROH} \xrightarrow{\text{KOH}} \text{H}_3\text{C}-\text{SO}_3\text{OR} + \text{CH}_2\text{N}_2 + \text{H}_2\text{O}
\]

\( R=\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2)_2\text{O} \)

A solution of Diazald\(^\circ\) 394 (10.0 g, 46.7 mmol) in 60.0 ml of anhydrous ether was slowly dripped into a mixture of KOH (2.80 g, 50.0 mmol) and di(ethyleneglycol)methylether (16.4 ml, 140 mmol) in 9.40 ml of a 1:1 mixture H\(_2\)O/ether placed at a temperature of 60 °C. The resultant diazomethane 395 was distilled as an ethereal solution.

Additional amount of ether (20.0–60.0 ml) was dripped into the distilling mixture till the distillate is colourless. The resultant ethereal solution is assumed to have 32.7 mmol of diazomethane 395 according to the literature. (70%)
Chapter IX: Experimental Procedure

1-(5’-benzyl-2’-methyl-1’,3’-dioxane-2’-yl)-2-diazoethanone (397):
To a solution of acid acetal 390 (0.55 g, 2.30 mmol) in DCM at -20 °C was added triethylamine, (Et₃N, 0.45 ml, 3.30 mmol) and isobutylchloroformate, (iBuOCOCl, 0.36 ml, 2.80 mmol). After 2 h (reaction followed by TLC), an excess of an ethereal solution of diazomethane 395 (CH₂N₂, 15.5 ml, 5.06 mmol) was added. The reaction mixture was allowed to warm up to room temperature and stirred overnight. When the reaction was complete, argon was bubbled through the solution with vigorous stirring and a small amount of dilute acetic acid was added to remove the excess diazomethane. The resulting mixture was successively washed with ammonium chloride (NH₄Cl), sodium bicarbonate (NaHCO₃) and brine. The organic phase was dried over magnesium sulphate (MgSO₄), filtered and concentrated in vacuo. The residue was then purified by flash column chromatography on silica gel (Petroleum ether/EtOAc: 9:1 then 8:2) to give the title diazoketone 397 (0.50 g, 85%) as a yellow solid.

mp.: 63-65 °C. νmax (ATR) : 3131, 2974-2871, 2107 (C=N₂), 1626 (C=O), 1335,1331, 1023, 829, 730, 700, 670 cm⁻¹. δH (400 MHz; CDCl₃) : 7.32-7.28 (2H, m, Ar-H), 7.23-7.10 (3H, m, Ar-H), 5.70 (1H, s, 2'-H), 3.85 (2H, dd, J 11.6, 4.5, 4'-Heq, 6'-Heq), 3.52 (2H, t, J 11.6, 4'-Hax, 6'-Hax), 2.40-2.30 (3H, m, 5'-H, 5'-CH₂Ph), 1.40 (3H, s, 2'-CH₃). δC (100.5 MHz; CDCl₃) : 194.4 (C-1), 138.0 (C-1’), 128.9 (Ar-C), 128.8 (Ar-C), 126.7 (Ar-C), 100.7 (C-2’), 67.8 (C-4’, C-6’), 53.8 (C-2), 35.2 (C-5’), 34.9 (5’-CH₂Ph), 26.1 (2’-CH₃). m/z (ES⁺) : 283.1 ([M+Na]+, 100 %). Anal. [Found : C, 64.2; H, 6.3; N, 10.4. C₁₄H₁₆N₂O₃ requires C, 64.6; H, 6.2; N, 10.7%].

4-benzyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-7-one (398):
A solution of diazoketone 397 (0.23 g, 0.89 mmol) in DCM (8.90 ml) making a solution of 100 mmol/L was added dropwise into a 1 mmol/L solution of rhodium (II) acetate dimer, Rh₂(OAc)₄ (7.80 mg, 0.018 mmol) in DCM (18.0 ml) over 24 h via a syringe pump at room temperature. When the addition was complete, silica gel was added and the reaction mixture was concentrated in vacuo. The residue was then immediately purified by flash column
chromatography (petroleum ether/EtOAc : 9/1), to give the C-H insertion product 398 (0.10 g, 50%) as a white solid.

\[\text{mp.: 80-82 °C. } \delta_{\text{H}}(400 \text{ MHz; CDCl}_3) : 7.30-7.25 (2H, m, 3'-\text{H}), 7.22-7.15 (1H, m, 4'-\text{H}), 7.12 (2H, d, J 7.2, 2'-\text{H}), 4.55 (1H, ddd, J 7.5, 3.4, 1.0, 5'-\text{H}), 3.88 (1H, ddd, J 12.1, 5.8, 1.0, 3-\text{H}_{eq}), 3.63 (1H, t, J 12.1, 3-\text{H}_{eq}), 2.85-2.80 (1H, m, 4'-\text{H}), 2.63 (1H, dd, J 18.4, 7.5, 6-\text{HH}), 2.48 (1H, d, J 18.4, 6-\text{HH}), 2.38 (2H, d, J 8.1, 4-\text{CH}_3\text{Ph}), 1.35 (3H, s, 1-\text{CH}_3). \delta_{\text{C}} (100.5 \text{ MHz; CDCl}_3) : 211.0 (\text{C-7}), 137.4 (\text{C-1'}), 128.9 (\text{Ar-C}), 128.6 (\text{Ar-C}), 126.8 (\text{Ar-C}), 98.0 (\text{C-1}), 74.5 (\text{C-5}), 66.0 (\text{C-3}), 38.8 (\text{C-4}), 35.9 (\text{C-6}), 34.8 (4-\text{CH}_3\text{Ph}), 18.2 (1-\text{CH}_3). \text{m/z (Cl, NH}_3) : 250 (\text{[M+NH}_4]^+, 29\%), 233 (\text{[M+H]^+}, 100), 217 (12), 203 (20), 187 (10), 144 (25), 129 (10), 91 (\text{PhCH}^+, 18), 77 (\text{Ph}^+, 5). \text{HRMS (ES}^+) \text{ found: 255.1223 (C}_{14}\text{H}_{16}\text{O}_3\text{Na requires [M+Na}]^+ 255.1259). \text{Anal. [Found: C, 71.3; H, 7.0. C}_{14}\text{H}_{16}\text{O}_3 \text{Na requires C, 71.4; H, 6.9%].}

\[(7R)-4\text{-benzyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (399)} :\]

NaBH\textsubscript{4} (0.02 g, 0.52 mmol) was added to a solution of bicyclic ketone 398 (0.10 g, 0.43 mmol) in MeOH (20.0 ml) at room temperature and the reaction mixture stirred at room temperature overnight. It was then diluted with DCM, saturated solution of ammonium chloride (NH\textsubscript{4}Cl) was added and the organic layer was then separated and washed with brine (NaCl). The organic extracts were dried over magnesium sulphate (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. The residue was then purified by flash column chromatography on silica gel (petrol/EtOAc: 8/2 then 7/3) to give alcohol 399 as a white crystalline solid (0.07 g, 70%).
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\( \nu_{\text{max}} \) (ATR) : 3670-2950 (broad OH), 1632, 1262, 1160, 1068, 1050, 745, 700, 702, 550 cm\(^{-1}\).

\( \delta_H \) (400 MHz; CDCl\(_3\)) : 7.21 (2H, t, J 7.2, 3'-H), 7.15 (1H, t, J 7.2, 4'-H), 7.05 (2H, d, J 7.2, 2'-H), 4.10 (1H, ddd, J 7.7, 2.9, 1.4, 5-H), 4.05 (1H, dd, J 11.0, 3.8, 7-H), 3.83 (1H, t, J 11.7, 3-H\(_{ax}\)), 3.77 (1H, ddd, J 11.7, 5.8, 1.3, 3-H\(_{eq}\)), 2.52-2.45 (1H, m, 4-H), 2.43 (1H, ddd, J 13.6, 11.0, 7.7, 6-HH), 2.28 (2H, m, 4-CH\(_2\)Ph), 1.93 (1H, bs, OH), 1.79 (1H, dd, J 13.6, 3.8, 6-HH), 1.31 (3H, s, 1-CH\(_3\)). \( \delta_C \) (100.5 MHz; CDCl\(_3\)) : 138.2 (C-1'), 128.8 (C-2', C-3'), 126.6 (C-4'), 120.7 (C-1), 77.1 (C-5), 75.4 (C-7), 65.7 (C-3), 38.9 (C-4), 35.0 (4-CH\(_2\)Ph), 32.7 (C-6), 22.2 (1-CH\(_3\)). m/z (ES\(^+\)) : 289.1 ([M+Na+MeOH]\(^+\), 100%), 257.1 ([M+Na]\(^+\), 39). Anal. [Found: C, 71.3; H, 7.7. C\(_{14}\)H\(_{18}\)O\(_3\) requires C, 71.7; H, 7.7%].

(7R)-4-benzyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-7-yltrifluoromethanesulfonate (412):

To a solution of the bicyclic alcohol 399 (0.18 g, 0.77 mmol) in DCM (10.0 ml), maintained at 0 °C was added 2,6-lutidine (0.28 ml, 2.31 mmol), after 30 min trifluoromethane sulfonic anhydride (Tf\(_2\)O, 0.40 ml, 2.31 mmol) was added dropwise, then the reaction was allowed to attain room temperature and stirred overnight. A saturated solution of brine (NaCl) was then added. The organic phase was separated and was successively washed with water (3 × 15.0 ml) and 1M CuSO\(_4\) (5 × 10.0 ml), dried using MgSO\(_4\), filtered and concentrated in vacuo. Following flash column chromatography using petroleum ether/EtOAc (8/2), the triflate product 412 was obtained (0.22 g, 78%) as a clear oil.

\( \nu_{\text{max}} \) (ATR) : 1454, 1413+1202 (OSO\(_2\)), 1391, 1246, 1142, 1035, 977, 949, 883, 734 cm\(^{-1}\). \( \delta_H \) (500 MHz; CDCl\(_3\)) : 7.30 (2H, t, J 7.4, 3'-H), 7.23 (1H, t, J 7.4, 4'-H), 7.11 (2H, d, J 7.4, 2'-H), 4.94 (1H, ddd, J 10.9, 3.7, 7-H), 4.22 (1H, d, J 7.7, 5-H), 3.89 (1H, dd, J 12.0, 5.8, 3-H\(_{eq}\)), 3.78 (1H, t, J 12.0, 3-H\(_{ax}\)), 2.71 (1H, ddd, J 14.5, 10.9, 6-HH), 2.63-2.56 (1H, m, 4-H), 2.41-2.32 (2H, m, 4-CH\(_2\)Ph), 2.12 (1H, dd, J 14.5, 3.7, 6-HH), 1.45 (3H, s, 1-CH\(_3\)). \( \delta_C \) (125 MHz; CDCl\(_3\)) : 137.4 (C-1'), 128.7 (C-3'), 128.6 (C-2'), 126.7 (C-4'), 118.6 (q, J 321.2, CF\(_3\)), 100.9 (C-1), 86.4 (C-7), 76.6 (C-5), 65.2 (C-3), 38.4 (C-4), 34.7 (4-CH\(_2\)Ph), 30.1 (C-6), 21.9 (1-CH\(_3\)). m/z (ES\(^+\)) : 479 (15%), 415 (9), 381 (10), 240 ([M-OTf+Na]\(^+\), 100). HRMS (ES\(^+\)) found: 217.1225 (C\(_{14}\)H\(_{17}\)O\(_2\) requires [M-OTf]\(^+\) 217.1223).

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(7S)-4-benzyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (413):
Potassium hydroxide (30 mg, 0.54 mmol) was added to a solution of 412 (100 mg, 0.27 mmol) in DMF (10.0 ml). 18-crown-6 (160 mg, 0.54 mmol) was then added and the reaction mixture heated to reflux for 16 hours. An ice-cooled solution of saturated ammonium chloride was added and the mixture was extracted with EtOAc. The organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc : 7/3) to yield an inseparable epimeric mixture of the alcohols 413 and 414 in a ratio of 3:1 respectively, as colourless oils (40 mg, 63%). Following silylation using tert-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), the inverted alcohol 413 was converted to the silylated derivative 415 while the epimer 414 remained unreacted (unsilylated), thus making separation by column chromatography feasible. A subsequent desilylation using excess tetrabutylammonium fluoride (TBAF) in THF at room temperature led to the isolation of the inverted alcohol 413 as a pure compound in 86% overall yield.

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\text{\textbullet} \quad \text{OH}
\]

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\text{\textbullet} \quad \text{H}
\]

\[
\text{\textbullet} \quad \text{O}
\]

\[
\gamma_{\text{max}} (\text{ATR}) : 3620-3170 (\text{broad OH}), 2942, 1604, 1495, 1386, 1269, 1212, 1162, 1034, 990, 740, 700, 662, 629 \text{ cm}^{-1}. \delta_{\text{H}} (700 \text{ MHz}; \text{CDCl}_3) : 7.28 (2H, t, J 7.7, 3'-H), 7.21 (1H, t, J 7.7, 4'-H), 7.10 (2H, d, J 7.7, 2'-H), 4.33 (1H, d, J 7.4, 7-H), 4.25 (1H, dd, J 7.4, 3.0, 5-H), 3.75 (1H, dd, J 11.7, 5.4, 3-H eq), 3.39 (1H, t, J 11.7, 3-H ax), 2.49 (1H, dd, J 13.8, 7.4, 6-HH), 2.47-2.42 (1H, m, 4-H), 2.34 (1H, dd, J 14.0, 7.8, 4-CHPh), 2.28 (1H, dd, J 14.0, 7.8, 4-CHPh), 2.10 (1H, bs, OHH), 1.83 (1H, ddd, J 13.8, 7.4, 3.0, 6-HHH), 1.43 (3H, s, 1-CH₃). \delta_{\text{C}} (175 \text{ MHz}; \text{CDCl}_3) : 138.0 (C-1’), 128.5 (C-2’,C-3’), 126.4 (C-4’), 106.3 (C-1), 76.8 (C-7), 75.3 (C-5), 64.7 (C-3), 38.8 (C-4), 35.5 (C-6), 34.6 (4-CH₂Ph), 19.6 (1-CH₃). m/z (EI) : 234 (M⁺, 2%), 216 (M⁺-H₂O, 5), 157 (M⁺-Ph, 10), 143 (M⁺-CH₂Ph, 10), 91 (CH₂Ph⁺, 100), 77 (Ph⁺, 5). HRMS (ASAP⁺) found: 235.1323 (C₁₄H₁₀O₃ requires [M+H]+ 235.1334).

[(7S)-4-benzyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-7-yloxy]tert-butyl]dimethylsilane (415):
To a solution of epimeric alcohols 413 and 414 (40 mg, 0.17 mmol) in DCM (10.0 ml) at room temperature under argon was added 2,6-lutidine (0.02 ml, 0.12 mmol), followed by tert-
butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf, 0.03 ml, 0.14 mmol). After stirring at room temperature overnight, a saturated solution of aqueous NaCl was added and the mixture was extracted with DCM (3 × 10.0 ml). The combined organic extracts were dried over MgSO\(_4\), filtered and the solvent evaporated under reduced pressure. Purification of the crude residue by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) afforded the title TBDMS protected inverted alcohol 415 as an oil (50 mg, 85%) and the alcohol 414 remained unsilylated (11 mg, 28%) as an impure fraction (413:414/1:1.4).

\[\begin{align*}
\text{\(\nu_{\text{max}}\) (ATR)} & : 3020-2855 (\text{CH}-\text{OSi}), 1496, 1472, 1387, 1258+837 (\text{Si}-\text{CH}_3), 1210, 1165, 1088, 836, 699 \text{ cm}^{-1}. \\
\delta_{\text{H}} & (500 \text{ MHz;} \text{CDCl}_3) : 7.27 (2\text{H, t, } J 7.3, 3'\text{-H}), 7.20 (1\text{H, t, } J 7.3, 4'\text{-H}), 7.10 (2\text{H, d, } J 7.3, 2'\text{-H}), 4.33 (1\text{H, d, } J 7.5, 5\text{-H}), 4.24 (1\text{H, dd, } J 7.5, 3.1, 7\text{-H}), 3.74 (1\text{H, dd, } J 11.5, 5.1, 3\text{-H}_{\text{eq}}), 3.39 (1\text{H, t, } J 11.5, 3\text{-H}_{\text{ax}}), 2.47-2.40 (1\text{H, m, } 4\text{-H}), 1.87 (1\text{H, ddd, } J 13.4, 7.5, 3.1, 6\text{-H H}), 1.37 (3\text{H, s, 1-CCH}_3), 0.91 (9\text{H, s, SiC(CH}_3)_3), 0.10 (3\text{H, s, Si(CH}_3)_2), 0.07 (3\text{H, s, Si(CH}_3)_2). \\
\delta_{\text{C}} & (125 \text{ MHz;} \text{CDCl}_3) : 138.1 (C-1'), 128.6 (C-2',C-3'), 126.4 (C-4'), 106.8 (C-1), 77.2 (C-5), 75.6 (C-7), 64.8 (C-3), 38.8 (C-4), 36.2 (C-6), 34.7 (4-C\text{H}_2\text{Ph}), 25.8 (\text{SiC(CH}_3)_3), 20.0 (1-C\text{H}_3), 18.1 (\text{SiC(CH}_3)_3), -4.6 (\text{SiC(CH}_3)_2), -4.9 (\text{SiC(CH}_3)_2). \\
m/z (\text{ES}^+) & : 371 ([\text{M+Na}]^+, 50\%), 349 ([\text{M+H}]^+, 100). \text{HRMS (ES}^+) \text{ found: 371.2017 (C}_{20}\text{H}_{32}\text{O}_3\text{NaSi requires [M+Na}]^+ 371.2013).}
\end{align*}\]

(2R,3S,5R)-6-benzyl-2-methyloxepane-3,5-diol (416, 417):

To a solution of bicyclic alcohol 413 (30 mg, 0.13 mmol) in DCM (5.00 ml), triethylsilane (Et\(_3\)SiH, 0.08 ml, 0.51 mmol) was added at -78 °C followed by the dropwise addition of 1 M solution of titanium tetrachloride (0.16 ml, 0.16 mmol) in DCM. The reaction mixture was stirred at -78 °C. After 6 h, the reaction mixture was quenched with an aqueous solution of NaCl and extracted with DCM (3 × 20.0 ml). The combined organic extracts were dried over MgSO\(_4\), filtered and concentrated in vacuo. The crude residue, containing a mixture of two oxepane isomers 416 and 417 in a 86:14 ratio, was purified by flash column chromatography...
on silica gel (petroleum ether/EtOAc : 8/2) to give the oxepanediol isomers 416 and 417 as an inseparable mixture (30 mg, 99%).

The analytical data for the major isomer 416 could be extracted from the mixture and is reported below. Unfortunately, the NMR signals for the minor isomer 417 were too weak and are therefore not reported.

\[\text{(2R,3S,5R)-6-benzyl-2-methyloxepane-3,5-diyli diacetate (420, 421):} \]

To a solution of the alcohols 416 and 417 (40 mg, 0.17 mmol) in DCM (10.0 ml), triethylamine (0.24 ml, 1.69 mmol) and a catalytic amount of dimethylaminopyridine (DMAP, 4 mg, 0.03 mmol) were added at room temperature and the reaction mixture stirred for 0.5 h when acetic anhydride (0.06 ml, 0.68 mmol) was added dropwise. After stirring at room temperature for a further 4 h, the reaction was quenched with saturated aqueous NaHCO₃, extracted with DCM (2 × 10.0 ml) and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to give an inseparable mixture (86:14) of the diacetate protected product 420 and 421 as a colourless oil (30 mg, 55%).

The analytical data for the major isomer 420 could be extracted from the mixture and is reported below. Unfortunately, the NMR signals for the minor isomer 421 were too weak and are therefore not reported.
\( \nu_{\text{max}} \) (ATR) : 2974, 1733 (C=O), 1604, 1546, 1364, 1230, 1067, 1023, 907, 748, 701, 606 cm\(^{-1}\).

\( \delta_H \) (700 MHz; CDCl\(_3\)) : 7.28 (2H, t, J 7.4, 3', H), 7.21-7.18 (3H, m, Ar-H), 4.84-4.83 (1H, m, 3-H), 4.02-3.93 (4H, m, 2-H, 5-H, 7-H\(_2\)), 2.96 (1H, dd, J 13.9, 4.7, 6-CH\(_3\)Ph), 2.64 (1H, dd, J 13.9, 9.0, CH\(_3\)Ph), 2.14-2.11 (1H, m, 6-H), 2.06 (3H, s, CH\(_3\)CO), 2.02 (3H, s, CH\(_3\)CO), 1.98 (1H, dd, J 13.7, 6.5, 4-HH), 1.94 (1H, dd, J 13.7, 5.6, 4-HH), 1.29 (3H, d, J 6.5, 2-CH\(_3\)).

\( \delta_C \) (175 MHz; CDCl\(_3\)) : 170.9 (5-CH\(_3\)CO), 170.7 (3-CH\(_3\)CO), 139.5 (C-1'), 129.2 (C-2'), 128.4 (C-3'), 126.1 (C-4'), 79.90 (C-2), 79.86 (C-3), 78.5 (C-5), 63.6 (C-7), 44.0 (C-6), 35.7 (C-4), 34.1 (6-CH\(_3\)Ph), 21.1 (CH\(_3\)CO), 20.9 (CH\(_3\)CO), 19.7 (2-CH\(_3\)).

\( m/z \) (ES\(^+\)) : 343 ([M+Na]\(^+\), 100%), 321 ([M+H]\(^+\), 30), 201 (10), 183 (5). HRMS (ES\(^+\)) found: 343.1518 (C\(_{18}\)H\(_{24}\)O\(_5\)Na requires [M+Na]\(^+\) 343.1516).

\( (4R,6S,7R)-3\)-benzyl-6-hydroxy-7-methyloxepan-4-yl acetate (422, 423) :

To a solution of the mixture of the oxepane diacetates 420 and 421 (30 mg, 0.09 mmol) in MeOH (4.00 ml) under argon at room temperature was added a 0.1 M solution of sodium methoxide (0.58 ml, 0.06 mmol). After stirring the reaction mixture for 2 h, an ion-exchange resin slurry in MeOH was added portionwise to lower the pH of the solution to 4 (as shown by indicator paper). The reaction mixture was then filtered through a sintered glass funnel and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to give a 86:14 ratio of the monoacetate protected product 422 and 423 as an inseparable mixture (7.9 mg, 30%).

The analytical data for the major isomer 422 could be extracted from the mixture and is reported below. Unfortunately, the NMR signals for the minor isomer 423 were too weak and are therefore not reported.
\[ \nu_{\text{max}} \text{(ATR)} : 3480-3308 \text{ (broad } \text{OH}) \]
\[ 2962, 1496, 1454, 1388, 1230, 1067, 1023, 907, 748, 701, 606 \text{ cm}^{-1}. \]
\[ \delta_{\text{H}} \text{(700 MHz; CDCl}_3\text{)} : 7.29-7.26 \text{ (2H, m, Ar-}H\text{)}, 7.20-7.18 \text{ (3H, m, Ar-}H\text{)}, 4.11-4.08 \text{ (1H, m, 6-}H_2\text{)}, 4.01-3.96 \text{ (3H, m, 2-}H_2\text{, 4-}H\text{)}, 3.85-3.82 \text{ (1H, m, 7-}H\text{), 2.94 \text{ (1H, dd, } J = 13.8, 5.1 \text{, 3-CH}_3\text{Ph)}, 2.66 \text{ (1H, dd, } J = 13.8, 9.1 \text{, 3-CH}_3\text{Ph)}, 2.12-2.09 \text{ (1H, m, 3-}H\text{), 2.01 \text{ (3H, s, CH}_3\text{CO}), 1.97-1.92 \text{ (1H, m, 5-}H_3\text{), 1.90-1.87 \text{ (1H, m, 5-}H_3\text{), 1.60 \text{ (1H, bs, } \text{OH})}, 1.25 \text{ (3H, d, } J = 6.4 \text{, 7-}CH_3\text{)}, \delta_{\text{C}} \text{(175 MHz; CDCl}_3\text{)} : 171.0 \text{ (4-CH}_3\text{COO), 139.6 \text{ (C-}1'\text{), 129.2 \text{ (C-}2'\text{), 128.4 \text{ (C-}3'\text{), 126.1 \text{ (C-}4'\text{), 82.2 \text{ (C-}7\text{), 77.9 \text{ (C-}6\text{), 77.8 \text{ (C-}4\text{), 63.7 \text{ (C-}2\text{), 44.2 \text{ (C-}3\text{), 38.4 \text{ (C-}5\text{), 34.1 \text{ (3-}CH_2\text{Ph), 20.9 \text{ (4-CH}_3\text{COO), 19.6 \text{ (7-}CH_3\text{). m/z (ES}^+\text{) : 342 ([M+Na+CH}_3\text{CN}]^+, 100\%), 301, ([M+Na}]^+, 20, 279 ([M+H}]^+, 80), 201 (40), 183 (10).} \]

\text{(2R,3S,5R)-5-acetoxy-6-benzyl-2-methyloxepan-3-yl-4'-bromobenzoate (424, 425)} : To a solution of the alcohols 422 and 423 (10 mg, 0.04 mmol) in DCM (4.00 ml), triethylamine (0.03 ml, 0.18 mmol) and a catalytic amount of dimethylaminopyridine (DMAP) (0.9 mg, 0.01 mmol) were added and the reaction mixture was stirred at room temperature for 0.5 h. 4-bromobenzoyl chloride (20 mg, 0.07 mmol) in DCM (1.00 ml) was then added portionwise to the reaction mixture. After stirring at room temperature for a further 4 h, the reaction was quenched with saturated aqueous NaHCO\textsubscript{3}, and then extracted with DCM (2 \times 10.0 ml) and the combined organic extracts were washed with brine, dried over MgSO\textsubscript{4}, filtered and concentrated in \textit{vacuo}. The crude residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to give a 86:14 ratio of the protected product 424 and 425 as an inseparable mixture (10 mg, 60%).

The analytical data for the major isomer 424 could be extracted from the mixture and is reported below. Unfortunately, the NMR signals for the minor isomer 425 were too weak and are therefore not reported.
\( \nu_{\text{max}} \) (ATR) : 1718 (C=O), 1590, 1484, 1398, 1268, 1234, 1172, 1034, 847, 756, 701 cm\(^{-1}\). \( \delta_H \) (700 MHz; CDCl\(_3\)) : 7.88 (2H, d, \( J = 8.6 \), 2\(^{''}\)-H), 7.59 (2H, d, \( J = 8.6 \), 3\(^{''}\)-H), 7.29 (2H, t, \( J = 7.7 \), 3\(^{'}\)-H), 7.58 (2H, d, \( J = 8.6 \), 7-\( HH \)), 4.08 (1H, m, 3\(^{-}\)-H), 4.13 (2H, m, 2\(^{-}\)-H, 5\(^{-}\)-H), 4.04 (1H, dd, \( J = 11.4 \), 5.9, 7\(^{-}\)-H), 2.98 (1H, dd, \( J = 14.0 \), 5.0, 6-\( CHH \)), 2.68 (1H, dd, \( J = 14.0 \), 8.7, 6-\( CHH \)), 2.13-2.07 (2H, m, 4-\( H_2 \)), 2.02 (3H, s, 5-\( CH_3 \)), 1.36 (3H, d, \( J = 6.5 \), 2-\( CH_3 \)). \( \delta_C \) (175 MHz; CDCl\(_3\)) : 170.9 (5-\( CH_3 \)), 165.5 (3-ArCOO), 139.4 (C-1\(^{-}\)), 131.8 (C-2\(^{-}\)), 131.1 (C-3\(^{-}\)), 129.2 (C-2\(^{-}\)), 128.9 (C-4\(^{-}\)), 128.4 (C-3\(^{-}\)), 128.3 (C-1\(^{-}\)), 126.2 (C-4\(^{-}\)), 80.7 (C-3), 79.9 (C-2), 78.7 (C-5), 63.7 (C-7), 44.0 (C-6), 35.8 (C-4), 34.2 (6-\( CH_2Ph \)), 20.9 (5-\( CH_3COO \)), 19.8 (2-\( CH_3 \)). \( m/z \) (EI) : 460 (M\(^{+}\), 6%), 200 (65), 185 (65), 109 (80), 96 (100), 83 (100), 55 (CH\(_3\)CO\(_2\)\(^{+}\), 2). HRMS (ASAP\(^{+}\)) found: 461.0948 (C\(_{23}\)H\(_{26}\)O\(_5\)\(^{79}\)Br requires [M+H]\(^{+}\) 461.0964).

\( (2R,3S,5R)\)-6-benzyl-2-methyloxepane-3,5-diyl bis(4-bromobenzoate) (426, 427) :

To a solution of the alcohols 416 and 417 (20 mg, 0.06 mmol) in DCM (6.00 ml), triethylamine (0.09 ml, 0.64 mmol) and a catalytic amount of DMAP (8 mg, 0.06 mmol) were added at room temperature and the reaction mixture stirred for 0.5 h when 4-bromobenzoyl chloride (60 mg, 0.25 mmol) in DCM (3.00 ml) was added portionwise. After stirring at room temperature for a further 4 h, the reaction was quenched with saturated aqueous NaHCO\(_3\), extracted with DCM (2 \( \times \) 10.0 ml) and the combined organic extracts were washed with brine, dried over MgSO\(_4\), filtered and concentrated in \textit{vacuo}. The crude residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to give a 86:14 ratio of the bisbenzoate protected product 426 and 427 as an inseparable solid mixture (26 mg, 68%).

The analytical data for the major isomer 426 could be extracted from the mixture and is reported below. Unfortunately, the NMR signals for the minor isomer 427 were too weak and are therefore not reported.
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\[ \text{1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-3-en-1-ol (259, 260):} \]

**Major isomer 259:**

To a stirred solution of aldehyde 176 (2.70 g, 13.1 mmol) in THF (70.0 ml) at -78 °C was added allylmagnesium bromide, 1 M in diethylether (21.0 ml, 21.0 mmol). The cooling bath was removed after the addition and the reaction was stirred at room temperature overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride (NH\(_4\)Cl) solution and extracted with diethylether (3 × 30.0 ml). Combined organic extracts were dried over MgSO\(_4\) and filtrate concentrated in vacuo. The crude residue was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 9:1) to give the title alcohol 259 as a clear oil (3.04 g, 94%).
Minor isomer 260:

To a solution of aldehyde 177 (0.72 g, 3.50 mmol) stirred in THF (20.0 ml) at -78 °C was added a solution of allylmagnesium bromide, 1 M in diethylether (6.00 ml, 5.59 mmol). The cooling bath was removed after the addition and reaction was stirred at room temperature overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride (NH₄Cl) solution and extracted with diethylether (3 × 30.0 ml). Combined organic extracts were dried over MgSO₄ and filtrate concentrated in vacuo. The crude residue was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 9:1, then 8:2) to give the title alcohol 260 as a clear oil (0.80 g, 92%).
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\( \nu_{\text{max}} \) (ATR) : 3570-3304 (OH br), 2873, 1641 (C=\( \equiv \)C), 1495, 1449, 1375, 1247, 1147, 1071, 911, 873, 755, 697 \text{ cm}^{-1}. \delta_{\text{H}} (700 \text{ MHz; CDCl}_3) : 7.34 (2H, t, \( J \ 7.7, 3''-\text{H} \)), 7.28 (1H, d, \( J \ 7.7, 4''-\text{H} \)), 7.21 (2H, d, \( J \ 7.7, 2''-\text{H} \)), 5.98-5.92 (1H, m, 3-\text{H}), 5.18 (1H, dd, \( J \ 17.0, 1.6, 4'-\text{HH} \)), 5.12 (1H, dd, \( J \ 10.1, 1.6, 4-\text{HH} \)), 4.07 (2H, t, \( J \ 11.5, 4'-\text{Heq}, 6'-\text{Heq} \)), 4.02-3.98 (2H, m, 4'-\text{Hax}, 6'-\text{Hax})), 3.60 (1H, td, \( J \ 10.1, 3.5, 1-\text{H} \)), 3.20-3.16 (1H, m, 5'-\text{H})), 2.48 (1H, m, 2-\text{HH})), 2.36 (1H, d, \( J \ 3.5, \text{OH} \)), 2.27-2.22 (1H, m, 2-\text{HH})), 1.53 (3H, s, 2'-\text{CH}_3 \)). \delta_{\text{C}} (175 \text{ MHz; CDCl}_3) : 138.0 (C-1''), 135.8 (C-3), 128.8 (C-3''), 127.6 (C-2''), 127.4 (C-4''), 117.0 (C-4), 99.1 (C-2'), 76.5 (C-1), 64.9 (C-4',C-6'), 41.4 (C-5'), 35.0 (C-2), 13.7 (2'-\text{CH}_3 \)). \text{m/z} \ (\text{ES}^+) : 312 ([M+Na+\text{CH}_3\text{CN}]^+, 100%), 271 ([M+Na]^+, 20), 249 ([M+H]^+, 5). \text{HRMS (ES}^+) \text{found: 271.1299 (C}_{15}\text{H}_{20}\text{O}_3\text{Na requires [M+Na]^+ 271.1305).}

\( \text{(E)}-1-(2'-\text{methyl-5'-phenyl-1',3'-dioxan-2-yl)-4-phenylbut-3-en-1-ol (310) :} \)

To a solution of allyl alcohol 259 (0.10 g, 0.41 mmol) in DCM (3.00 ml) was added styrene 303 (0.23 ml, 2.03 mmol) and the entire solution was agitated for 2 mins to give a homogenous mixture. Reaction flask was then placed in a pre-heated oil bath at 40 °C followed by the immediate addition of Grubbs’s 2\textsuperscript{nd} generation catalyst 305 (0.02 g, 0.02 mmol) in DCM (7.00 ml). After 14 h of reflux under argon, the reaction mixture was concentrated in \textit{vacuo} and the residue was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2 then 7/3) to give alcohol 310 as an off-white crystalline solid (0.11 g, 85%).

\[
\begin{align*}
\text{mp.:} & \ 121-123 \ ^\circ \text{C.} \\
\nu_{\text{max}} \ (\text{ATR}) & : 3491-3350 (\text{OH}), 2910, 1598 (C=\text{C}), 1493, 1451, 1382, 1145, 1076, 970, 864, 755, 696 \text{ cm}^{-1}. \delta_{\text{H}} (700 \text{ MHz; CDCl}_3) : 7.38 (2H, d, \( J \ 7.7, 2a''-\text{H} \)), 7.36-7.33 (4H, m), 7.30 (2H, t, \( J \ 7.7, 3a''-\text{H} \)), 7.27 (1H, t, \( J \ 6.9, 4b''-\text{H} \)), 7.21 (1H, t, \( J \ 7.7, 4a''-\text{H} \)), 6.52 (1H, d, \( J \ 15.9, 4-\text{H} \)), 6.37 (1H, td, \( J \ 15.9, 7.3, 3-\text{H} \)), 4.22-4.17 (3H, m, 1-\text{H}, 4'-\text{Hax}, 6'-\text{Hax}), 4.10 (1H, dd, \( J \ 11.7, 6.9, 4'-\text{Heq} \)), 4.04 (1H, dd, \( J \ 11.7, 6.9, 6'-\text{Heq} \)), 3.04-3.01 (1H, m, 5'-\text{H}), 2.57 (1H, dd, \( J \ 14.6, 7.3, 2-\text{HH} \)), 2.39-2.34 (1H, m, 2-\text{HH})), 2.19 (1H, s, \text{OH}), 1.47 (3H, s, 2'-
\end{align*}
\]
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\[
\text{CH}_3. \quad \delta_{\text{C}} (175 \text{ MHz; CDCl}_3): 140.3 (C-1a'), 137.5 (C-1b'), 132.1 (C-4), 128.6 (C-2b'''), 128.5 (C-3b'''), 127.8 (C-3a''), 127.3 (C-3), 127.07 (C-4b'''), 127.06 (C-4a''), 126.1 (C-2a''), 99.8 (C-2'), 71.2 (C-1), 64.7 (C-4'), 64.2 (C-6'), 39.9 (C-5'), 34.6 (C-2), 17.3 (2'-CH_3). \ m/z (EI): 324 (M^+), 291 (M^+-H_2O), 6, 291 (M^+-H_2O-Me, 2), 177 (100), 117 (70), 91 (PhCH_2^+), 77 (Ph^+, 40). \text{Anal. [Found: C, 77.2; H, 7.5. C}_{21}H_{24}O_3 \text{ requires C, 77.7; H, 7.5%].}
\]

3-methyl-1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-3-en-1-ol (313):

To a stirred solution of aldehyde 176 (1.41 g, 6.84 mmol) in THF (20.0 ml) at -78 °C was added 2-methylallylmagnesium chloride 312, 0.5 M in THF (22.0 ml, 11.0 mmol). The cooling bath was removed after the addition and reaction mixture was stirred at room temperature overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride (NH_4Cl) solution and extracted with diethylether (3 × 30.0 ml). Combined organic extracts were dried over MgSO_4 and filtrate concentrated in vacuo. The crude residue was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 9:1) to give the title alcohol 313 as a clear oil (1.10 g, 61%).

\[\text{\begin{center} \includegraphics{Diagram.png} \end{center}}\]

\[\nu_{\text{max}} (\text{ATR}): 3510-3488 (\text{OH} \text{ br}), 2874, 1648 (C=\text{C}), 1496, 1452, 1393, 1143, 1076, 881, 756 \text{ cm}^{-1}. \quad \delta_{\text{H}} (700 \text{ MHz; CDCl}_3): 7.34 (4H, sd, J 2.4, 2''-H, 3''-H), 7.28-7.25 (1H, m, 4''-H), 4.88 (1H, s, 4-HH), 4.87 (1H, s, 4-HH), 4.24 (1H, d, J 10.8, 1-H), 4.21 (1H, dd, J 11.6, 4.6, 4'-H_{eq}), 4.17 (1H, dd, J 11.6, 4.6, 6'-H_{eq}), 4.11 (1H, dd, J 11.6, 7.0, 4'-H_{ax}), 4.02 (1H, dd, J 11.6, 7.0, 6'-H_{ax}), 3.04-3.01 (1H, dd, J 7.0, 4.6, 5'-H), 2.35 (1H, d, J 14.6, 2-HH), 2.15 (1H, dd, J 14.6, 10.8, 2-HH), 2.08 (1H, bs, OH), 1.84 (3H, s, 3-CH_3), 1.44 (3H, s, 2'-CH_3). \quad \delta_{\text{C}} (175 \text{ MHz; CDCl}_3): 143.1 (C-3), 140.3 (C-1''), 128.7 (C-3'''), 127.8 (C-2'''), 127.1 (C-4''), 112.7 (C-4), 99.9 (C-2'), 69.1 (C-1), 64.7 (C-4'), 64.2 (C-6'), 39.9 (C-5'), 39.2 (C-2), 22.6 (3-CH_3), 17.4 (2'-CH_3). \ m/z (ES^+): 285 ([M+Na]^+, 10%), 263 ([M+H]^+, 10), 245 ([M+H+H_2O]^+, 100).\]
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1-(2',5'-diphenyl-1',3'-dioxan-2'-yl)but-3-en-1-ol (261, 262):

Major isomer 261:

To a solution of aldehyde 178 (2.67 g, 9.96 mmol) stirred in THF (50.0 ml) at -78 °C was added allylmagnesium bromide, 1 M in diethylether (16.0 ml, 15.9 mmol). The cooling bath was removed after the addition and the reaction was stirred at room temperature overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride (NH₄Cl) solution and extracted with diethylether (3 x 30.0 ml). Combined organic extracts were dried over MgSO₄ and filtrate concentrated in vacuo. The crude residue was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 9:1) to give the title alcohol 261 as a white solid (2.23 g, 72%).

Minor isomer 262:

To a stirred solution of aldehyde 179 (0.89 g, 3.32 mmol) in THF (22.0 ml) at -78 °C was added allylmagnesium bromide, 1 M in diethylether (5.30 ml, 5.31 mmol). The cooling bath was removed after the addition and reaction was stirred at room temperature overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride (NH₄Cl)
solution and extracted with diethylether (3 × 30.0 ml). Combined organic extracts were dried over MgSO₄ and filtrate concentrated in vacuo. The crude residue was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 9:1) to give the title alcohol 262 as a clear oil (0.67 g, 65%).

\[
\begin{align*}
\nu_{\text{max}} \text{(ATR)} & : 3503 \text{ (OH), } 1640 \text{ (C=O), } 1494, 1446, 1390, 1134, 1027, 912, 756 \text{ cm}^{-1}. \\
\delta_{\text{H}} \text{(700 MHz; CDCl}_{3} \text{)} & : 7.48-7.45 \text{ (4H, m, Ar-H), } 7.40 \text{ (1H, t, } J \text{ 6.8, Ar-H), } 7.23 \text{ (2H, t, } J \text{ 7.2, Ar-H), } 7.19 \text{ (1H, t, } J \text{ 7.2, Ar-H), } 6.98 \text{ (2H, d, } J \text{ 7.2, Ar-H), } 5.85-5.79 \text{ (1H, m, } 3\text{-H), } 5.05 \text{ (1H, dd, } J \text{ 17.2, 1.3, H), } 5.02 \text{ (1H, dd, } J \text{ 10.3, 1.3, H), } 4.08-4.02 \text{ (2H, m, } 4\text{-H}_{\text{eq}}, 6\text{-H}_{\text{eq}), } 3.88 \text{ (1H, t, } J \text{ 11.7, H), } 3.85 \text{ (1H, t, } J \text{ 11.7, H), } 3.69 \text{ (1H, dt, } J \text{ 10.2, 3.0, H), } 3.43-3.30 \text{ (1H, m, } 5\text{-H), } 2.51 \text{ (1H, d, } J \text{ 3.0, H), } 2.29-2.26 \text{ (1H, m, } 2\text{-H), } 2.12-2.07 \text{ (1H, m, } 2\text{-H).} \\
\delta_{\text{C}} \text{(175 MHz; CDCl}_{3} \text{)} & : 137.6 \text{ (Ar-C), } 135.8 \text{ (Ar-C), } 135.5 \text{ (C-3), } 128.7 \text{ (Ar-C), } 128.64 \text{ (Ar-C), } 128.60 \text{ (Ar-C), } 128.5 \text{ (Ar-C), } 127.5 \text{ (Ar-C), } 127.3 \text{ (Ar-C), } 116.9 \text{ (C-4), } 101.8 \text{ (C-2'), } 77.3 \text{ (C-1), } 66.3 \text{ (C-4'), } 66.1 \text{ (C-6'), } 41.2 \text{ (C-5'), } 34.7 \text{ (C-2).} \\
m/z \text{ (ES\textsuperscript{+}) : 643 ([M+Na]+, 10%), 374 ([M+Na+CH}_{3}CN]+, 100), 333 ([M+Na]+,10). HRMS (ES\textsuperscript{+}) found: 311.1642 (C\textsubscript{20}H\textsubscript{23}O\textsubscript{3} requires [M+H]\textsuperscript{+} 311.1642).}
\end{align*}
\]
mp.: 110-112 °C. \( \nu_{\text{max}} \) (ATR) : 3560 (OH), 2915, 1641 (C=), 1494, 1449, 1375, 1142, 1019, 914, 746, 701 cm\(^{-1}\)  
\( \delta_\text{H} \) (700 MHz; CDCl\(_3\)) : 7.43-7.41 (4H, m, Ar-\( \text{H} \)), 7.37-7.35 (1H, m, Ar-\( \text{H} \)), 7.31 (2H, t, \( J = 7.5 \)), 7.25-7.21 (3H, m, Ar-\( \text{H} \)), 5.89-5.83 (1H, m, 3-\( \text{H} \)), 5.09 (1H, dd, \( J = 17.2 \), 1.6, 3-\( \text{H} \)), 5.05 (1H, dd, \( J = 10.2 \), 1.6, 4-HH), 3.91 (2H, dd, \( J = 9.4 \), 2.7, 4'-H\(_\text{eq}\)), 3.72 (2H, t, \( J = 9.4 \)), 3.68 (1H, dd, \( J = 3.9 \), 2.7, 1-\( \text{H} \))  
\( \delta_\text{C} \) (175 MHz; CDCl\(_3\)) : 140.3 (Ar-C), 136.2 (Ar-C), 135.7 (C-3), 129.3 (Ar-C), 128.50 (Ar-C), 128.47 (Ar-C), 128.45 (Ar-C), 128.3 (Ar-C), 126.1 (Ar-C), 116.8 (C-4), 102.1 (C-2'), 77.5 (C-1), 63.9 (C-4'), 63.8 (C-6'), 36.0 (C-5'), 35.8 (5'-CH\(_2\)Ph), 34.7 (C-2). m/z (EI) : 324 (M\(^+\), 5%), 253 (M\(^+\)-CHOHCH\(_2\)CH=CH\(_2\), 100), 131 (70), 91 (PhCH\(_2\)\(^+\), 20), 77(Ph\(^+\), 10). HRMS (ES\(^+\)) found: 325.1798 (C\(_{21}\)H\(_{25}\)O\(_3\) requires [M+H]\(^+\) 325.1804).

1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-3-en-1-one (264, 265) and (E)-1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-2-en-1-one (268, 269) :  
Major isomer 264, 268 :  
To a stirred mixture of powdered 4Å molecular sieves (3.90 g) and pyridinium dichromate (PDC) (0.60 g, 1.67 mmol) in dry DCM (12.0 ml) under argon at room temperature was added a solution of alcohol 259 (0.10 g, 0.40 mmol) in DCM (3.00 ml). After stirring at room temperature for 4 h, the reaction mixture was filtered through a bed of Celite\(^\text{®}\), washed with DCM (3 x 20.0 ml) and the filtrate was concentrated in vacuo. The crude residue (which contained an 11:1 mixture of isomeric ketones) was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 9:1 then 8:2) to afford an inseparable mixture of the title ketones 264 and 268 as a colourless oil (11:1 ratio, 0.07 g, 76%).  
Careful separation of fractions enabled small analytical samples of each isomer to be obtained.
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Isomer 264:

\[
\begin{align*}
\text{\(\nu_{\text{max}}\) (ATR)} &: 2965, 1728 (\text{C=O}), 1702, 1630 (\text{C=C}), 1496, 1453, 1372, 1241, 1133, 1026, 880, 756, 625 \text{ cm}^{-1}. \\
\delta_{\text{H}} (500 MHz; \text{CDCl}_3) &: 7.30 (2H, t, J 7.4, \text{Ar-H}), 7.25 (1H, t, J 7.4, \text{Ar-H}), 7.10 (2H, d, J 7.4, \text{Ar-H}), 6.05-5.99 (1H, m, 3-H), 5.23 (1H, dd, J 10.2, 1.3, 4-HH), 5.19 (1H, dd, J 17.2, 1.3, 4-HH), 4.06 (2H, dd, J 11.5, 4.7, 4'-H_{\text{eq}}, 6'-H_{\text{eq}}), 3.80 (2H, t, J 11.5, 4'-H_{\text{ax}}, 6'-H_{\text{ax}}), 3.41 (2H, d, J 6.9, 2-H_2), 3.24-3.20 (1H, m, 5'-H), 1.49 (3H, s, 2'-CH_3). \\
\delta_{\text{C}} (125 MHz; \text{CDCl}_3) &: 208.1 (\text{C-1}), 137.2 (\text{C-1'}), 130.4 (\text{C-3}), 128.8 (\text{Ar-C}), 127.6 (\text{Ar-C}), 127.5 (\text{Ar-C}), 119.0 (\text{C-4}), 100.8 (\text{C-2'}), 67.9 (\text{C-4'}, 6'-H_{\text{eq}}), 41.9 (\text{C-2}), 40.3 (\text{C-5'}), 24.7 (2'-CH_3). \\
m/z (ES^+) &: 515 ([2M+Na]^+, 10\%), 310 ([M+Na+CH_3CN]^+, 70), 307 (100), 269 ([M+Na]^+, 90), 247 ([M+H]^+, 70). \text{HRMS (ES^+)} \text{ found: } 269.1150 (\text{C}_{15}\text{H}_{18}\text{O}_3\text{Na requires } [\text{M+Na}]^+ 269.1148).
\end{align*}
\]

Isomer 268:

\[
\begin{align*}
\text{\(\nu_{\text{max}}\) (ATR)} &: 2964, 1705 (\text{C=O}), 1627 (\text{C=C}), 1495, 1443, 1369, 1296, 1190, 1043, 881, 755, 667, 529 \text{ cm}^{-1}. \\
\delta_{\text{H}} (500 MHz; \text{CDCl}_3) &: 7.27-7.19 (4H, m, \text{Ar-H}, 3-H), 7.07 (2H, d, J 7.3, \text{Ar-H}), 6.63 (1H, d, J 15.4, 2-H), 4.02 (2H, dd, J 12.2, 4.7, 4'-H_{\text{eq}}, 6'-H_{\text{eq}}), 3.81 (2H, t, J 12.2, 4'-H_{\text{ax}}, 6'-H_{\text{ax}}), 3.25-3.20 (1H, m, 5'-H), 1.95 (3H, d, J 6.9, 4'-H_3), 1.44 (3H, s, 2'-CH_3). \\
\delta_{\text{C}} (125 MHz; \text{CDCl}_3) &: 198.2 (\text{C-1}), 146.3 (\text{C-3}), 137.4 (\text{C-1'}), 128.7 (\text{Ar-C}), 127.6 (\text{Ar-C}), 127.4 (\text{Ar-C}), 125.9 (\text{C-2}), 100.7 (\text{C-2'}), 67.8 (\text{C-4'}, 6'-H_{\text{eq}}), 40.5 (\text{C-5'}), 24.9 (2'-CH_3), 18.6 (\text{C-4}), m/z (ES^+) &: 575 (40\%), 413 (15), 269 ([M+Na]^+, 100), 229 (45). \text{HRMS (ES^+)} \text{ found: } 269.1150 (\text{C}_{15}\text{H}_{18}\text{O}_3\text{Na requires } [\text{M+Na}]^+ 269.1148).
\end{align*}
\]
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Minor isomer 265, 269:
To a stirred mixture of powdered 4Å molecular sieves (17.0 g) and PDC (2.77 g, 7.36 mmol) in dry DCM (100 ml) under argon at room temperature was added a solution of alcohol 260 (0.44 g, 1.77 mmol) in DCM (20.0 ml). After stirring at room temperature for 4 h, the reaction mixture was filtered through a bed of Celite®, washed with DCM (3 × 20.0 ml) and the filtrate was concentrated in vacuo. The crude residue (which contained a 12:1/265:269 mixture of isomeric ketones) was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 9:1 then 8:2) to afford the title allylketone 265 as a clear oil (0.28 g, 64%) and vinylketone 269 as an oil (0.02 g, 5%).

Isomer 265:

\[
\begin{align*}
\text{ν}_{\text{max}} \text{(ATR)} & : 2877, 1729 \,(C=O), 1641 \,(C=C), 1496, 1451, 1392, 1319, 1247, 1171, 1023, 919, 869, 755, 632 \,\text{cm}^{-1}. \\
\delta_H \,(700 \text{ MHz; CDCl}_3) & : 7.37 \,(2H, d, J \,7.0, 3''-H), 7.35 \,(2H, t, J \,7.0, 2''-H), 7.28 \,(1H, t, J \,7.0, 4''-H), 6.00 \,(1H, m, 3-H), 5.22 \,(1H, dd, J \,10.2, 1.4, 4HH), 5.18 \,(1H, dd, J \,17.0, 1.4, 4HH), 4.13-4.09 \,(4H, m, 4''-H_{eq}, 6''-H_{ax}, 6''-H_{eq}, 4''-H_{ax}).
\end{align*}
\]

\[
\begin{align*}
\delta_C \,(175 \text{ MHz; CDCl}_3) & : 206.0 \,(C-1), 139.9 \,(C-1''), 130.6 \,(C-3), 128.7 \,(C-3''), 127.9 \,(C-2'''), 127.2 \,(C-4''), 118.7 \,(C-4), 99.7 \,(C-2'), 66.0 \,(C-4', C-6''), 41.0 \,(C-2), 39.8 \,(C-5'), 19.5 \,(2'-CH_3). \\
m/z \,(\text{ES}^+) & : 310 \,([M+Na+CH_3CN]^+, 80\%), 269 \,([M+Na]^+, 100). \\
\text{HRMS (ES}^+) \text{ found: 269.1144 (C_{13}H_{18}O_3Na requires [M+Na]^+ 269.1148).}
\end{align*}
\]
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Isomer 269:

![Chemical Structure](image1.png)

$\nu_{\text{max}}$ (ATR) : 2965, 1703 (C=O), 1627 (C=C), 1495, 1444, 1372, 1293, 1179, 1110, 1029, 972, 876, 753, 698, 629 cm$^{-1}$. $\delta_H$ (700 MHz; CDCl$_3$) : 7.47 (2H, d, J 7.6, 2''-H), 7.35 (2H, t, J 7.6, 3''-H), 7.28 (1H, d, J 7.6, 4''-H), 7.20 (1H, dq, J 15.4, 7.0, 3-H), 6.68 (1H, d, J 15.4, 2-H), 4.18 (2H, dd, J 12.0, 3.8, 4'-H$_{ax}$, 6'-H$_{ax}$), 4.10 (2H, dd, J 12.0, 4.0, 4'-H$_{eq}$, 6'-H$_{eq}$), 2.79-2.78 (1H, m, 5'-H), 1.97 (3H, d, J 7.0, 4-H$_3$), 1.51 (3H, s, 2'-CH$_3$). $\delta_C$ (175 MHz; CDCl$_3$) : 197.0 (C-1), 146.0 (C-3), 141.3 (C-1'''), 128.5 (C-3'''), 128.1 (C-2''), 126.9 (C-4'''), 125.6 (C-2), 100.2 (C-2'), 66.4 (C-4', C-6'), 39.2 (C-5'), 22.2 (2'-CH$_3$), 18.6 (C-4). m/z (ES$^+$) : 310 ([M+Na+CH$_3$CN]$^+$, 70%), 269 ([M+Na]$^+$, 80), 242 (100). HRMS (ES$^+$) found: 269.1149 (C$_{15}$H$_{18}$O$_3$Na requires [M+Na]$^+$ 269.1148).

3-methyl-1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-3-en-1-one (314):

To a stirred mixture of powdered 4Å molecular sieves (15.0 g) and PDC (6.71 g, 17.8 mmol) in dry DCM (60.0 ml) under argon at room temperature was added a solution of alcohol 313 (0.85 g, 3.24 mmol) in DCM (10.0 ml). After stirring at room temperature for 4 h, the reaction mixture was filtered through a bed of Celite®, washed with DCM (3 × 20.0 ml) and the filtrate was concentrated in vacuo. The crude residue was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 9:1 then 8:2) to afford the title allylketone 314 as a clear oil (0.56 g, 66%).
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\[ \nu_{\text{max}} \ (\text{ATR}) : 2966, 1726 \ (C=O), \ 1648 \ (C=C), \ 1495, \ 1448, \ 1372, \ 1242, \ 1193, \ 1131, \ 1039, \ 884, \ 755, \ 698 \ \text{cm}^{-1}. \ \delta_{\text{H}} (700 \ \text{MHz; CDCl}_3) : 7.30 \ (2H, t, J 7.7, 3''\, H), \ 7.25 \ (1H, t, J 7.7, 4''\, H), \ 7.10 \ (2H, d, J 7.7, 2''\, H), \ 5.01 \ (1H, t, J 1.6, 4\, H), \ 4.87 \ (1H, dd, J 1.6, 0.9, 4\, H), \ 4.07 \ (2H, dd, J 11.9, 4.7, 4''\, H, eq, 6''\, H, eq), \ 3.84 \ (2H, t, J 11.9, 4''\, H, ax, 6''\, H, ax), \ 3.37 \ (2H, s, 2\, H), \ 3.24 \ (1H, tt, J 9.5, 4.7, 5''\, H), \ 1.84 \ (3H, dd, J 1.6, 0.9, 3\, CH_3), \ 1.50 \ (3H, s, 2''\, CH_3). \ \delta_{\text{C}} (175 \ \text{MHz; CDCl}_3) : \ 207.7, (C-1), \ 138.6 (C-3), \ 137.3 (C-1''), \ 128.8 (C-3''), \ 127.6 (C-2''), \ 127.5 (C-4''), \ 115.4 (C-4), \ 100.9 (C-2'), \ 67.9 (C-4', C-6'), \ 45.8 (C-2'), \ 40.4 (C-5'), \ 24.8 (2''\, CH_3), \ 22.9 (3\, CH_3). \ m/z \ (\text{ES}^+) : \ 324 \ ([M+Na]+CH_3CN]^+, \ 100\%), \ 283 \ ([M+Na]^+, \ 10). \ \text{HRMS (ES}^+) \ : \ 261.1480 \ (\text{C}_{16}\text{H}_{21}\text{O}_3 \text{requires [M+H]}^+ \ 261.1485). \n
1-(2',5'-diphenyl-1',3'-dioxan-2'-yl)but-3-en-1-one (266) and (Z)-1-(2',5'-diphenyl-1',3'-dioxan-2'-yl)but-2-en-1-one (270) :

To a stirred mixture of powdered 4Å molecular sieves (3.90 g) and PDC (14.3 g, 38.0 mmol) in dry DCM (60.0 ml) under argon at room temperature was added a solution of alcohol 261 (2.14 g, 6.90 mmol) in DCM (10.0 ml). After stirring at room temperature for 4 h, the reaction mixture was filtered through a bed of Celite®, washed with DCM (3 × 40.0 ml) and the filtrate was concentrated in vacuo. The crude residue (which contained a 13:1 mixture of isomeric ketones) was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 9:1 then 8:2) to afford an inseparable mixture of the title ketones 266 and 270 as a colourless oil (1.44 g, 68%).

Careful separation of fractions enabled small analytical sample of the major isomer 266 to be obtained.

Major isomer 266 :

\[ \nu_{\text{max}} \ (\text{ATR}) : 2978, 1730 \ (C=O), \ 1700, \ 1638 \ (C=C), \ 1500, \ 1456, \ 1396, \ 1310, \ 1252, \ 1156, \ 1080, \ 1040, \ 976, \ 916, \ 753, \ 702 \ \text{cm}^{-1}. \ \delta_{\text{H}} (500 \ \text{MHz; CDCl}_3) : 7.63 \ (2H, d, J 8.2, 2b''\, H), \ 7.43-7.38 \ (3H, m, 3b''\, H, 4b''\, H), \ 7.33 \ (2H, t, J 7.4, 3a''\, H), \ 7.28 \ (1H, t, J 7.4, 4a''\, H), \ 7.21 \ (2H, d, J 7.2) \ 2.14 \text{ ml) under argon at room temperature was added a solution of alcohol 261 (2.14 g, 6.90 mmol) in DCM (10.0 ml). After stirring at room temperature for 4 h, the reaction mixture was filtered through a bed of Celite®, washed with DCM (3 × 40.0 ml) and the filtrate was concentrated in vacuo. The crude residue (which contained a 13:1 mixture of isomeric ketones) was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 9:1 then 8:2) to afford an inseparable mixture of the title ketones 266 and 270 as a colourless oil (1.44 g, 68%).

Careful separation of fractions enabled small analytical sample of the major isomer 266 to be obtained.

Major isomer 266 :

\[ \nu_{\text{max}} \ (\text{ATR}) : 2978, 1730 \ (C=O), \ 1700, \ 1638 \ (C=C), \ 1500, \ 1456, \ 1396, \ 1310, \ 1252, \ 1156, \ 1080, \ 1040, \ 976, \ 916, \ 753, \ 702 \ \text{cm}^{-1}. \ \delta_{\text{H}} (500 \ \text{MHz; CDCl}_3) : 7.63 \ (2H, d, J 8.2, 2b''\, H), \ 7.43-7.38 \ (3H, m, 3b''\, H, 4b''\, H), \ 7.33 \ (2H, t, J 7.4, 3a''\, H), \ 7.28 \ (1H, t, J 7.4, 4a''\, H), \ 7.21 \ (2H, d, J
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7.4, 2a’’-H), 5.87-5.78 (1H, m, 3-H), 5.11 (1H, dd, J 10.1, 1.4, 4-HH), 5.02 (1H, dd, J 17.2, 1.4, 4-HH), 4.27 (2H, dd, J 12.1, 4.8, 4’-H eq, 6’-H eq), 4.08 (2H, t, J 12.1, 4’-H ax, 6’-H ax), 3.29 (2H, d, J 7.0, 2-H2), 3.27-3.22 (1H, m, 5’-H). δC (125 MHz; CDCl3): 205.6 (C-1), 137.9 (C-1a’’), 136.8 (C-1b’’), 130.3 (C-3), 129.3 (C-4b’’), 128.8 (C-3a’’), 128.6 (C-3b’’), 127.7 (C-2a’’), 127.5 (C-4a’’), 126.0 (C-2b’’), 118.8 (C-4), 101.3 (C-2), 67.8 (C-4’, C-6’), 41.4 (C-2), 40.3 (C-5’). m/z (EI): 308 (M+, 5%), 239 (M+COCH2CH=CH2, 100), 117 (60), 105 (70), 77 (Ph+, 20). HRMS (ASAP) found: 309.1480 (C13H21O3Na requires [M+H] 309.1491).

1-(5’-benzyl-2’-phenyl-1’,3’-dioxan-2’-yl)but-3-en-1-one (267) and (Z)-1-(5’-benzyl-2’-phenyl-1’,3’-dioxan-2’-yl)but-2-en-1-one (271):

To a stirred mixture of powdered 4Å molecular sieves (4.50 g) and PDC (16.7 g, 44.3 mmol) in dry DCM (60.0 ml) under argon at room temperature was added a solution of alcohol 263 (2.61 g, 8.06 mmol) in DCM (10.0 ml). After stirring at room temperature for 4 h, the reaction mixture was filtered through a bed of Celite®, washed with DCM (3 × 40.0 ml) and the filtrate was concentrated in vacuo. The crude residue (which contained a 13:1 mixture of isomeric ketones) was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 9:1 then 8:2) to afford an inseparable mixture of the title ketones 267 and 271 as a colourless oil (1.85 g, 71%).

Careful separation of fractions enabled small analytical sample of the major isomer 267 to be obtained.

Major isomer 267:

\[ \text{\includegraphics{structure}} \]

ν max (ATR): 2922, 2876, 1738 (C=O), 1640 (C=C), 1504, 1451, 1392, 1314, 1248, 1152, 1046, 1010, 980, 924, 756, 700 cm

δ (700 MHz; CDCl3): 7.54 (2H, d, J 7.4, 2b’’-H), 7.38 (2H, t, J 7.4, 3b’’-H), 7.35 (1H, t, J 7.4, 4b’’-H), 7.29 (2H, t, J 7.5, 3a’’-H), 7.22 (1H, t, J 7.5, 4a’’-H), 7.16 (2H, d, J 7.5, 2a’’-H), 5.85-5.79 (1H, m, 3-H), 5.11 (1H, dd, J 10.2, 1.4, 4-HH), 5.03 (1H, dd, J 17.1, 1.4, 4-HH), 4.03 (2H, dd, J 11.7, 4.0, 4’-H eq, 6’-H eq), 3.71 (2H, dd, J 11.7, 7.3, 4’-H ax, 6’-H ax), 3.33 (2H, d, J 6.9, 2-H2), 2.67 (2H, d, J 7.8, 5’-CH2Ph), 2.11-2.06 (1H, m, 5’-
Chapter IX: Experimental Procedure

2-diazo-1-(2’-methyl-5’-phenyl-1’3’-dioxan-2’-yl)but-3-en-1-one (279, 280):

Major isomer 279:

A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.40 ml, 2.68 mmol) in CH$_2$CN (2.00 ml) was added to a stirred mixture of the inseparable ketones of 264 and 268 (0.11 g, 0.45 mmol) and p-acetamidobenzenesulfonyl azide (p-ABSA) (0.21 g, 0.89 mmol) dissolved in CH$_2$CN (5.00 ml) at 0 °C. After stirring for 3 h at room temperature, a saturated ammonium chloride solution (NH$_4$Cl) (20 ml) was added, and the mixture was extracted with DCM (3 × 20.0 ml), the combined organic extracts were dried using MgSO$_4$ and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether: 1:9 then 2:8) to give the title vinylidiazoketone 279 as a shiny orange oil (0.11 g, 90%).

$\delta$C (175 MHz; CDCl$_3$): 204.5 (C-1), 138.7 (C-1a”), 136.2 (C-1b’”), 130.4 (C-3), 129.1 (C-4b’”), 128.9 (C-2a’’), 128.7 (C-3b’’), 128.5 (C-3a’’), 126.6 (C-2b’’), 126.4 (C-4a’’), 118.6 (C-4), 101.5 (C-2’), 66.6 (C-4’, C-6’), 40.9 (C-2), 45.7 (C-5’), 35.1 (5’-CH$_2$Ph). m/z (ES$^+$): 667 ([M+Na]$, 20\%$), 386 ([M+Na+CH$_3$CN]$^+$, 50), 345 ([M+Na]$^+$, 100), 323 ([M+H]$^+$, 80). HRMS (ES$^+$) found: 323.1650 (C$_{21}$H$_{21}$O$_3$Na requires [M+H]$^+$ 323.1647).

$\nu$ max (ATR): 2924, 2082 (C=O), 1648 (C=O), 1609 (C=C), 1495, 1453, 1374, 1263, 1133, 1025, 981, 842, 755, 640 cm$^{-1}$. $\delta_H$ (500 MHz; CDCl$_3$): 7.30 (2H, t, J 7.5, 3”-H), 7.25 (1H, t, J 7.5, 4”-H), 7.11 (2H, d, J 7.5, 2”-H), 6.52 (1H, d, J 17.2, 11.2, 3-H), 5.27 (1H, d, J 11.2, 4-HH), 4.87 (1H, d, J 17.2, 4-HH), 4.10 (2H, dd, J 11.8, 4.0, 4”-H$_{eq}$, 6”-H$_{eq}$), 3.92 (2H, t, J 11.8, 4”-H$_{ax}$, 6”-H$_{ax}$), 3.28-3.25 (1H, tt, J 11.8, 4.0, 5”-H), 1.56 (3H, s, 2’-CH$_3$). $\delta_C$ (125 MHz; CDCl$_3$): 191.0 (C-1), 137.0 (C-1’’), 128.8 (C-3”’), 127.7 (C-4”’), 127.6 (C-2’’), 120.8 (C-3), 108.3 (C-4), 100.8 (C-2’), 67.8 (C-4’, C-6’), 66.7 (C-2), 40.2 (C-5’), 25.5 (2’-CH$_3$). m/z (ES$^+$): 567 ([M+Na]$^+$, 85%), 336 ([M+Na+CH$_3$CN]$^+$, 70), 308 ([M-N$_2$+Na+CH$_3$CN]$^+$, 100), 267 ([M-N$_2$+Na]$^+$, 25). HRMS (ES$^+$) found: 295.1054 (C$_{13}$H$_{16}$O$_3$N$_2$Na requires 295.1053).
Chapter IX: Experimental Procedure

Minor isomer 280:

A solution of DBU (4.40 ml, 29.3 mmol) in CH₃CN (8.00 ml) was added to a stirred mixture of the inseparable ketones 265 and 269 (0.90 g, 3.65 mmol) and p-ABSA (1.76 g, 7.32 mmol) dissolved in CH₃CN (35.0 ml) at rt. After stirring for 3 h, a saturated ammonium chloride solution (NH₄Cl) (20.0 ml) was added, and the mixture was extracted with DCM (3 × 20.0 ml), the combined organic extracts were dried using MgSO₄ and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 1:9 then 2:8) to give the title vinyl Diazoketone 280 as shiny orange oil (0.72 g, 72%).

\[
\text{\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}}
\]

\[\nu_{\text{max}} (\text{ATR}) : 2974, 2886, 2088 (C=O), 1650 (C=O), 1614 (C=C), 1496, 1456, 1344, 1260, 1156, 1032, 990, 878, 760, 643 \text{ cm}^{-1}. \ \delta_{\text{H}} (700 \text{ MHz; CDCl}_3) : 7.43 (2H, d, J 7.7, 2''-H), 7.35 (2H, t, J 7.7, 3'''-H), 7.28 (1H, t, J 7.7, 4'''-H), 6.50 (1H, dd, J 17.3, 9.9, 3-H), 5.23 (1H, d, J 9.9, 4-HH), 4.86 (1H, d, J 17.3, 4-HH), 4.24 (2H, dd, J 11.9, 3.5, 4'-H_{ax}, 6'-H_{ax}), 4.15 (2H, dd, J 11.9, 5.2, 4'-H_{eq}, 6'-H_{eq}), 2.89 (1H, tt, J 5.2, 3.5, 5'-H), 1.62 (3H, s, 2'-CH₃). \ \delta_{C} (175 \text{ MHz; CDCl}_3) : 189.5 (C-1), 140.3 (C-1'''), 128.6 (C-3'''), 127.9 (C-2'''), 127.1 (C-4'''), 121.0 (C-3), 108.0 (C-4), 100.6 (C-2'''), 96.8 (C-2'), 66.3 (C-4', C-6'), 38.9 (C-5'), 21.5 (2'-CH₃). m/z (ES⁺) : 567 ([M+Na]+, 30%), 336 ([M+Na+CH₃CN]+, 80), 273 ([M+H]+, 40), 245 ([M+H-N₂]+, 100). HRMS (ES⁺) found: 273.1230 (C_{15}H_{17}O_{3}N_{2} requires [M+H]+ 273.1239).

2-diazo-3-methyl-1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-3-en-1-one (315):

A solution of DBU (2.60 ml, 17.2 mmol) in CH₃CN (10.0 ml) was added to a stirred solution of 314 (0.56 g, 2.15 mmol) and p-ABSA (1.03 g, 4.31 mmol) dissolved in CH₃CN (10.0 ml) at rt. After stirring for 3 h, a saturated ammonium chloride solution (NH₄Cl) (20.0 ml) was added, and the mixture was extracted with DCM (3 × 20.0 ml), the combined organic extracts were dried using MgSO₄ and the solvent was evaporated under reduced pressure. The crude residue
was then purified by flash column chromatography on silica gel (ether/petroleum ether : 1:9 then 2:8) to give the title vinyldiazoketone 315 as an orange oil (0.35 g, 57%).

\[
\begin{align*}
\text{\(\nu_{\text{max}}\) (ATR) : 2964, 2077 (C=\text{N}_2), 1649 (C=\text{O}), 1609 (C=C), 1496, 1452, 1375, 1332, 1187, 1135, 1044, 884, 817, 756, 699 \text{ cm}^{-1}.} \\
\text{\(\delta_{\text{H}}\) (700 MHz; CDCl\textsubscript{3}) : 7.30 (2H, \textit{t}, J 7.7, 3''-\text{H}), 7.25 (1H, \textit{t}, J 7.7, 4''-\text{H}), 7.12 (2H, \textit{d}, J 7.7, 2''-\text{H}), 5.58 (1H, \textit{qd}, J 1.0, 0.8, 4-HH), 5.15 (1H, \textit{qd}, J 1.4, 1.0, 4-HH), 4.10 (2H, \textit{dd}, J 11.9, 4.7, 4'-H\textsubscript{eq}, 6'-H\textsubscript{eq}), 3.98 (2H, \textit{t}, J 11.9, 4'-H\textsubscript{ax}, 6'-H\textsubscript{ax}), 3.26 (1H, \textit{tt}, J 11.9, 4.7, 5'-H), 2.02 (3H, \textit{dd}, J 1.4, 0.8, 3-CH\textsubscript{3}), 1.57 (3H, s, 2'-CH\textsubscript{3}).} \\
\text{\(\delta_{\text{C}}\) (175 MHz; CDCl\textsubscript{3}) : 192.0 (C-1), 137.1 (C-1''), 128.8 (C-3''), 128.0 (C-3), 127.6 (C-2'''), 127.5 (C-4''), 113.5 (C-4), 100.8 (C-2'), 70.0 (C-2), 67.8 (C-4', C-6'), 40.2 (C-5'), 25.4 (2'-CH\textsubscript{3}), 21.5 (3-CH\textsubscript{3}).} \\
m/z (ES\textsuperscript{+}) : 322 ([M-N\textsubscript{2}+Na+CH\textsubscript{3}CN]\textsuperscript{+}, 100\%), 177 (90). HRMS (ES\textsuperscript{+}) found: 287.1384 (C\textsubscript{16}H\textsubscript{19}O\textsubscript{3}N\textsubscript{2} requires [M+H]\textsuperscript{+} 287.1385).
\end{align*}
\]

2-diazo-1-(2',5'-diphenyl-1',3'-dioxan-2'-yl)but-3-en-1-one (281):
A solution of DBU (5.60 ml, 37.4 mmol) in CH\textsubscript{3}CN (18.0 ml) was added to a stirred solution of the inseparable ketones 266 and 270 (1.44 g, 4.68 mmol) and \(p\)-ABSA (2.24 g, 9.35 mmol) dissolved in CH\textsubscript{3}CN (30.0 ml) at rt. After stirring for 3 h, a saturated ammonium chloride solution (NH\textsubscript{4}Cl) (30.0 ml) was added, and the mixture was extracted with DCM (3 \times 20.0 ml), the combined organic extracts were dried using MgSO\textsubscript{4} and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 1:9 then 2:8) to give the title vinyldiazoketone 281 as a bright orange oil (1.08 g, 69%).
Chapter IX: Experimental Procedure

\( \nu_{\text{max}} \) (ATR): 2923, 2884, 2081 (C=N), 1643 (C=O), 1606 (C=C), 1495, 1452, 1298, 1249, 1139, 1095, 1025, 981, 859, 757, 697 cm\(^{-1}\). \( \delta_H \) (400 MHz; CDCl\(_3\)): 7.68 (2H, d, J 8.1, 2b''''-H), 7.42-7.37 (3H, m, 3b''''-H, 4b''''-H), 7.34-7.24 (3H, m, 3a''''-H, 4a''''-H), 7.17 (2H, d, J 7.7, 2a''''-H), 6.49 (1H, dd, J 17.2, 10.9, 3-H), 5.14 (1H, d, J 10.9, 4-HH), 4.74 (1H, d, J 17.2, 4-HH), 4.30 (2H, dd, J 11.7, 4.8, 4'-H\text{eq}, 6'-H\text{eq}), 4.23 (2H, t, J 11.7, 4'-H\text{ax}, 6'-H\text{ax}), 3.42-3.29 (1H, tt, J 11.7, 4.8, 5'-H). \( \delta_C \) (100 MHz; CDCl\(_3\)): 188.4 (C-1), 137.0 (C-1a'''), 136.8 (C-1b'''), 129.0 (C-4a'''), 128.5 (C-2a'''), 128.2 (C-3a'''), 127.3 (C-3b'', C-4b'''), 125.2 (C-2b'''), 120.4 (C-3), 107.8 (C-4), 100.7 (C-2'), 69.1 (C-2), 67.9 (C-4', C-6'), 39.9 (C-5'). m/z (ES\(^+\)): 691 ([2M+Na\(^+\), 30%], 357 ([M+Na\(^+\], 50), 335 ([M+H\(^+\], 100), 307 ([M+H-N\(_2\)]\(^+\), 100). HRMS (ES\(^+\)) found: 335.1405 (C\(_{20}\)H\(_{19}\)O\(_3\)N\(_2\) requires [M+H\(^+\]+ 335.1396).

**1-(5'-benzyl-2'-phenyl-1',3'-dioxan-2'-yl)-2-diazobut-3-en-1-one (282):**

A solution of DBU (3.20 ml, 21.4 mmol) in CH\(_3\)CN (12.0 ml) was added to a stirred solution of the inseparable ketones 267 and 271 (0.86 g, 2.67 mmol) and p-ABSA (1.28 g, 5.34 mmol) dissolved in CH\(_3\)CN (25.0 ml) at rt. After stirring for 3 h, a saturated ammonium chloride solution (NH\(_4\)Cl) (20.0 ml) was added, and the mixture was extracted with DCM (3 × 20.0 ml), the combined organic extracts were dried using MgSO\(_4\) and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 1:9 then 2:8) to give the title vinylidiazoketone 282 as an orange oil (0.75 g, 81%).

![Diagram](image-url)
Chapter IX: Experimental Procedure

126.5 (C-4b’’), 125.6 (C-2b’’), 120.9 (C-3), 107.9 (C-4), 101.3 (C-2’), 77.2 (C-2), 67.9 (C-4’, C-6’), 35.4 (C-5’), 34.8 (5’-CH2Ph). m/z (ES+) : 413 ([M+Na+CH3CN]+, 40%), 371 ([M+Na]+, 70), 349 ([M+H]+, 90), 321 ([M+H-N2]+, 100). HRMS (ES+) found: 349.1547 (C23H21O3N2 requires [M+H]+ 349.1552).

(E/Z)-6-ethylidene-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one (285, 286) and (Z)-7-allylidene-1-methyl-4-phenyl-2,6,8-trioxabicyclo[3.2.1]octane (287):

A solution of vinylidiazoketone 279 (0.11 g, 0.40 mmol, 100 mmol/L) in benzene (4.00 ml), was added via syringe pump over 20 h to a solution of rhodium (II) perfluorobutyrate, Rh2(CO2C3F7)4 (5 mol%, 1 mmol/L) in benzene (20.0 ml) maintained at room temperature. Upon complete addition, silica gel was added and the reaction mixture was concentrated in vacuo. The residue was then immediately purified by flash column chromatography on silica gel (ether/petroleum ether : 1/9 then 2/8) to afford white solids of the title bicyclic ketones 285 (0.03 g, 31%) and 286 (0.01 g, 10%) as a separable mixture of geometrical isomers (in a combined yield of 0.04 g, 41%). The trioxabicycle 287 was also isolated as an oil (0.01 g, 10%).

(E)-6-ethylidene-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one 285:

![Chemical Structure of 285](image)

mp.: 95-97 °C. v_max (ATR) : 2940, 2882, 1739 (C=O), 1664 (C=O), 1441, 1382, 1173, 1105, 1020, 874, 835, 759, 733, 700 cm^-1. δ_H (700 MHz; CDCl3) : 7.31 (2H, t, J 7.4, Ar-H), 7.28 (1H, t, J 7.4, Ar-H), 7.13 (2H, d, J 7.4, Ar-H), 6.28 (1H, q, J 7.3, 6-CHCH3), 5.09 (1H, bs, 5-H), 4.29 (1H, t, J 12.1, 3-H_eq), 4.09 (1H, dd, J 12.1, 5.5, 3-H_eq), 3.87-3.84 (1H, m, 4-H), 1.47 (3H, s, 1-CH3), 1.07 (3H, d, J 7.3, 6-CHCH3). δ_C (175 MHz; CDCl3) : 199.3 (C-7), 135.9 (C-1’), 133.8 (6-CHCH3), 133.7 (C-6), 128.9 (Ar-C), 127.9 (Ar-C), 127.8 (Ar-C), 99.8 (C-1), 78.7 (C-5), 64.4 (C-3), 44.1 (C-4), 18.5 (1-CH3), 14.9 (6-CHCH3). m/z (EI) : 227 (2%), 214 (M+2 × Me, 6), 202 (M+Me-C2H4, 40), 104 (100), 91 (PhCH2+, 10), 77 (Ph+, 5). Anal. [Found: C, 72.9; H, 6.7. C15H16O3 requires C, 73.7; H, 6.6%].
Chapter IX: Experimental Procedure

(Z)-6-ethylidene-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one (286):

\[
\begin{align*}
&\text{mp.: } 76-79 \, ^\circ\text{C.} \\
&\nu_{\text{max}} (\text{ATR}): 2948, 2878, 1739 (C=O), 1663 (C=C), 1496, 1439, 1383, 1284, 1173, 1021, 873, 758, 734, 638 \, \text{cm}^{-1}. \\
&\delta_H (700 \, \text{MHz; CDCl}_3): 7.32 (2H, t, J 7.4, Ar-H), 7.28 (1H, d, J 7.4, Ar-H), 7.11 (2H, d, J 7.4, Ar-H), 5.61 (1H, q, J 7.5, 6-C\text{H}_3), 4.80 (1H, d, J 3.2, 5-H), 4.24 (1H, t, J 12.1, 3-H_{ax}), 4.08 (1H, dd, J 12.1, 5.6, 3-H_{eq}), 3.79 (1H, s, 1-C\text{H}_3). \\
&\delta_C (175 \, \text{MHz; CDCl}_3): 201.6 (C-1), 138.7 (6-C\text{H}_3), 136.1 (C-6), 131.1 (C-1'), 128.7 (\text{Ar-C}), 127.9 (Ar-C), 127.7 (Ar-C), 100.6 (C-1), 81.1 (C-5), 64.7 (C-3), 44.5 (C-4), 18.6 (1-C\text{H}_3), 14.3 (6-C\text{H}_3). \\
&\text{m/z (EI)}: 244 (M^+, 2\%), 214 (M^+-2 \times \text{Me}, 6), 202 (M^+-\text{Me-C}_2\text{H}_5, 40), 104 (100), 91 (\text{PhCH}_2^+, 5), 77 (\text{Ph}^+, 2). \\
&\text{HRMS (ASAP) found: } 245.1183 (\text{C}_{15}\text{H}_{17}\text{O}_3 \text{requires } [M+H]^+ 245.1178). \\
\end{align*}
\]

(Z)-7-allylidene-1-methyl-4-phenyl-2,6,8-trioxabicyclo[3.2.1]octane (287):

\[
\begin{align*}
&\nu_{\text{max}} (\text{ATR}): 1685 (C-O), 1656 (C=C), 1493, 1421, 1318, 1107, 1020, 932, 801, 756, 640 \, \text{cm}^{-1}. \\
&\delta_H (700 \, \text{MHz, CDCl}_3): 7.35 (4H, m, Ar-H), 7.30 (1H, m, Ar-H), 6.84 (1H, dt, J 17.2, 10.5, 7-C\text{HCH}=\text{CH}_2), 5.81 (1H, s, 5-H), 5.35 (1H, d, J 10.5, 7-C\text{HCH}=\text{CH}_2), 5.32 (1H, d, J 17.2, 7-C\text{HCH}=\text{CHH}), 5.19 (1H, d, J 10.5, 7-C\text{HCH}=\text{CHH}), 4.09 (1H, t, J 11.3, 3-H_{ax}), 4.03 (1H, dd, J 11.3, 6.3, 3-H_{eq}), 3.44 (1H, dd, J 11.3, 6.3, 4-H), 1.66 (3H, s, 1-C\text{H}_3). \\
&\delta_C (175 \, \text{MHz; CDCl}_3): 151.1 (C-7, enol ether), 135.9 (C-1'), 130.0 (7-C\text{HCH}=\text{CH}_2), 128.7 (Ar-C), 128.6 (Ar-C), 127.8 (Ar-C), 115.0 (7-C\text{HCH}=\text{CH}_2), 104.1 (C-5), 102.2 (C-1), 98.2 (7-C\text{HCH}=\text{CH}_2), 66.1 (C-}
\]
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3), 46.0 (C-4), 20.3 (1-CH₃). m/z (ES⁺) : 267 ([M+Na]⁺, 20%), 245 ([M+H]⁺, 10), 227 (40), 115 (100).

1-(4’-tert-butylylsulfonyl)pyrrolidine-2-carboxylic acid (293) : To a solution of (±)-pyrrolidine-2-carboxylic acid 291 (1.00 g, 8.70 mmol) and sodium carbonate (2.77 g, 26.1 mmol) in water (120 ml) was added 4-tert-butybenzene-1-sulfonyl chloride 292 (2.43 g, 10.4 mmol). The mixture was stirred at 20 °C for 12 h, then washed with ether (3 x 20.0 ml), acidified with concentrated HCl to pH 1.5, saturated with NaCl and extracted with DCM. Rotary evaporation of the solvents afforded the title product 293 (1.90 g, 70%).

Dirhodium (II) tetrakis (heptafluorobutyramide) (295) : To a solution containing rhodium (II) acetate 288 (0.50 g, 1.10 mmol) in 50.0 ml of chlorobenzene was added perfluorobutyramide 294 (12.0 g, 57.0 mmol). The mixture was subsequently refluxed under a Soxhlet extractor equipped with a thimble, containing a 1:1 Na₂CO₃/sand mixture, which was changed daily. After 60 h, the solution was concentrated under reduced pressure and the excess perfluorobutyramide removed by sublimation to afford a purple solid. Following flash column chromatography of the resulting solid on neutral alumina
using a 1:1 hexane/ethylacetate mixture as aluent, the purple fraction was collected and concentration in *vacuo* and dried in an oven to yield a navy blue solid of the title compound 295 (1.02 g, 85%).

![Image](image-url)

mp.: >250 °C. Anal. [Found: C, 18.7; H, 0.7; N, 5.8. C₁₆H₁₄O₄F₂₈N₄Rh₂ requires C, 18.2; H, 0.4; N, 5.3%].

1-methyl-4-phenyl-6-(propan-2-ylidene)-2,8-dioxabicyclo[3.2.1]octan-7-one and 3-methyl-1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-3-ene-1,2-dione (316, 317):
A solution of vinyl diazoketone 315 (0.08 g, 0.28 mmol, 100 mmol/L) in benzene (3.00 ml), was added *via* syringe pump over 20 h to a solution of tetrakis[1-[(4-tert-butylphenyl)sulfonyl]-2S]-pyrrolidinecarboxylate]dirhodium (II), Rh₂(S-TBSP)₄ (3 mol%, 1 mmol/L) in benzene (14.0 ml) maintained at room temperature. Upon complete addition, silica gel was added and the reaction mixture was concentrated *in vacuo*. The residue was then immediately purified by flash chromatography on silica gel (ether/petroleum ether : 1/9 then 2/8) to afford a 2:1 ratio of an inseparable mixture of 316 and 317 as a yellow oil (0.03 g, 42%).

1-methyl-4-phenyl-6-(propan-2-ylidene)-2,8-dioxabicyclo[3.2.1]octan-7-one (316):

![Image](image-url)

νₘₐₓ (ATR) : 2990, 2906, 1734 (C=O), 1650 (C=C), 1476, 1388, 1184, 1097, 926, 890, 833, 745, 715 cm⁻¹. δₗ (700 MHz; CDCl₃) : 7.30 (2H, t, J 7.3, 3'-H), 7.25 (1H, t, J 7.3, 4'-H), 7.13
Chapter IX: Experimental Procedure

(2H, d, J 7.3, 2'-H), 5.05 (1H, d, J 3.9, 5-H), 4.33 (1H, t, J 11.7, 3-Ha), 4.06 (1H, dd, J 11.7, 5.7, 3-Heq), 3.83 (1H, ddd, J 11.7, 5.7, 3.9, 4-H), 2.26 (3H, s, 6-C(CH3)2), 1.44 (3H, s, 1-CH3), 1.03 (3H, s, 6-C(CH3)2). δC (175 MHz; CDCl3) : 200.5 (C-7), 151.6 (C-6), 136.4 (C-1’), 128.8 (C-2’), 128.0 (C-3’), 126.9 (6-C(CH3)2), 100.6 (C-1), 80.1 (C-5), 64.3 (C-3), 44.8 (C-4), 23.6 (6-C(CH3)2), 20.3 (6-C(CH3)2), 18.8 (1-CH3). m/z (GCMS, EI), tR = 9.78 min : 216 (M+-C3H6, 50%), 198 (10), 142 (40), 104 (100), 91 (10), 77 (Ph+, 10). HRMS (ES+) found: 259.1331 (C16H19O3 requires [M+H]+ 259.1329).

3-methyl-1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-3-ene-1,2-dione (317):

(7RS,E/Z)-6-ethyldiene-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (318, 319):

A solution of vinylidazoketone 279 (0.08 g, 0.29 mmol, 100 mmol/L) in benzene (2.60 ml), was added via syringe pump over 20 h to a solution of Rh2(NHCOCH3)2 (5 mol%, 1 mmol/L) in benzene (9.00 ml) maintained at room temperature. After complete addition, the crude solution containing 6-ethenyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one 283 was slowly added into a solution of DIBAL (0.17 ml of a 1 M solution in toluene) in DCM (15.0 ml) at rt. Upon complete addition, the reaction was maintained at this temperature for 16 h, methanol was added and the solution stirred at room temperature for 1 h. Water was then added and the resultant gelatinous precipitate stirred with Celite® until a granular solid was obtained. After filtration through a bed of Celite® and washing of the filter-cake with ethyl acetate, the
Chapter IX: Experimental Procedure

filtrate was concentrated *in vacuo*. The crude residue (which contained a 1:1/318:319 mixture of geometric isomeric enols) was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 9:1 then 8:2) to afford the title bicyclic enols 318 (17 mg, 24%) and 319 (13 mg, 18%) as clear oils.

*(7RS,E)-6-ethylidene-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (318)*

![Chemical Structure of 318](image)

\(\nu_{\text{max}}\) (ATR) : 3398 (OH), 2894, 1668 (C=C), 1610, 1500, 1448, 1389, 1262, 1146, 1098, 1028, 871, 831, 791, 756, 699 cm\(^{-1}\). \(\delta\)\(_{HH}\) (700 MHz; CDCl\(_3\)) : 7.31 (2H, t, J 7.8, 3’-H), 7.25 (1H, t, J 7.8, 4’-H), 7.16 (2H, d, J 7.8, 2’-H), 5.03 (1H, q, J 7.1, 6-CHCH\(_3\)), 4.53 (2H, bd, J 6.5, 5-H, 7-H), 4.42 (1H, t, J 12.2, 3-H\(_{ax}\)), 4.05 (1H, ddd, J 12.2, 5.6, 1.6, 3-H\(_{eq}\)), 3.52 (1H, ddd, J 12.2, 5.6, 3.1, 4-H), 2.16 (1H, d, J 6.5, OH), 1.80 (3H, d, J 7.1, 6-CHCH\(_3\)), 1.52 (3H, s, 1-CH\(_3\)). \(\delta\)\(_{CC}\) (175 MHz; CDCl\(_3\)) : 136.8 (C-1’), 128.4 (C-3’), 128.2 (C-2’), 127.6 (C-6), 127.3 (C-4’), 123.0 (6-CHCH\(_3\)), 103.6 (C-1), 82.6 (C-5), 74.8 (C-7), 64.7 (C-3), 44.5 (C-4), 22.2 (1-CH\(_3\)), 13.7 (6-CHCH\(_3\)). \(m/z\) (ASAP\(^+\)) : 247 ([M+H]\(^+\), 100%), 229 ([M+H\(-\text{H}_2\text{O}\)]\(^+\), 20). HRMS (ASAP\(^+\)) found: 247.1336 (C\(_{15}\)H\(_{10}\)O\(_3\)) requires [M+H]\(^+\) 247.1334.

*(7RS,Z)-6-ethylidene-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (319)*

![Chemical Structure of 319](image)

\(\nu_{\text{max}}\) (ATR) : 3406 (OH), 2894, 1665 (C=C), 1525, 1401, 1391, 1298, 1256, 1153, 1101, 1030, 971, 875, 755, 698, 647 cm\(^{-1}\). \(\delta\)\(_{HH}\) (700 MHz; CDCl\(_3\)) : 7.29 (2H, t, J 7.3, 3’-H), 7.24 (1H, t, J 7.3, 4’-H), 7.17 (2H, d, J 7.3, 2’-H), 5.72 (1H, q, J 7.0, 6-CHCH\(_3\)), 4.85 (1H, bs, 5-H), 4.59 (1H, t, J 11.8, 3-H\(_{ax}\)), 4.32 (1H, s, 7-H), 4.06 (1H, ddd, J 11.8, 5.4, 1.4, 3-H\(_{eq}\)), 3.61 (1H, dd, J 9.5, 4.5, 4.5, 3.5, 1.5).
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5.4, 3.4, 4-H), 2.23 (1H, s, OH), 1.49 (3H, s, 1-CH₃), 0.82 (3H, d, J 7.0, 6-CHCH₃). δ (175 MHz; CDCl₃) : 136.8 (C-1'), 128.8 (C-6), 128.6 (C-3'), 128.1 (C-2'), 127.4 (C-4'), 122.0 (6-CHCH₃), 102.9 (C-1), 80.3 (C-5), 76.6 (C-7), 64.0 (C-3), 44.4 (C-4), 22.3 (1-CH₃), 14.7 (6-CHCH₃). m/z (ASAP⁺) : 247 ([M+H]+, 100%), 229 ([M+H-H₂O]+, 50). HRMS (ASAP⁺) found: 247.1326 (C₁₅H₁₀O₃ requires [M+H]+ 247.1334).

(6SR,7RS)-6-ethyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (320, 322):

Major isomer 320:

A solution of vinyl diazoketone 279 (0.34 g, 1.25 mmol, 100 mmol/L) in benzene (13.0 ml), was added via syringe pump over 20 h to a solution of Rh₂(S-TBSP)₄ (3 mol%, 1 mmol/L) in benzene (38.0 ml) maintained at room temperature. After complete reaction, the mixture was concentrated in vacuo and the crude solution containing 6-ethyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one 283 (0.43 g, 1.76 mmol) taken up in DCM (6.00 ml) was slowly added into a solution of DIBAL (3.50 ml of a 1 M solution in toluene) in DCM (3.00 ml) at -78 °C. Upon complete addition, the reaction was maintained at this temperature for 15 min, methanol was added and the solution stirred at room temperature for 10 min. Water was then added and the resultant gelatinous precipitate stirred with Celite⁰ until a granular solid was obtained. After filtration through a bed of Celite⁰ and washing of the filter-cake with ethyl acetate, the filtrate was concentrated in vacuo. The crude residue was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 9:1 then 8:2) to afford the title bicyclic vinlylalcohol 320 (0.14 g, 45%) as a white solid, [α]²⁰⁻¹D = - 31.2° (c = 0.4, CDCl₃).

Similarly, conducting the initial diazo decomposition step with the achiral Rh₂(hfb)₄ gave the title product 320 in 41% overall yield.
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4.71 (1H, dd, J 10.3, 1.6, 6-CH=CHH), 4.40 (1H, dd, J 11.1, 5.8, 3-H$_{eq}$), 4.17 (1H, dd, J 10.3, 4.1, 7-H), 3.63-3.60 (1H, m, 4-H), 3.30 (1H, td, J 7.1, 6-H), 2.25 (1H, d, J 4.1, OH), 1.53 (3H, s, 1-CH$_3$). $\delta$ C (175 MHz; CDCl$_3$): 173.4 (C-1’), 131.0 (6-CH=CH$_2$), 128.2 (C-3’), 126.5 (C-4’), 126.2 (C-2’), 119.0 (6-CH=CH$_2$), 103.5 (C-1), 81.5 (C-5), 76.3 (C-7), 64.3 (C-3), 49.7 (C-6), 40.0 (C-4), 22.9 (1-CH$_3$). m/z (EI): 246 (M$^+$, 2%), 231 (M$^+$-Me, 6), 143 (40), 104 (100), 91 (PhCH$_2^+$, 10), 77 (Ph$^+$, 5). Anal. [Found: C, 72.6; H, 7.3. C$_{15}$H$_{18}$O$_3$ requires C, 73.1; H, 7.4%].

Minor isomer 322:
A solution of vinyldiazoketone 280 (0.38 g, 1.37 mmol, 100 mmol/L) in benzene (14.0 ml) was added via syringe pump over 20 h to a solution of Rh$_2$(S-TBSP)$_4$ (61 mg, 3 mol%, 1 mmol/L) in benzene (41.0 ml) maintained at room temperature. After complete reaction, the mixture was concentrated in vacuo and the crude solution containing 6-ethenyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one 321 (0.36 g, 1.48 mmol) taken up in DCM (4.00 ml) was slowly added into a solution of DIBAL (3.00 ml of a 1 M solution in toluene) in DCM (3 ml) at -78 °C. On complete addition, the reaction was maintained at this temperature for 15 min, methanol was added and the solution stirred at room temperature for 10 min. Water was then added and the resultant gelatinous precipitate stirred with Celite$^\text{®}$ until a granular solid was obtained. After filtration through a bed of Celite$^\text{®}$ and washing of the filter-cake with ethyl acetate, the filtrate was concentrated in vacuo. The crude residue was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 9:1 then 8:2) to afford the title bicyclic vinylalcohol 322 (0.12 g, 36%) as a colourless oil.

Similarly, conducting the initial diazo decomposition step with the achiral Rh$_2$(hfb)$_4$ gave the title product 322 in 35% overall yield.
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\[ \nu_{\text{max}} \text{(ATR)} : 3450 \text{(OH), 2962, 2930, 1610 (C=O), 1493, 1390, 1116, 1086, 948, 869, 756, 702, 636, 540 cm}^{-1}. \delta_{\text{H}} \text{(500 MHz; CDCl}_3\text{): 7.47 (2H, d, J 7.4, 2'-H), 7.34 (2H, t, J 7.4, 3'-H), 7.25 (1H, t, J 7.4, 4'-H), 6.21-6.14 (1H, m, 6-CH=CH}_2\text{), 5.40 (1H, dd, J 10.4, 1.8, 6-CH=CH}_2\text{H), 5.34 (1H, dd, J 17.0, 1.8, 6-CH=CH}_2\text{H), 4.46 (1H, dd, J 11.8, 5.6, 3-H\text{eq}), 4.27 (1H, bd, J 3.3, 5-H), 4.15 (1H, d, J 10.4, 7-H), 4.02 (1H, dd, J 11.8, 1.3, 3-H\text{ax}), 3.30 (1H, td, J 10.4, 3.3, 6-H), 2.86-2.82 (1H, m, 4-H), 2.05 (1H, s, \text{OH}), 1.53 (3H, s, 1-CH}_3\text{). } \delta_C \text{(125 MHz; CDCl}_3\text{): 142.9 (C-1'), 131.3 (6-CH=CH}_2\text{), 128.4 (C-3'), 128.3 (C-4'), 126.5 (C-2'), 120.5 (6-CH=CH}_2\text{), 103.6 (C-1), 83.3 (C-5), 75.9 (C-7), 64.3 (C-3), 48.7 (C-6), 39.6 (C-4), 23.1 (1-CH}_3\text{). } m/z \text{(EI)} : 246 (M^+, 10%), 231 (M^+-Me, 20), 143 (30), 104 (100), 77 (Ph^+, 10). HRMS (ES^+) found: 247.1324 (C_{15}H_{19}O_3 \text{ requires [M+H]^+ 247.1334).}

(6RS)-6-ethyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one (436, 437):

Major isomer 436:

A two-neck flask filled with 10 wt % palladium-carbon (0.02 g) was argon purged before adding ethanol (2.00 ml). The flask was again argon purged after adding the crude solution containing 6-ethylnyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one 283 (0.10 g, 0.41 mmol) [prepared from a reaction between vinylidiazoketone 279 and Rh$_2$(hfb)$_4$ as per procedure earlier described] in ethanol (5.00 ml) and immediately attaching a high vacuo tap carrying a balloon of hydrogen gas through the second neck. The reaction was stirred for 2 h at room temperature when CHCl$_3$ was added and the solution filtered through a plug of Celite® followed by concentration in vacuo. The residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8 then 3/7) to give the bicyclic ketone 436 as a white crystalline solid (0.04 g, 40%).

\[
\begin{align*}
\text{mp.: } & 69-71 \degree C. \nu_{\text{max}} \text{(ATR): 2874, 1757 (C=O), 1670, 1455, 1382, 1174, 1016, 850, 811, 701, 627 cm}^{-1}. \delta_{\text{H}} \text{(700 MHz; CDCl}_3\text{): 7.32 (2H, t, J 7.6, 3'-H), 7.24 (1H, t, J 7.6, 4'-H), 7.12 (2H, d, J 7.6, 2'-H), 5.09 (1H, dd, J 6.9, 3.6, 5-H ), 4.32 (2H, d, J 4.3, 3-H$_2$), 3.90-3.87 (1H, td, J 4.3, 3.6, 4-H), 2.62 (1H, dt, J 8.7, 6.9, 6-H), 1.61-1.54 (1H, m, 6-CHHCH}_3\text{), 1.45 (3H, s, 1-}
\end{align*}
\]
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(CH), 1.03-0.97 (1H, m, 6-CHHCH3), 0.48 (3H, t, J 7.5, 6-CH2CH3). δ C (175 MHz; CDCl3) : 214.2 (C-7), 136.4 (C-1’), 128.7 (C-2’), 127.0 (C-4’), 126.4 (C-3’), 99.6 (C-1), 79.0 (C-5), 64.3 (C-3), 53.6 (C-6), 41.2 (C-4), 18.6 (1-CH3), 17.2 (6-CH2CH3), 12.0 (6-CH2CH3). m/z (EI) : 246 (M+, 2%), 218 (M+-C2H4, 10), 158 (70), 145 (100), 129 (50), 91 (PhCH2+, 10), 77 (Ph+, 5). HRMS (ASAP+) found: 247.1327 (C15H19O3 requires [M+H]+ 247.1334).

Minor isomer 437:
A two-neck flask filled with 10 wt % palladium-carbon (0.05 g) was argon purged before adding ethanol (2.00 ml). The flask was again argon purged after adding the crude solution containing 6-ethenyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one 321 (0.23 g, 0.94 mmol) [prepared from a reaction between vinyldiazoketone 280 and Rh2(hfb)4 as per procedure earlier described] in ethanol (5.00 ml) and immediately attaching a high vacuo tap carrying a balloon of hydrogen gas through the second neck. The reaction proceeded for 2 h at room temperature when CHCl3 was added and the solution filtered through a plug of Celite® followed by concentration in vacuo. The residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8 then 3/7) to give the bicyclic ketone 437 as a white crystalline solid (85 mg, 37%).

mp.: 81-82 °C. νmax (ATR) : 2962, 2876, 1756 (C=O), 1601, 1457, 1381, 1171, 1074, 987, 844, 765, 741, 701 cm⁻¹, δH (700 MHz; CDCl3) : 7.56 (2H, d, J 7.3, 2’-H), 7.38 (2H, t, J 7.3, 3’-H), 7.30 (1H, t, J 7.3, 4’-H), 4.70 (1H, d, J 7.2, 5-H), 4.19 (1H, dd, J 12.9, 4.8, 3-Hax), 4.11 (1H, t, J 12.9, 3-Heq), 2.73-2.70 (2H, m, 4-H, 6-H), 2.05-1.99 (1H, m, 6-CHHCH3), 1.57-1.51 (1H, m, 6-CHHCH3), 1.44 (3H, s, 1-CH3), 1.17 (3H, t, J 7.5, 6-CH2CH3). δ C (175 MHz; CDCl3) : 214.4 (C-7), 142.4 (C-1’), 128.6 (C-3’), 128.4 (C-2’), 126.9 (C-4’), 99.7 (C-1), 79.6 (C-5), 65.6 (C-3), 52.1 (C-6), 38.7 (C-4), 18.9 (1-CH3), 16.9 (6-CH2CH3), 12.5 (6-CH2CH3). m/z (EI) : 246 (M+, 2%), 218 (M+-C2H4, 6), 158 (60), 145 (100), 91 (PhCH2+, 10), 77 (Ph+, 5). HRMS
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(ASAP\textsuperscript{+}) found: 247.1330 (C\textsubscript{15}H\textsubscript{19}O\textsubscript{3} requires [M+H]\textsuperscript{+} 247.1334). Anal. [Found: C, 73.0; H, 7.4. C\textsubscript{15}H\textsubscript{18}O\textsubscript{3} requires C, 73.2; H, 7.3\%].

3’-ethyl-5-phenylspiro[(1,3)-dioxane-2,1’-inden]-2’(3’H)-one (440):

A two-neck flask filled with 10 wt % palladium-carbon (0.22 g) was argon purged before adding ethanol (7.00 ml). The flask was again argon purged after adding the crude solution containing 3’-ethenyl-5-phenylspiro[(1,3)-dioxane-2,1’-inden]-2’(3’H)-one 438 (1.08 g, 3.53 mmol) [prepared from a reaction between vinyldiazoketone 281 and Rh\textsubscript{2}(hf)\textsubscript{4} as per procedure earlier described] in ethanol (10.0 ml) and immediately attaching a high vacuo tap carrying a balloon of hydrogen gas through the second neck. The reaction went on for 2 h at room temperature before diluting with CHCl\textsubscript{3}, filtered through a plug of Celite\textsuperscript{®} and concentrated in vacuo. The residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8 then 3/7) to give the spiro-ketone 440 as a white crystalline solid (0.45 g, 41\%).

\[
\text{mp.: 134-136 } \degree\text{C. } \nu_{\text{max}} \text{(ATR)} : 2968, 1736 (C=O), 1498, 1462, 1330, 1284, 1076, 1013, 984, 872, 756, 699 \text{ cm}^{-1}. \delta_{\text{H}} (700 \text{ MHz; CDCl}_3) : 7.65 (1H, d, J 7.6, 7’-H), 7.47 (1H, t, J 7.6, 6’-H), 7.43 (1H, t, J 7.6, 5’-H), 7.39-7.36 (4H, m, 2’’-H, 3’’-H), 7.33 (1H, d, J 7.6, 4’-H), 7.32-7.28 (1H, m, 4’’-H), 4.89 (1H, t, J 11.8, 4-H\textsubscript{ax}), 4.79 (1H, t, J 11.8, 6-H\textsubscript{ax}), 4.08 (2H, dd, J 11.8, 5.2, 4-H\textsubscript{eq}, 6-H\textsubscript{eq}), 3.59 (1H, t, J 5.8, 3’-H), 3.53 (1H, tt, J 11.8, 5.2, 5’-H), 2.11-2.05 (1H, m, 3’-CH\textsubscript{2}CH\textsubscript{3}), 2.02-1.96 (1H, m, 3’-CH\textsubscript{2}CH\textsubscript{3}), 0.95 (3H, t, J 7.5, 3’-CH\textsubscript{2}CH\textsubscript{3}). \delta_{\text{C}} (175 \text{ MHz; CDCl}_3) : 213.1 (C-2’), 140.1 (C-8’), 139.5 (C-9’), 137.7 (C-1’’), 130.7 (C-7’), 128.7 (C-2’’), 128.2 (C-3’’), 128.0 (C-4’’), 127.5 (C-4’), 124.4 (C-6’), 124.1 (C-5’), 94.7 (C-2), 67.1 (C-4), 66.8 (C-6), 50.8 (C-3’), 41.3 (C-5), 24.4 (3’-CH\textsubscript{2}CH\textsubscript{3}), 10.6 (3’-CH\textsubscript{2}CH\textsubscript{3}). m/z (ES\textsuperscript{+}) : 372 ([M+Na+CH\textsubscript{3}CN]\textsuperscript{+}, 40\%), 331 ([M+Na]\textsuperscript{+}, 10), 328 (100), 309 ([M+H]\textsuperscript{+}, 80). HRMS (ES\textsuperscript{+}) found: 309.1486 (C\textsubscript{20}H\textsubscript{20}O\textsubscript{3} requires [M+H]\textsuperscript{+} 309.1491). Anal. [Found: C, 77.2; H, 6.5. C\textsubscript{20}H\textsubscript{20}O\textsubscript{3} requires C, 77.9; H, 6.5\%].
5-benzyl-3’-ethylspiro[(1,3)-dioxane-2,1’-inden]-2’(3’H)-one (441):
A two-neck flask filled with 10 wt% palladium-carbon (0.09 g) was argon purged before adding ethanol (4.00 ml). The flask was again argon purged after adding the crude solution containing 5-benzyl-3’-ethenylspiro[(1,3)dioxane-2,1’-inden]-2’(3’H)-one 439 (0.47 g, 1.47 mmol) [prepared from a reaction between vinyldiazoketone 282 and Rh₂(hfb)_₄ as per procedure earlier described] in ethanol (5.00 ml) and immediately attaching a high vacuo tap carrying a balloon of hydrogen gas through the second neck. The reaction went on for 2 h at room temperature before diluting with CHCl₃, filtered through a plug of Celite® and concentrated in vacuo. The residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8 then 3/7) to give the spiro-ketone 441 as a white crystalline solid (0.12 g, 25%).

mp.: 153-155 °C. ν_max (ATR) : 2966, 1732 (C=O), 1478, 1461, 1325, 1281, 1070, 1010, 976, 860, 754, 654 cm⁻¹. δ_H (700 MHz; CDCl₃) : 7.52 (1H, d, J 7.9, 7’-H), 7.42 (1H, t, J 7.9, 6’-H), 7.36 (1H, t, J 7.9, 5’-H), 7.31 (2H, t, J 7.5, 3’-H), 7.28 (1H, d, J 7.9, 4’-H), 7.23 (1H, t, J 7.5, 4’’-H), 7.19 (2H, d, J 7.5, 2’’-H), 4.46 (1H, t, J 11.5, 4-H_ax), 4.38 (1H, t, J 11.5, 6-H_ax), 3.91-3.88 (2H, m, 4-H_equ, 6-H_equ), 3.51 (1H, t, J 5.8, 3’-H), 2.63-2.56 (1H, m, 5’-H), 2.52 (2H, d, J 7.6, 5-CH_2Ph), 2.05-1.99 (1H, m, 3’-CH_HCH₃), 1.97-1.91 (1H, m, 3’-CH_HCH₃), 0.91 (3H, t, J 7.6, 3’-CH_2CH₃). δ_C (175 MHz; CDCl₃) : 213.1 (C-2’), 140.0 (C-8’), 139.6 (C-9’), 138.2 (C-1’’), 130.6 (C-7’), 128.7 (C-2’’), 128.5 (C-3’’), 128.1 (C-4’’), 126.4 (C-4’), 124.4 (C-6’), 124.1 (C-5’), 95.0 (C-2), 67.1 (C-4), 66.9 (C-6), 50.7 (C-3’), 36.0 (C-5), 34.8 (5-CH_2Ph), 24.4 (3’-CH_2CH₃), 10.7 (3’-CH_2CH₃). m/z (ES⁺) : 323 ([M+H]^+, 100). HRMS (ES⁺) found: 323.1651 (C₁₂H₂₁O₃ requires [M+H]^+ 323.1647). Anal. [Found: C, 77.8; H, 6.9. C₁₂H₂₁O₃ requires C, 78.2; H, 6.9%].

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(2SR)-((6’RS,7’RS)-6’-ethenyl-1’-methyl-4’-phenyl-2’,8’dioxabicyclo[3.2.1]octan-7’-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (323, 324):

Oxalyl chloride (53 µl, 0.61 mmol) was added to a solution of (S)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) (30 mg, 0.13 mmol) and DMF (9.00 µl, 0.13 mmol) in hexane (0.50 ml) at room temperature. A white precipitate formed immediately. After 1 h the mixture was filtered and concentrated in vacuo. A solution of bicyclic alcohol 320 (21 mg, 0.09 mmol) – obtained using chiral Rh₂(S-TBSP)₄ catalyst, triethylamine (36 µl, 0.26 mmol) and a catalytic amount of DMAP (3 mg, 0.02 mmol) in CDCl₃ (50 µl) were added to the residue. After 24 h, ¹H NMR revealed complete conversion into the diastereomeric Mosher’s esters. The reaction was quenched with saturated aqueous NaHCO₃, extracted with DCM (3 × 2.00 ml) and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to give an inseparable mixture (77:23) of diastereomeric title product 323 and 324 as an oil (34 mg, 86%).

The use of bicyclic alcohol 320 obtained using the achiral Rh₂(hfb)₄ catalyst led to an inseparable mixture of diastereomeric Mosher’s esters 323 and 324 (60%) in ratio 1:1.

Major diastereoisomer 323:

νₖₐₓₙ (ATR) : 2974, 1752 (C=O), 1649 (C=C), 1451, 1389, 1249, 1169, 1065, 1024, 990, 870, 757, 697 cm⁻¹. δₕ (700 MHz; CDCl₃) : 7.64 (2H, d, J 7.1, 2b’’-H), 7.44-7.40 (3H, m, 3b’’-H, 4b’’-H), 7.24 (2H, t, J 7.6, 3a’’-H), 7.18 (1H, t, J 7.6, 4a’’-H), 6.98 (2H, d, J 7.6, 2a”-H), 5.45 (1H, d, J 10.9, 7’-H), 5.19 (1H, dt, J 16.7, 10.3, 6’-CH=CH₂), 4.87 (1H, dd, J 16.7, 1.7, 6’-CH=CHH), 4.78 (1H, bd, J 4.5, 5’-H), 4.53 (1H, dd, J 10.3, 1.7, 6’-CH=CHH), 4.52 (1H, t, J 12.0, 3’-Hₐₐ), 4.29 (1H, dd, J 12.0, 5.7, 3’-Hₑₒₓ), 3.65-3.63 (1H, m, 4’-H), 3.62 (3H, s, 2-OCH₃), 3.51-3.45 (1H, m, 6’-H), 1.57 (3H, s, 1’-CH₃). δₜ (376.3 MHz; CDCl₃) : -71.26. δₐ (175 MHz; CDCl₃) : 165.6 (C-1), 136.9 (C-1a’’), 132.4 (C-1b’’), 129.6 (C-2b’’), 128.9 (6’-CH=CH₂), 128.4 (C-4b’’), 128.3 (C-3a’’), 127.3 (C-2b’’), 126.6 (C-4a’’), 126.2 (C-2a’’), 124.2
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(CF₃), 122.6 (C-2), 119.8 (6'-CH=CH₂), 102.8 (C-1'), 81.7 (C-5'), 77.9 (C-7'), 63.6 (C-3'), 55.6 (2-OCH₃), 48.6 (C-6'), 39.8 (C-4'), 23.6 (1'-CH₃). m/z (GCMS, EI), tᵣ = 11.16 min : 462 (M⁺, 5%), 434 (M⁺-C₅H₄, 10), 229 (30), 189 (80), 104 (100), 91 (10), 77 (Ph⁺,5). m/z (ASAP⁺) : 463 ([M+H]⁺, 20%), 446 ([M-Me₄C]⁺, 10), 214 ([M-Me₄CPh(CF₃)(OCH₃)COO]⁺, 90), 141 (100). HRMS (ASAP⁺) found: 463.1725 (C₂₅H₂₆O₇F₃ requires [M+H]⁺ 463.1732).

Minor diastereoisomer 324:
δ₀H (700 MHz; CDCl₃) : 7.58 (2H, d, J 7.1, 2b''-H), 7.44-7.40 (3H, m, 3b''-H, 4b''-H), 7.24 (2H, t, J 7.6, 3a''-H), 7.18 (1H, t, J 7.6, 4a''-H), 6.98 (2H, d, J 7.6, 2a''-H), 5.41 (1H, d, J 10.9, 7''-H), 5.37 (1H, dt, J 16.7, 10.3, 6'-CH=CH₂), 4.95 (1H, dd, J 16.7, 1.7, 6'-CH=CHH), 4.78 (1H, bd, J 4.5, 5''-H), 4.66 (1H, dd, J 10.3, 1.7, 6'-CH=CHH), 4.33 (1H, t, J 12.0, 3''-Hₐ), 4.12 (1H, dd, J 12.0, 5.7, 3''-Hₑq), 3.60-3.57 (1H, m, 4''-H), 3.55 (3H, s, 2-OCH₃), 3.41-3.39 (1H, m, 6''-H), 1.59 (3H, s, 1''-CH₃). δ₀C (175 MHz; CDCl₃) : 165.7 (C-1), 137.0 (C-1a'''), 132.0 (C-1b'''), 129.5 (C-2b'''), 128.7 (6'-CH=CH₂), 128.3 (C-4b'''), 128.3 (C-3a'''), 127.6 (C-2b'''), 126.6 (C-4a'''), 126.2 (C-2a'''), 124.1 (CF₃), 122.5 (C-2), 119.7 (6'-CH=CH₂), 103.0 (C-1'), 81.4 (C-5'), 78.4 (C-7'), 63.5 (C-3'), 55.5 (2-OCH₃), 48.5 (C-6'), 39.7 (C-4'), 23.7 (1'-CH₃). m/z (GCMS, EI), tᵣ = 11.21 min : 462 (M⁺, 5%), 434 (M⁺-C₂H₄, 10), 229 (20), 189 (70), 133 (20), 104 (100), 91 (10), 77 (Ph⁺,5).

(6RS,7RS)-6-ethenyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octa-7-yl-4-bromobenzoate (361):
To a solution of bicyclic alcohol 320 (0.03 g, 0.12 mmol) in DCM (2.00 ml), triethylamine (0.09 ml, 0.61 mmol) and a catalytic amount of DMAP (7.4 mg, 0.06 mmol) were added at room temperature and the reaction mixture was stirred for 0.5 h. 4-bromobenzoyl chloride (0.05 g, 0.24 mmol) in DCM (1.00 ml) was added dropwise to the reaction mixture and further stirring continued at room temperature overnight. The reaction was quenched with saturated aqueous NaHCO₃, extracted with DCM (2 × 8.00 ml) and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to give the protected product 361 as an oil (0.05 g, 96%).
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\[\text{\textit{ tert-butylidimethyl\[(6RS,7RS)-1-methyl-4-phenyl-6-ethenyl-2,8-dioxabicyclo[3.2.1]octan-7-yloxy\]silane}} (362) :\]

To a solution of bicyclic alcohol 320 (0.09 g, 0.36 mmol) in DCM (5.00 ml) at room temperature under argon was added triethylamine (0.40 ml, 2.89 mmol), and tert-butylidimethylsilyl trifluoromethanesulphonate (TBDSOTf) (30 µl, 0.14 mmol). After stirring at room temperature overnight, a saturated solution of aqueous NaCl was added and the mixture was extracted with DCM (3 x 10.0 ml). The combined organic extracts were dried over MgSO\(_4\), filtered and solvent was evaporated under reduced pressure. Purification of the crude residue by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) afforded the title TBDMS product 362 as an oil (0.10 g, 80%).
\( v_{\text{max}} \) (ATR) : 2956, 2940-2862 (CH-OSi), 1468 (C=C), 1388, 1256+838 (Si-CH\(_3\)), 1188, 1130, 1040, 990, 906, 778, 760, 698, 664 cm\(^{-1}\). \( \delta_{\text{H}} \) (700 MHz; CDCl\(_3\)) : 7.26 (2H, t, J 7.5, 3'-\text{-H}), 7.18 (1H, t, J 7.5, 4'-\text{-H}), 7.08 (2H, d, J 7.5, 2'-\text{-H}), 5.55 (1H, td, J 17.1, 10.2, 6-CH=CH\(_2\)), 4.89 (1H, t, J 11.3, 3-\text{-H\(_{ax}\)}), 4.82 (1H, dd, J 17.1, 2.0, 6-CH=CHH), 4.74 (1H, ddd, J 7.1, 3.3, 1.5, 5-\text{-H}), 4.60 (1H, dd, J 10.2, 2.0, 6-CH=CHH), 4.32 (1H, ddd, J 11.3, 5.7, 1.5, 3-\text{-H\(_{eq}\)}), 4.14 (1H, d, J 10.2, 7-\text{-H}), 3.61-3.58 (1H, m, 4-\text{-H}), 3.27 (1H, td, J 10.2, 7.1, 6-\text{-H}), 1.47 (3H, s, 1-CH\(_3\)), 0.95 (9H, s, SiC(CH\(_3\))\(_3\)), 0.10 (3H, s, Si(CH\(_3\))\(_2\)), 0.01 (3H, s, Si(CH\(_3\))\(_3\)). \( \delta_{\text{C}} \) (175 MHz; CDCl\(_3\)) : 137.9 (C-1'), 132.4 (6-CH=CH\(_2\)), 128.1 (C-3'), 126.3 (C-2'), 126.3 (C-4'), 117.8 (6-CH=CH\(_2\)), 103.4 (C-1), 81.8 (C-5), 77.3 (C-7), 63.9 (C-3), 50.5 (C-6), 40.3 (C-4), 25.9 (SiC(CH\(_3\))\(_3\)), 23.2 (1-CH\(_3\)), 18.1 (SiC(CH\(_3\))\(_3\)), -4.3 (Si(CH\(_3\))\(_2\)), -4.6 (Si(CH\(_3\))\(_2\)). m/z (ES\(^+\)) : 401 ([M+Na+H\(_2\)O]\(^+\), 10%), 383 ([M+Na]\(^+\), 5), 378 ([M+H\(_2\)O]\(^+\), 30), 361 ([M+H]\(^+\), 60), 360 (M\(^+\), 70). HRMS (ES\(^+\)) found: 361.2195 (C\(_{21}\)H\(_{33}\)O\(_3\)Si requires [M+H]\(^+\) 361.2194).

(6SR,7RS)-6-ethyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (370, 373):

Major isomer 370:

NaBH\(_4\) (10 mg, 0.26 mmol) was added to a solution of bicyclic ketone 436 (0.04 g, 0.16 mmol) in MeOH (5.00 ml) at room temperature and the reaction mixture stirred at room temperature overnight. It was then diluted with DCM, saturated solution of ammonium chloride (NH\(_4\)Cl) was added and the organic layer was then separated, this layer was washed with brine (NaCl). The organic extracts were dried over magnesium sulphate (MgSO\(_4\)), filtered and concentrated in vacuo. The residue was subsequently purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2 then 7/3) to give alcohol 370 as a clear oil (30 mg, 76%).
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$\nu_{\text{max}}$ (ATR): 3445-3231 (broad $\text{OH}$), 1604, 1499, 1182, 1110, 1027, 881, 754, 698, 622 cm$^{-1}$. $\delta_{\text{H}}$ (700 MHz; CDCl$_3$): 7.30 (2H, t, J 7.7, 3'-$\text{H}$), 7.21 (1H, t, J 7.7, 4'-$\text{H}$), 7.14 (2H, d, J 7.7, 2'-$\text{H}$), 4.77 (1H, t, J 11.5, 3-$\text{H}_{\text{ax}}$), 4.67-4.65 (1H, bs, 5-$\text{H}$), 4.29 (1H, dd, J 11.5, 5.8, 3-$\text{H}_{\text{eq}}$). 4.15 (1H, d, J 10.2, 7-$\text{H}$), 3.60-3.57 (1H, m, 4-$\text{H}$), 2.47-2.42 (1H, m, 6-$\text{H}$), 1.97-2.04 (1H, bs, $\text{OH}$), 1.51 (3H, s, 1-$\text{CH}_3$), 1.39-1.33 (1H, m, 6-$\text{CHHCH}_3$), 0.87-0.81 (1H, m, 6-$\text{CHHCH}_3$). 0.56 (3H, t, J 7.2, 6-$\text{CH}_2\text{CH}_3$). $\delta_{\text{C}}$ (175 MHz; CDCl$_3$): 137.6 (C-1'), 128.4 (C-2'), 126.51 (C-4'), 126.48 (C-3'), 103.8 (C-1), 81.4 (C-5), 75.5 (C-7), 64.0 (C-3), 47.4 (C-6), 40.6 (C-4), 23.1 (1-$\text{CH}_3$), 16.5 (6-$\text{CH}_2\text{CH}_3$), 13.4 (6-$\text{CH}_2\text{CH}_3$). $m/z$ (ES$^+$): 303 (60%), 289 ([M+CH$_3$CN]$^+$, 20), 249 ([M+H]$^+$, 20). HRMS (ES$^+$) found: 249.1486 (C$_{15}$H$_2$O$_3$) requires [M+H]$^+$ 249.1485.

Minor isomer 373:

NaBH$_4$ (10 mg, 0.26 mmol) was added to a solution of bicyclic ketone 437 (0.03 g, 0.12 mmol) in MeOH (5.00 ml) at room temperature and the reaction mixture stirred at room temperature overnight. It was then diluted with DCM, saturated solution of ammonium chloride (NH$_4$Cl) was added and the organic layer was then separated, this layer was washed with brine (NaCl). The organic extracts were dried over magnesium sulphate (MgSO$_4$), filtered and concentrated in vacuo. The residue was subsequently purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 8/2 then 7/3) to give alcohol 373 as a clear oil (25 mg, 86%).

$\nu_{\text{max}}$ (ATR): 3452-3430 (broad $\text{OH}$), 2962, 1603, 1493, 1390, 1162, 1080, 948, 868, 756, 699, 592 cm$^{-1}$. $\delta_{\text{H}}$ (700 MHz; CDCl$_3$): 7.43 (2H, d, J 7.6, 2'-$\text{H}$), 7.34 (2H, t, J 7.6, 3'-$\text{H}$), 7.25 (1H, t, J 7.6, 4'-$\text{H}$), 4.28-4.26 (2H, m, 3-$\text{H}_{\text{eq}}$, 5-$\text{H}$), 4.07 (1H, dd, J 9.3, 6.8, 7-$\text{H}$), 3.94 (1H, dd, J 11.5, 4.6, 3-$\text{H}_{\text{ax}}$), 2.84-2.82 (1H, m, 4-$\text{H}$), 2.41-2.36 (1H, m, 6-$\text{H}$), 2.28 (1H, d, J 6.8, $\text{OH}$), 1.79-1.73 (1H, m, 6-$\text{CHHCH}_3$), 1.53-1.49 (1H, m, 6-$\text{CHHCH}_3$), 1.52 (3H, s, 1-$\text{CH}_3$), 1.05 (3H, t, J 7.2, 6-$\text{CH}_2\text{CH}_3$). $\delta_{\text{C}}$ (175 MHz; CDCl$_3$): 142.9 (C-1'), 128.5 (C-3'), 128.1 (C-2'), 126.6 (C-4'), 103.7 (C-1), 82.6 (C-5), 75.6 (C-7), 64.2 (C-3), 46.4 (C-6), 39.9 (C-4), 23.1 (1-$\text{CH}_3$), 22.8.

(2RS,3RS,4SR,5SR,1’RS)-4-ethenyl-5-(2’-Hydroxy-1’-phenylethyl)-2-methyltetrahydrofuran-3-ol (357, 358) :
To a solution of bicyclic alcohol 320 (0.03 g, 0.12 mmol) in DCM (5.00 ml) at -78 °C was added triethylsilane (80 µl, 0.48 mmol) followed by the dropwise addition of a 1 M solution of titanium tetrachloride (0.15 ml, 0.14 mmol). After stirring at this temperature for 2 h, the reaction mixture was quenched with an aqueous solution of NaCl and extracted with DCM (3 × 20.0 ml). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The crude residue, containing a mixture of two tetrahydrofuran isomers 357 and 358 in a 6:4 ratio, was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to afford the title isomers 357 as a colourless oil (20 mg, 66%) and 358 as an oil (10 mg, 33%).

4-ethenyl-5-(2’-Hydroxy-1’-phenylethyl)-2-methyltetrahydrofuran-3-ol (357) :

\[
\begin{align*}
&\text{H} \\
&\text{O} \\
&\text{CH₃} \\
&\text{H} \\
&\text{O} \\
&\text{OH} \\
&\text{OH} \\
\end{align*}
\]

ν_max (ATR) : 3411 (OH), 2875, 1642 (C=O), 1460, 1388, 1234, 1071, 999, 918, 751, 700, 665 cm⁻¹. δ_H (700 MHz; CDCl₃) : 7.41 (2H, d, J 7.3, 2’-H), 7.36 (2H, t, J 7.3, 3’-H), 7.29 (1H, t, J 7.3, 4’-H), 5.86 (1H, dt, J 17.3, 10.1, 4-CCH=CH₂), 5.32 (1H, dd, J 10.1, 1.6, 4-CH=C(HH), 5.25 (1H, dd, J 17.3, 1.6, 4-CH=C(HH), 4.34 (1H, dd, J 7.7, 5.7, 5-H), 4.00 (1H, dd, J 5.8, 4.9, 3-H), 3.93 (1H, dq, J 6.4, 4.9, 2-H), 3.88 (1H, dd, J 10.8, 7.3, 2’-H), 3.85 (1H, dd, J 10.8, 5.7, 2’-H), 3.11 (1H, ddd, J 10.1, 7.7, 5.8, 4-H), 3.01 (1H, dt, J 7.3, 5.7, 1’-H), 1.48 (1H, bs, OH), 1.18 (3H, d, J 6.4, 2-CCH₃). δ_C (175 MHz; CDCl₃) : 139.2 (C-1’’), 132.9 (4-CH=C(HH), 129.7 (C-2’’), 128.8 (C-3’’), 127.5 (C-4’’), 120.2 (4-CH=C(HH), 79.5 (C-5), 77.6 (C-2), 74.9 (C-3), 65.5 (C-2’), 52.6 (C-4), 49.3 (C-1’), 14.8 (2-CCH₃). m/z (ASAP⁺) : 272 ([M+H+Na]⁺, 10%), 231 ([M+H-H₂O]⁺, 100), 213 ([M+H+2×H₂O]⁺, 40), 185 ([M+H-2×H₂O-C₃H₄]⁺, 60), 157 (70). HRMS (ASAP⁺) found: 231.1383 (C₁₃H₁₉O₂ requires [M+H-H₂O]⁺ 231.1385).
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4-ethyl-5-(2'-Hydroxyl-1' -phenylethyl)-2-methyltetrahydrofuran-3-ol (358):

\[
\begin{align*}
\begin{array}{c}
\text{\textbf{\textit{H}}}
\end{array}
\end{align*}
\]

\(v_{\text{max}}\) (ATR) : 3380 (OH), 2914, 1642 (C=C), 1460, 1384, 1061, 969, 919, 752, 699, 666 cm\(^{-1}\).

\(\delta_{\text{H}}\) (700 MHz; CDCl\(_3\)) : 7.35 (2H, t, \text{J} 7.5, 3''-H), 7.31 (2H, d, \text{J} 7.5, 2''-H), 7.27 (1H, t, \text{J} 7.5, 4''-H), 5.93 (1H, dt, \text{J} 17.1, 10.4, 4-CH=CH\(_2\)), 5.47 (1H, dd, \text{J} 10.4, 1.6, 4-CH=CH\(_2\)), 5.37 (1H, dd, \text{J} 17.1, 1.6, 4-CH=CH\(_2\)), 4.47 (1H, dd, \text{J} 9.2, 4.4, 5-H), 3.98 (1H, dd, \text{J} 13.0, 6.3, 3-H), 3.80 (1H, dd, \text{J} 11.5, 4.7, 2'-HH), 3.78 (1H, dq, \text{J} 13.0, 6.4, 2-H), 3.74 (1H, dd, \text{J} 11.5, 7.2, 2'-HH), 3.05-3.01 (2H, m, 4-H, 1'-H), 1.43 (1H, s, OH), 1.22 (3H, d, \text{J} 6.4, 2-CH\(_3\)).

\(\delta_{\text{C}}\) (175 MHz; CDCl\(_3\)) : 139.3 (C-1'''), 131.8 (4-CH=CH\(_2\)), 128.8 (C-2''', C-3'''), 127.2 (C-4'''), 122.1 (4-CH=CH\(_2\)), 79.5 (C-3), 78.8 (C-2), 78.1 (C-5), 64.5 (C-2'), 52.1 (C-1'), 49.6 (C-4), 19.5 (2-CH\(_3\)).


(2RS,3RS,4SR,5SR,1'SR)-4-ethyl-5-(2'-Hydroxyl-1' -phenylethyl)-2-methyltetrahydrofuran-3-ol (359, 360):

To a solution of bicyclic alcohol 322 (33 mg, 0.13 mmol) in DCM (5.00 ml) at -78 °C was added triethylsilane (90 µl, 0.53 mmol) followed by the dropwise addition of a 1 M solution of titanium tetrachloride (0.16 ml, 0.16 mmol). After stirring at this temperature for 2 h, the reaction mixture was quenched with an aqueous solution of NaCl and extracted with DCM (3 × 10.0 ml). The combined organic extracts were dried over MgSO\(_4\), filtered and concentrated in vacuo. The crude residue, containing a mixture of two tetrahydrofuran isomers 359 and 360 in a 6:4 ratio, was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to afford the title isomers 359 (14 mg, 42%) and 360 (10 mg, 29%) as colourless oils.
4-ethyl-5-(2’-Hydroxyl-1’-phenylethyl)-2-methyltetrahydrofuran-3-ol (359):

\[
\text{\[M+H\]}^{+} = 182.9 (700 MHz; CDCl}_3, 5.24 (1H, ddd, J 10.3, 2.0, 4-CH=CHH), 4.92 (1H, dd, J 17.4, 2.0, 4-CH=CHH), 4.26 (1H, bd, J 10.3, 3-H), 4.21 (1H, dd, J 9.5, 5.2, 5-H), 4.13 (1H, q, J 6.4, 2-H), 4.00 (2H, d, J 3.9, 2’-H), 3.14 (1H, td, J 9.5, 3.9, 1’-H), 2.72 (1H, dt, J 10.3, 5.2, 4-H), 1.84 (1H, bs, OH), 1.26 (3H, d, J 6.4, 2-CH\textsubscript{3}). \delta \text{C (175 MHz; CDCl}_3) = 139.1 (C-1’’), 132.0 (4-CH=CH\textsubscript{2}), 128.5 (C-2’’), 128.3 (C-3’’), 127.0 (C-4’’), 121.1 (4-CH=CH\textsubscript{2}), 82.9 (C-5), 77.7 (C-2), 73.9 (C-3), 67.6 (C-2’), 52.3 (C-4), 48.4 (C-1’), 15.7 (2-CH\textsubscript{3}). m/z (ES\textsuperscript{+}) = 312 ([M+Na\textsubscript{+}]\textsuperscript{+}, 40%), 271 ([M+Na\textsubscript{+}]\textsuperscript{+}, 80), 231 ([M+H-H\textsubscript{2}O\textsuperscript{+}], 100), 213 ([M+H-2 \times H\textsubscript{2}O\textsuperscript{+}], 20). HRMS (ES\textsuperscript{+}) found: 249.1497 (C\textsubscript{15}H\textsubscript{21}O\textsubscript{3} requires [M+H]\textsuperscript{+} 249.1491).

4-ethyl-5-(2’-Hydroxyl-1’-phenylethyl)-2-methyltetrahydrofuran-3-ol (360):

\[
\text{\[M+H\]}^{+} = 182.9 (700 MHz; CDCl}_3, 5.24 (1H, ddd, J 10.3, 2.0, 4-CH=CHH), 4.92 (1H, dd, J 17.4, 2.0, 4-CH=CHH), 4.26 (1H, bd, J 10.3, 3-H), 4.21 (1H, dd, J 9.5, 5.2, 5-H), 4.13 (1H, q, J 6.4, 2-H), 4.00 (2H, d, J 3.9, 2’-H), 3.14 (1H, td, J 9.5, 3.9, 1’-H), 2.72 (1H, dt, J 10.3, 5.2, 4-H), 1.84 (1H, bs, OH), 1.26 (3H, d, J 6.4, 2-CH\textsubscript{3}). \delta \text{C (175 MHz; CDCl}_3) = 139.1 (C-1’’), 132.0 (4-CH=CH\textsubscript{2}), 128.5 (C-2’’), 128.3 (C-3’’), 127.0 (C-4’’), 121.1 (4-CH=CH\textsubscript{2}), 82.9 (C-5), 77.7 (C-2), 73.9 (C-3), 67.6 (C-2’), 52.3 (C-4), 48.4 (C-1’), 15.7 (2-CH\textsubscript{3}). m/z (ES\textsuperscript{+}) = 312 ([M+Na\textsubscript{+}]\textsuperscript{+}, 40%), 271 ([M+Na\textsubscript{+}]\textsuperscript{+}, 80), 231 ([M+H-H\textsubscript{2}O\textsuperscript{+}], 100), 213 ([M+H-2 \times H\textsubscript{2}O\textsuperscript{+}], 20). HRMS (ES\textsuperscript{+}) found: 249.1497 (C\textsubscript{15}H\textsubscript{21}O\textsubscript{3} requires [M+H]\textsuperscript{+} 249.1491).
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128.5 (C-2’’), 128.3 (C-3’’), 127.1 (C-4’’), 122.5 (4-CH=CH2), 83.2 (C-3), 79.3 (C-2), 78.7 (C-5), 67.8 (C-2’), 52.2 (C-1’), 48.9 (C-4), 19.6 (2-CH3). m/z (ES\(^{+}\)) : 271 ([M+Na]\(^+\), 90%), 249 ([M+H]\(^+\), 100), 231 ([M+H-H2O]\(^+\), 70). HRMS (ES\(^{+}\)) found: 249.1482 (C\(_{15}\)H\(_{21}\)O\(_3\) requires [M+H]\(^+\) 249.1491).

\((2'SR,3'SR,4'SR,5'SR,1'SR)\)-4'-ethenyl-5’-(2’’-Hydroxy-1’’-phenylethyl)-2’-methyltetrahydrofuran-3’-yl-4-bromobenzoate (363, 364) :

To a solution of bromobenzoyl protected bicyclic alcohol 361 (0.04 g, 0.09 mmol) in DCM (3.00 ml) at -78 °C was added triethylsilane (60 µl, 0.35 mmol) followed by the dropwise addition of a 1 M solution of titanium tetrachloride (0.10 ml, 0.10 mmol). After stirring at this temperature for 2 h, the reaction mixture was quenched with an aqueous solution of NaCl and extracted with DCM (3 × 10.0 ml). The combined organic extracts were dried over MgSO\(_4\), filtered and concentrated in vacuo. The crude residue, containing a mixture of two tetrahydrofuran isomers 363 and 364 in an 8:2 ratio, was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to afford the title isomers 363 as a colourless oil (30 mg, 80%) and 364 as an oil (5 mg, 12%).

\(4’\)-ethenyl-5’-(2’’-Hydroxy-1’’-phenylethyl)-2’-methyltetrahydrofuran-3’-yl-4-bromobenzoate (363) :

\[\text{\begin{align*}
\begin{array}{c}
\text{Br} \\
\text{\prop} \\
\text{\prop} \\
\text{\prop} \\
\text{\prop} \\
\text{\prop} \\
\text{\prop} \\
\end{array}
\end{align*}\]

\(\nu_{\text{max}}\) (ATR) : 3488-3358 (OH), 2930, 2878, 1720 (C=O), 1632 (C=C), 1588, 1490, 1398, 1274, 1104, 1070, 1010, 922, 846, 751, 699 cm\(^{-1}\), \(\delta\)H (500 MHz; CDCl\(_3\)) : 7.68 (2H, d, J 8.6, 2b’’-H), 7.54 (2H, d, J 8.6, 3b’’-H), 7.39-7.35 (3H, m, 3a’’-H, 4a’-H), 7.32 (2H, d, J 7.5, 2a’’-H), 5.82 (1H, dt, J 16.6, 10.5, 4’-CH=CH\(_2\)), 5.51 (1H, t, J 6.6, 3’-H), 5.16 (1H, dd, J 16.6, 1.7, 4’-CH=CH\(_2\)), 5.15 (1H, dd, J 10.5, 1.7, 4’-CH=CH\(_2\)), 4.25 (1H, dd, J 8.3, 5.8, 5’-H), 4.13 (1H, dq, J 6.6, 6.4, 2’-H), 3.84 (1H, dd, J 10.8, 5.0, 2’’-HH), 3.78 (1H, dd, J 10.8, 7.5, 2’’-HH),

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3.37 (1H, ddd, J 10.5, 6.6, 5.8, 4'-\textit{H}), 3.06 (1H, ddd, J 8.3, 7.5, 5.0, 1''-\textit{H}), 1.24 (3H, d, J 6.4, 2'-'CH\textsubscript{3}). \(\delta\textsubscript{C} (125 MHz; CDCl\textsubscript{3}) : 164.9 (C-1), 139.7 (C-1a''), 132.3 (C-1b'', C-4b''), 131.7 (C-3b''), 131.1 (C-2b''), 129.2 (4'-CH=CH\textsubscript{2}), 128.6 (C-2a'', C-3a''), 127.0 (C-4b'), 119.8 (4'-CH=CH\textsubscript{2}), 79.2 (C-5'), 76.5 (C-3'), 75.6 (C-2''), 64.6 (C-2'''), 50.9 (C-4'), 48.9 (C-1''), 15.5 (2'-'CH\textsubscript{3}). \(m/z\) (ES\textsuperscript{+}) : 885 ([2M+Na]\textsuperscript{+}, 40%), 431 ([M+H]\textsuperscript{+}, 100). HRMS (ES\textsuperscript{+}) found: 431.0866 (C\textsubscript{22}H\textsubscript{24}O\textsubscript{4}\textsuperscript{79}Br requires [M+H]\textsuperscript{+} 431.0858).

\(4'\text{-ethenyl-5'-}(2''\text{-Hydroxyl-1''-phenylethyl})-2'-methylyrhetahydrofuran-3-yl-4-bromobenzoate\) (364) :

\[\text{\includegraphics{image.png}}\]

\(v_{\text{max}}\) (ATR) : 3482-3388 (\textit{OH}), 2966, 2920, 1724 (C\textless{}=O), 1638 (C=C), 1596, 1490, 1397, 1268, 1174, 1093, 1015, 912, 799, 699 cm\textsuperscript{-1}. \(\delta\textsubscript{H} (500 MHz; CDCl\textsubscript{3}) : 7.80 (2H, d, J 8.6, 2b''-\textit{H}), 7.57 (2H, d, J 8.6, 3b''-\textit{H}), 7.36 (2H, t, J 7.3, 3a''-\textit{H}), 7.31 (2H, d, J 7.3, 2a''-\textit{H}), 7.27 (1H, t, J 7.3, 4a''-\textit{H}), 5.92 (1H, dt, J 17.0, 10.4, 4'-CH=CH\textsubscript{2}), 5.22 (1H, dd, J 10.4, 1.6, 4'-CH=CH\textsubscript{2}), 5.18 (1H, dd, J 17.0, 1.6, 4'-CH=CH\textsubscript{2}), 5.10 (1H, t, J 6.4, 3'-\textit{H}), 4.53 (1H, dd, J 9.7, 4.4, 5'-\textit{H}), 4.24 (1H, dq, J 6.4, 6.3, 2'-\textit{H}), 3.80 (1H, dd, J 10.8, 4.5, 2''-\textit{HH}), 3.72 (1H, dd, J 10.8, 7.2, 2''-\textit{HH}), 3.41 (1H, dd, J 10.4, 6.4, 4.4, 4'-\textit{H}), 3.07 (1H, dd, J 9.7, 7.2, 4.5, 1''-\textit{H}), 1.29 (3H, d, J 6.3, 2'-CH\textsubscript{3}). \(\delta\textsubscript{C} (125 MHz; CDCl\textsubscript{3}) : 164.5 (C-1), 138.4 (C-1a''), 132.6 (C-1b'', C-4b''), 131.7 (C-3b''), 131.1 (C-2b''), 128.8 (4'-CH=CH\textsubscript{2}), 128.7 (C-2a'', C-3a''), 127.2 (C-4b''), 120.1 (4'-CH=CH\textsubscript{2}), 79.7 (C-5'), 76.9 (C-3'), 74.9 (C-2''), 64.2 (C-2'''), 50.3 (C-4'), 49.0 (C-1''), 15.9 (2'-CH\textsubscript{3}). \(m/z\) (ES\textsuperscript{+}) : 431 ([M+H]\textsuperscript{+}, 100%). HRMS (ES\textsuperscript{+}) found: 431.0863 (C\textsubscript{22}H\textsubscript{24}O\textsubscript{4}\textsuperscript{79}Br requires [M+H]\textsuperscript{+} 431.0858).
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2-[(2RS,2’SR,3’RS,4’RS,5’RS)-4’-(tert-butyldimethylsilyloxy)-3’-ethenyl-5’-methyltetrahydrofuran-2’-yl]-2-phenylethanol (366, 367) and (3RS,4SR,5RS,6RS,7SR)-6-(tert-butyldimethylsilyloxy)-5-ethenyl-7-methyl-3-phenoxepan-4-ol (368):

To a solution of TBDMS protected bicyclic alcohol 362 (68 mg, 0.19 mmol) in DCM (5.00 ml) at -78 °C was added triethylsilane (0.12 ml, 0.76 mmol) followed by the dropwise addition of a 1 M solution of titanium tetrachloride (0.23 ml, 0.23 mmol). After stirring at this temperature for 2 h, the reaction mixture was quenched with an aqueous solution of NaCl and extracted with DCM (3 x 20.0 ml). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The crude residue, containing mixtures of silylated tetrahydrofurans and oxepane isomers 366, 367 and 368 in a 2:1:2 ratio was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to afford inseparable mixture of the title isomers 366, 367 and 368 as a colourless oil (55 mg, 81%).

Careful separation of fractions enabled small analytical sample of the major THF 366 and oxepane 368 isomers to be obtained. The signals for the minor THF 367 were too weak and are not reported.

\[
\text{\begin{tikzpicture}
\node[draw, circle, label=above:{$\text{H}$}] (A) at (0,0) {};
\node[draw, circle, label=above:{$\text{H}$}] (B) at (0,1) {};
\node[draw, circle, label=above:{$\text{H}$}] (C) at (1,0) {};
\node[draw, circle, label=above:{$\text{H}$}] (D) at (1,1) {};
\node[draw, circle, label=above:{$\text{Si}$}] (E) at (2,0) {};
\node[draw, circle, label=above:{$\text{Bu}$}] (F) at (2,1) {};
\node[draw, circle, label=above:{$\text{CH}_3$}] (G) at (3,0) {};
\node[draw, circle, label=above:{$\text{O}$}] (H) at (3,1) {};
\node[draw, circle, label=above:{$\text{CH}_3$}] (I) at (4,0) {};
\node[draw, circle, label=above:{$\text{CH}_3$}] (J) at (4,1) {};
\end{tikzpicture}}
\]

υₘₐₓ (ATR) : 3464-3376 (OH), 2942, 2866, 1641 (C=C), 1468, 1380, 1256, 1140, 1086, 997, 880, 840, 776, 706, 656 cm⁻¹. δH (500 MHz; CDCl₃) : 7.35 (2H, d, J 7.3, 2’-H), 7.31-7.26 (3H, m, 3’-H, 4’-H), 5.95 (1H, dt, J 17.1, 10.4, 3’-CH=CH₂), 5.31 (1H, dd, J 10.4, 1.9, 3’-CH=CHH), 5.19 (1H, dd, J 17.1, 1.9, 3’-CH=CHH), 4.42 (1H, dd, J 10.4, 4.3, 2’-H), 4.04 (1H, t, J 6.5, 4’-H), 3.85 (1H, dq, J 6.5, 6.3, 5’-H), 3.83-3.79 (1H, m, 1-HH), 3.75-3.69 (1H, m, 1-HH), 3.22 (1H, d, J 10.0, 6.2, 2-H), 2.89 (1H, ddd, J 10.4, 6.5, 4.3, 3’-H), 1.18 (3H, d, J 6.3, 5’-CH₃), 0.90 (9H, s, Si(CH₃)₃), 0.08 (3H, s, Si(CH₃)₂), 0.07 (3H, s, Si(CH₃)₂). δC (125 MHz; CDCl₃) : 139.6 (C-1’’), 133.6 (3’-CH=CH₂), 129.0 (C-2’’), 128.6 (C-3’’), 126.9 (C-4’’), 119.1 (3’-CH=CH₂), 80.7 (C-4’), 78.1 (C-5’), 77.9 (C-2’), 64.2 (C-1), 52.8 (C-3’), 49.6 (C-2), 35.0 (C-5), 29.1 (C-3), 21.9 (C-4), 14.1 (C-6), 13.4 (C-7), 1.0 (Si(CH₃)₃).
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25.7 (SiC(CH$_3$)$_3$), 19.4 (5'-CH$_3$), 18.1 (SiC(CH$_3$)$_3$), -4.5 (Si(CH$_3$)$_2$), -4.9 (Si(CH$_3$)$_2$). m/z (ES$^+$) : 363 ([M+H]$^+$, 100%). HRMS (ES$^+$) found: 363.2361 (C$_2$H$_{35}$O$_3$Si requires [M+H]$^+$ 363.2355).

(3RS,4SR,5RS,6RS,7SR)-6-(tert-butylimidethylsilyloxy)-5-ethenyl-7-methyl-3-phenyloxepane-4-ol (368) :

\[
\text{\includegraphics{image.png}}
\]

$\nu_{\text{max}}$ (ATR) : 3434 (OH), 2936, 2860, 1642 (C=C), 1502, 1461, 1374, 1256, 1098, 1028, 998, 911, 835, 771, 700, 623 cm$^{-1}$. $\delta_H$ (500 MHz; CDCl$_3$) : 7.36-7.30 (3H, m, 3'-H, 4'-H), 7.28 (2H, d, J 7.6, 2'-H), 6.11 (1H, td, J 17.4, 9.7, 5-CH=CH$_2$), 5.24 (1H, dd, J 9.7, 1.6, 5-CH=CHH), 5.22 (1H, dd, J 17.4, 1.6, 5-CH=CHH), 4.22 (1H, t, J 9.7, 4-H), 4.19 (1H, dd, J 12.4, 9.7, 2-HH), 3.95-3.93 (2H, m, 6-H, 7-H), 3.58 (1H, dd, J 12.4, 3.7, 2-HH), 2.93 (1H, dt, J 9.7, 3.7, 3-H), 2.70 (1H, t, J 9.7, 5-H), 1.24 (3H, d, J 6.4, 7-CH$_3$), 1.05 (9H, s, SiC(CH$_3$)$_3$), 0.18 (3H, s, Si(CH$_3$)$_2$), 0.15 (3H, s, Si(CH$_3$)$_2$). $\delta_C$ (125 MHz; CDCl$_3$) : 140.0 (C-1'), 134.6 (5-CH=CH$_2$), 128.7 (C-3'), 128.0 (C-2'), 126.9 (C-4'), 117.3 (5-CH=CH$_2$), 79.0 (C-6), 77.1 (C-7), 72.1 (C-4), 66.4 (C-2), 56.0 (C-3), 54.2 (C-5), 26.3 (SiC(CH$_3$)$_3$), 18.6 (7-CH$_3$), 17.9 (SiC(CH$_3$)$_3$), -3.4 (Si(CH$_3$)$_2$), -4.2(Si(CH$_3$)$_2$). m/z (ES$^+$) : 363 ([M+H]$^+$, 100%), 345 ([M+H-H$_2$O]$^+$, 40). HRMS (ES$^+$) found: 363.2363 (C$_{30}$H$_{35}$O$_3$Si requires [M+H]$^+$ 363.2360).

(2RS,3RS,4SR,5SR,1’RS)-4-ethenyl-5-(2’-Hydroxy-1’-phenylethyl)-2-methyltetrahydrofuran-3-ol (357, 358) and (2SR,3RS,4RS,5SR,6RS)-4-ethenyl-2-methyl-6-phenyloxepane-3,5-diol (369) :

To a solution of the TBDMS product 362 (37 mg, 0.10 mmol) in DCM (2.00 ml) at -78 $^\circ$C was added triethylsilane (0.06 ml, 0.41 mmol) followed by the dropwise addition of a 1 M solution of titanium tetrachloride (0.12 ml, 0.12 mmol) in DCM. After stirring at this temperature for 2 h, the reaction mixture was quenched with an aqueous solution of NaCl and extracted with DCM (3 x 20.0 ml). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated in vacuo. The crude residue, containing mixtures of silylated tetrahydrofurans and oxepane isomers 366, 367 and 368 in a 2:1:2 ratio was subsequently treated with a 1 M
solution of tetrabutylammonium fluoride (1.60 ml, 1.59 mmol) in THF and at room temperature. After 4 h, the reaction mixture was quenched with saturated aqueous NaHCO₃, extracted with EtOAc and the organic extracts washed with brine and water. The organic layer was then concentrated in vacuo and purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to afford the title isomers 357 (8 mg, 32%), 358 (4 mg, 18%) and 369 (8 mg, 33%) as colourless oils.

The analytical data for the desilylated oxepane isomer 369 is reported below.

\[ (2R,3R,4R,5S,6R)\text{-4-ethenyl-2-methyl-6-phenyloxepane-3,5-diol} \text{ (369)} : \]

\begin{center}
\includegraphics[width=0.2\textwidth]{oxepane.png}
\end{center}

\( \nu_{\text{max}} \) (ATR) : 3385 (OH), 2969, 2888, 1641 (C=O), 1598, 1493, 1379, 1253, 1109, 1016, 973, 910, 726, 694, 656 cm\(^{-1}\). \( \delta_H \) (700 MHz; CDCl\(_3\)) : 7.34 (2H, t, J 7.7, 3'-H), 7.26-7.25 (3H, m, 2'-H, 4'-H), 6.17 (1H, dt, J 17.2, 10.4, 4-CH=CH\(_2\)), 5.28 (1H, dd, J 10.4, 1.8, 4-CH=C\(_2\)H), 5.25 (1H, d, J 17.2, 1.8, 4-CH=CH\(_2\)), 4.16 (1H, t, J 10.4, 5-H), 3.95-3.92 (2H, m, 2-H, 7-HH), 3.88 (1H, d, J 12.5, 6.2, 7-HH), 3.70 (1H, d, J 8.2, 3-H), 3.10 (1H, dt, J 10.4, 6.2, 6-H), 2.41 (1H, t, J 10.4, 4-H), 2.23 (1H, dt, J 8.2, 3-OH), 1.59 (1H, t, J 10.4, 5-OH), 1.29 (3H, d, J 6.5, 2-CH\(_3\)). \( \delta_C \) (175 MHz; CDCl\(_3\)) : 140.5 (C-1'), 138.6 (4-CH=CH\(_2\)), 128.8 (C-3'), 128.5 (C-2'), 127.1 (C-4'), 118.3 (4-CH=CH\(_2\)), 75.5 (C-3), 75.0 (C-2), 71.0 (C-7), 69.4 (C-5), 57.4 (C-4), 54.2 (C-6), 18.3 (2-CH\(_3\)). \( m/z \) (ES\(^+\)) : 271 ([M+Na\(^+\), 40%], 249 ([M+H\(^+\], 10), 231 ([M+H-H\(_2\)O\(^+\], 100). HRMS (ES\(^+\)) found: 231.1389 (C\(_{12}\)H\(_19\)O\(_2\) requires [M+H-H\(_2\)O\(^+\] 231.1385).

\[ (2S,3RS,4SR,5SR,1'RS)\text{-4-ethyl-5-(2'-Hydroxy-1'-phenylethyl)-2-methyltetrahydrofuran-3-ol} \text{ (371, 372)} : \]

To a solution of bicyclic alcohol 370 (14 mg, 0.06 mmol) in DCM (2.00 ml) at -78 °C was added triethylsilane (0.04 ml, 0.23 mmol) followed by the dropwise addition of a 1 M solution of titanium tetrachloride (0.07 ml, 0.07 mmol). After stirring at this temperature for 2 h, the reaction mixture was quenched with an aqueous solution of NaCl and extracted with DCM (3 × 10.0 ml). The combined organic extracts were dried over MgSO\(_4\), filtered and concentrated in vacuo. The crude residue, containing a mixture of two tetrahydrofuran isomers 371 and 372 in
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a 7:3 ratio, was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to afford the title isomers 371 as a colourless oil (6 mg, 41%) and 372 as an oil (3 mg, 18%). The analytical data for the major isomer 371 is reported below. NMR signals of the minor isomer 372 were too weak to be accurately discerned and are therefore not reported.

4-ethyl-5-(2’-Hydroxyl-1’-phenylethyl)-2-methyltetrahydrofuran-3-ol (371):

\[ \text{\begin{figure}} \]

\[ \text{\begin{figure}} \]

\[ \nu_{\text{max}} \text{ (ATR): 3540-3294 (OH), 2972, 2878, 1490, 1456, 1386, 1250, 1161, 1064, 987, 893, 852, 765, 706, 654 cm}^{-1}. \delta_{\text{H}} \text{ (500 MHz; CDCl}_3 \text{): 7.51 (2H, d, J 7.6, 2’-H), 7.37 (2H, t, J 7.6, 3”-H), 7.31 (1H, t, J 7.6, 4”-H), 4.51 (1H, dd, J 10.3, 1.5, 5-H), 3.96-3.90 (2H, m, 2’-H), 3.85 (1H, qd, J 6.2, 2.6, 2-H), 3.67-3.64 (1H, m, 3-H), 2.91 (1H, td, J 7.1, 1.5, 1’-H), 2.39-2.33 (1H, m, 4-H), 1.80-1.65 (2H, bs, OH), 1.48-1.41 (1H, m, 4-CHHCH3), 1.22 (3H, d, J 6.2, 2-CH3), 0.81-0.90 (1H, m, 4-CHHCH3), 0.91 (3H, t, J 7.3, 4-CH2CH3). \delta_{\text{C}} \text{ (125 MHz; CDCl}_3 \text{): 139.8 (C-1’), 130.5 (C-2’), 128.8 (C-3’), 127.9 (C-4’), 79.7 (C-5), 78.4 (C-2’), 73.2 (C-3’), 66.9 (C-2’), 50.4 (C-4’), 49.7 (C-1’), 17.5 (4-CH2CH3), 14.0 (2-CH3), 13.4 (4-CH2CH3). \text{m/z (ES}^+ \text{): 314 ([M+Na+CH3CN]’, 20%), 273 ([M+Na]’, 40), 251 ([M+H]’, 100).} \]

\[ (2RS,3RS,4SR,5SR,1’S)R-4-ethyl-5-(2’-Hydroxyl-1’-phenylethyl)-2-methyltetrahydrofuran-3-ol (374, 375):

To a solution of bicyclic alcohol 373 (21 mg, 0.08 mmol) in DCM (2.00 ml) at -78 °C was added triethylsilane (0.05 ml, 0.33 mmol) followed by the dropwise addition of a 1 M solution of titanium tetrachloride (0.10 ml, 0.10 mmol). After stirring at this temperature for 2 h, the reaction mixture was quenched with an aqueous solution of NaCl and extracted with DCM (3 × 20.0 ml). The combined organic extracts were dried over MgSO4, filtered and concentrated in vacuo. The crude residue, containing a mixture of two tetrahydrofuran isomers 374 and 375 in a 7:3 ratio, was purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) to afford the title isomers 374 (13 mg, 60%) and 375 (5 mg, 24%) as colourless oils.
4-ethyl-5-(2’-Hydroxyl-1’-phenylethyl)-2-methyltetrahydrofuran-3-ol (374):

\[
\begin{align*}
\nu_{\text{max}} \text{(ATR)} & : 3386-3278 (\text{OH}), 2938, 2882, 1458, 1392, 1312, 1158, 1086, 1046, 994, 914, 872, 704, 628 \text{ cm}^{-1}. \\
\delta_H (700 \text{ MHz}; \text{CDCl}_3) & : 7.29 (2H, t, J 7.7, 3’-H), 7.23 (2H, d, J 7.7, 2”-H), \\
& 7.21 (1H, t, J 7.7, 4”-H), 4.55 (1H, dd, J 9.1, 8.2, 5-H), 4.03-4.00 (2H, m, 2’-HH, 3-H), 3.96 \\
& (1H, qd, J 6.4, 2.8, 2-H), 3.60 (1H, dd, J 11.2, 2.7, 2’-HH), 3.21 (1H, td, J 8.2, 2.7, 1’-H), \\
& 2.28-2.24 (1H, m, 4-H), 2.12 (1H, bs, OH), 1.66 (1H, s, OH), 1.61-1.55 (1H, m, 4-CHHCH3), \\
& 1.37 (3H, d, J 6.4, 2-CH3), 1.06-1.01 (1H, m, 4-CHHCH3), 0.82 (3H, t, J 7.5, 4-CH2CH3). \\
\delta_C (175 \text{ MHz}; \text{CDCl}_3) & : 141.4 (C-1’’’), 128.6 (C-3’’’), 128.2 (C-2’’’), 126.6 (C-4’’’), 83.5 (C-5), 78.2 \\
& (C-2), 73.9 (C-3), 67.7 (C-2’), 50.4 (C-4), 49.4 (C-1’), 18.2 (4-CH2CH3), 14.4 (2-CH3), 13.2 \\
& (4-CH2CH3). m/z (ES+) : 523 ([2M+Na]+, 20%), 314 ([M+Na+CH3CN]+, 40), 273 ([M+Na]+, \\
\end{align*}
\]

4-ethyl-5-(2’-Hydroxyl-1’-phenylethyl)-2-methyltetrahydrofuran-3-ol (375):

\[
\begin{align*}
\nu_{\text{max}} \text{(ATR)} & : 3466-3218 (\text{OH}), 2962, 2874, 1454, 1381, 1310, 1148, 1054, 1044, 990, 868, 831, \\
& 757, 625 \text{ cm}^{-1}. \\
\delta_H (700 \text{ MHz}; \text{CDCl}_3) & : 7.29 (2H, t, J 7.4, 3’-H), 7.23 (2H, d, J 7.4, 2”-H), \\
& 7.21 (1H, t, J 7.4, 4”-H), 4.62 (1H, dd, J 9.5, 8.9, 5-H), 4.20 (1H, qd, J 6.6, 4.2, 2-H), 4.02 \\
& (2H, m, 2’-HH, 3-H), 3.65 (1H, dd, J 11.1, 4.1, 2’-HH), 3.33 (1H, td, J 8.9, 4.1, 1’-H), 2.15- \\
& 2.11 (1H, m, 4-H), 2.10 (1H, bs, OH), 1.46-1.39 (1H, m, 4-CHHCH3), 1.25 (3H, d, J 6.6, 2- \\
& CH3), 1.08-1.05 (1H, m, 4-CHHCH3), 0.75 (3H, t, J 7.4, 4-CH2CH3). \\
\delta_C (175 \text{ MHz}; \text{CDCl}_3) & : 140.6 (C-1’’’), 128.3 (C-3’’’), 128.2 (C-2’’’), 126.7 (C-4’’’), 84.2 (C-5), 81.5 (C-3), 78.5 (C-2), \\
& 68.2 (C-2’), 48.9 (C-4), 48.4 (C-1’), 19.9 (4-CH2CH3), 17.1 (2-CH3), 13.3 (4-CH2CH3). m/z
(ES\(^{+}\)) : 273 ([M+Na\(^{+}\), 50\%], 251 ([M+H\(^{+}\), 100], 233 ([M+H-H\(_2\)O\(^{+}\), 80]). HRMS (ES\(^{+}\)) found: 251.1638 (C\(_{15}\)H\(_{23}\)O\(_3\) requires [M+H\(^{+}\) 251.1647).

**General method for the preparation of samarium (II) iodide (SmI\(_2\)) solution (A9):**

Samarium metal (99.9\%, 1.00 g, 6.65 mmol) and a magnetic stirrer bar were placed in a Schlenk flask equipped with a septum inlet and attached to a high vacuo line. After the flask was heated (using heat gun), it was allowed to cool under vacuo and back filled with argon (this was repeated 3 times). Then THF (33.0 ml) was added with the aid of a syringe through the rubber septum with continuous stirring, and finally diiodomethane (0.89 g, 3.33 mmol) was added. The flask was shut to vacuo line and the mixture was stirred at room temperature. After 30-60 min, a dark-blue solution was obtained which was stirred for a further 3 h to give a 0.1 M THF solution of SmI\(_2\).\(^6\)\(^7\)

\((2S,5R,6R)-6\)-benzyl-5-hydroxy-2-methyloxepan-3-one (432, 433) :

To a stirred solution of freshly prepared 0.1 M solution of samarium (II) iodide (8.00 ml, 0.80 mmol) was added distilled hexamethylphosphoramide (HMPA) (0.15 ml, 0.80 mmol) to give a purple colour. After stirring for 15 min, the resulting mixture was added quite slowly (over ~10 mins) into a stirring solution of bicyclic ketone 398 (29 mg, 0.13 mmol) in THF (2.00 ml) under argon at room temperature. Upon complete addition, the reaction was immediately quenched with saturated aqueous NaHCO\(_3\), an excess of Celite\(^\circ\) and Et\(_2\)O were added, the solution was filtered and the filtrate extracted with ethyl acetate. Evaporation of the solvent followed by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) afforded an inseparable mixture (7:3 ratio) of oxepanones 432 and 433 (19 mg, 67\%) as colourless oils. The analytical data for the oxepanone isomers 432 and 433 was obtained on the mixture and is reported below.

Major isomer 432 :
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\( \nu_{\text{max}} \text{(ATR)} : 3458 (\text{OH}), 2932, 1753 (C=O), 1495, 1453, 1368, 1240, 1179, 1030, 745, 700 \text{ cm}^{-1} \). \( \delta_H \) (700 MHz; CDCl\(_3\)) : 7.30 (2H, t, \( J = 7.5 \)), 7.23-7.21 (3H, m, 2'-H, 4'-H), 4.48 (1H, td, \( J = 7.7, 6.4 \), 5'-H), 4.15 (1H, q, \( J = 7.3 \), 2-H), 3.65 (2H, bd, \( J = 4.3 \), 7-H\(_2\)), 2.83 (1H, dd, \( J = 13.8, 5.2 \), 6-CH\(_2\)Ph), 2.71 (1H, dd, \( J = 13.8, 9.2 \), 6-CH\(_2\)Ph), 2.55 (2H, d, \( J = 7.7 \), 4-H\(_2\)), 2.20-2.16 (1H, m, 6-H), 1.94 (1H, s, OH), 1.27 (3H, d, \( J = 7.3 \), 2-CH\(_3\)). \( \delta_C \) (175 MHz; CDCl\(_3\)) : 216.3 (C-3), 139.4 (C-1'), 129.0 (C-2'), 128.5 (C-3'), 126.3 (C-4'), 76.5 (C-5), 76.0 (C-2), 62.1 (C-7), 45.9 (C-6), 39.4 (C-4), 33.0 (6-CH\(_2\)Ph), 15.9 (2-CH\(_3\)). \( m/z \) (GCMS, EI), \( t_J = 8.22 \text{ min} : 234 \text{ (M}^+, 50\%) \), 216 (M\(^+\)-H\(_2\)O, 10), 129 (30), 91 (PhCH\(_2\)^+, 100), 77 (Ph\(^+\),20). HRMS (ASAP\(^+\)) found: 233.1171 (C\(_{14}\)H\(_{17}\)O\(_3\) requires 233.1178).

Minor isomer 433 :

\[ \begin{align*}
\delta_H \text{(700 MHz; CDCl\(_3\)) : 7.30 (2H, t, } J = 7.5, \text{ m, 2'-H, 4'-H), 4.28 (1H, m, 5'-H), 3.82 (1H, q, J = 6.7, 2-H), 3.69 (2H, bd, J = 6.2, 7-H\(_2\)), 2.78 (1H, dd, J = 13.8, 6.0, 6-CH\(_2\)Ph), 2.63 (1H, dd, J = 13.8, 7.5, 6-CH\(_2\)Ph), 2.50 (1H, dd, J = 17.9, 6.1, 4-HH), 2.45 (1H, dd, J = 17.9, 10.8, 4-HH), 2.31-2.29 (1H, m, 6-H), 1.68 (1H, s, OH), 1.34 (3H, d, J = 6.7, 2-CH\(_3\)). \delta_C \text{(175 MHz; CDCl\(_3\)) : 215.6 (C-3), 139.3 (C-1'), 129.0 (C-2'), 128.5 (C-3'), 126.3 (C-4'), 77.8 (C-5), 77.6 (C-2), 62.3 (C-7), 45.3 (C-6), 39.2 (C-4), 33.1 (6-CH\(_2\)Ph), 15.8 (2-CH\(_3\)). m/z \text{(GCMS, EI), } t_J = 8.13 \text{ min} : 234 \text{ (M}^+, 10\%) \), 216 (M\(^+\)-H\(_2\)O, 20), 129 (30), 91 (PhCH\(_2\)^+, 100), 77 (Ph\(^+\),40). \\
\end{align*} \]

\((2SR,5RS,6RS)-6\text{-benzyl-2-methyl-5-(trimethylsilyloxy)oxepan-3-one (434, 435)} \) and \((2SR,5RS,6RS)-6\text{-benzyl-5-hydroxy-2-methyloxepan-3-one (432, 433)} : \)

To a stirred solution of freshly prepared 0.1 M solution of samarium (II) iodide (6.50 ml, 0.65 mmol) was added distilled HMPA (0.10 ml, 0.65 mmol) to give a purple solution. After stirring for 15 min, the resulting mixture was added quite slowly (over ~10 mins) into a stirring solution of bicyclic ketone 398 (0.05 g, 0.22 mmol) and trimethylsilyl chloride (0.08 ml, 0.65 mmol) in THF under argon at room temperature. Upon complete addition, the reaction was immediately quenched with saturated aqueous NaHCO\(_3\), an excess of Celite\textsuperscript{®} and Et\(_2\)O were

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added, the solution was filtered and the filtrate extracted with ethyl acetate. Evaporation of the solvent followed by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) afforded as colourless oils a 7:3 ratio of both the title TMS protected oxepanone 434, 435 (12 mg, 18%) and the unprotected oxepanone 432, 433 (10 mg, 21%). Starting material 398 was also recovered (21 mg).

The analytical data for the major isomer 434 was obtained from the mixture and is reported below. NMR signals of the minor isomer 435 [(GCMS, EI), tR = 8.10 min] were too weak to be accurately discerned and are therefore not reported.

6-benzyl-2-methyl-5-(trimethylsilyloxy)oxepan-3-one (434):

\[
\begin{align*}
\nu_{\text{max}} \text{(ATR)} & : 2920, 2856 (\text{CHOSi}), 1756 (\text{C=O}), 1456, 1254+840 (\text{Si-CH}_3), 1086, 745, 699, 664 \text{ cm}^{-1}. \delta_H (700 \text{ MHz; CDCl}_3) : 7.28 (2H, t, J 7.6, 3'-H), 7.22-7.20 (3H, m, 2'-H, 4'-H), 4.36 (1H, dt, J 7.7, 7.2, 5'-H), 4.08 (1H, q, J 7.2, 2-H), 3.55 (1H, dd, J 10.4, 3.8, 7-HH), 3.46 (1H, dd, J 10.4, 5.4, 7-HH), 2.94 (1H, dd, J 13.8, 4.5, 6-CHPh), 2.67 (1H, dd, J 13.8, 9.2, 6-CHPh), 2.55 (2H, d, J 7.2, 4-H_2), 2.05-2.02 (1H, m, 6-H), 1.27 (3H, d, J 7.2, 2-CH_3), 0.05 (9H, s, Si(CH_3)_3). \delta_C (175 \text{ MHz; CDCl}_3) : 217.3 (C-3), 140.1 (C-1'), 129.2 (C-2'), 128.3 (C-3'), 126.0 (C-4'), 75.7 (C-5), 75.6 (C-2), 60.9 (C-7), 46.8 (C-6), 40.3 (C-4), 33.2 (6-CH_2Ph), 16.1 (2-CH_3), -0.7 (Si(CH_3)_3). m/z (GCMS, EI), tR = 8.15 min : 306 (M^+, 90%), 216 (M^+-TMSOH, 70), 201 (M^+-TMSOH-Me, 5), 125 (M^+-TMSOH-PhCH_2^+, 80), 91 (PhCH_2^+, 100), 77 (Ph^+,50). HRMS (ASAP^+) found: 305.1577 (C_{17}H_{25}O_3Si requires 305.1573).
\end{align*}
\]

(2SR,4RS,5SR,6SR)-4-ethyl-5-hydroxy-2-methyl-6-phenyloxepan-3-one (442, 443):

To a stirred solution of freshly prepared 0.1 M solution of samarium (II) iodide (5.60 ml, 0.56 mmol) was added distilled HMPA (0.10 ml, 0.56 mmol) to give a purple solution. After stirring for 15 min, the resulting mixture was added quite slowly (over ~10 mins) into a stirring solution of bicyclic ketone 437 (23 mg, 0.09 mmol) in THF (1.00 ml) under argon at room
temperature. Upon complete addition, the reaction was immediately quenched with saturated aqueous NaHCO₃, an excess of Celite® and Et₂O were added, the solution was filtered and the filtrate extracted with ethyl acetate. Evaporation of the solvent followed by flash column chromatography on silica gel (petroleum ether/EtOAc : 8/2) afforded an inseparable mixture (6:4) of oxepanones 442 and 443 (19 mg, 85%) as a colourless oil.

The analytical data for the oxepanone isomers 442 and 443 was obtained on the mixture and is reported below.

**Major isomer 442**:

![](image)

\[ \nu_{\text{max}} \text{ (ATR)} : 3552-3396 (\text{OH}), 2978, 2882, 1749 (C=O), 1458, 1382, 1228, 1182, 1060, 1014, 988, 752, 701 \text{ cm}^{-1}. \delta_H (700 \text{ MHz}; \text{CDCl}_3) : 7.33 (2H, t, J 7.6, 3'-\text{H}), 7.27 (1H, t, J 7.6, 4'-\text{H}), 7.20 (2H, d, J 7.6, 2'-\text{H}), 4.61 (1H, dd, J 10.8, 5.0, 5'-\text{H}), 3.93 (1H, q, J 6.9, 2'-\text{H}), 3.83-3.79 (2H, m, 7'-\text{H}), 3.25-3.22 (1H, m, 6'-\text{H}), 2.79 (1H, bs, OH), 2.03 (1H, dt, J 10.6, 5.0, 4'-\text{H}), 1.54-1.47 (2H, m, 4-\text{CH}_2\text{CH}_3), 1.36 (3H, d, J 6.9, 2-\text{CH}_3), 0.82 (3H, t, J 7.5, 4-\text{CH}_2\text{CH}_3). \delta_C (175 \text{ MHz}; \text{CDCl}_3) : 217.3 (C-3), 138.0 (C-1'), 129.0 (C-2'), 127.9 (C-3'), 127.5 (C-4'), 82.4 (C-5), 78.2 (C-2), 67.8 (C-7), 49.6 (C-4), 47.9 (C-6), 18.4 (4-\text{CH}_2\text{CH}_3), 16.4 (2-\text{CH}_3), 11.0 (4-\text{CH}_2\text{CH}_3). m/z (GCMS, EI), t_R = 7.99 \text{ min} : 248 (M^+, 10%), 230 (M^+\text{-H}_2\text{O}, 10), 145 (20), 104 (100), 77 (Ph^+, 40). HRMS (ASAP*) found: 247.1332 (C_{12}H_{19}O_3 \text{ requires 247.1334}).

**Minor isomer 443**:

![](image)

\[ \delta_H (700 \text{ MHz}; \text{CDCl}_3) : 7.33 (2H, t, J 7.6, 3'-\text{H}), 7.27 (1H, t, J 7.6, 4'-\text{H}), 7.20 (2H, d, J 7.6, 2'-\text{H}), 4.61 (1H, dd, J 10.5, 5.6, 5'-\text{H}), 3.93 (1H, q, J 7.0, 2'-\text{H}), 4.04-3.98 (2H, m, 7'-\text{H}), 3.18-3.15 (1H, m, 6'-\text{H}), 2.72 (1H, bs, OH), 2.13 (1H, dt, J 10.2, 5.6, 4'-\text{H}), 1.67-1.55 (2H, m, 4-]
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\( \text{CH}_2\text{CH}_3 \), 1.34 (3H, d, \( J \) 7.0, 2-\( \text{CH}_3 \)), 0.77 (3H, t, \( J \) 7.5, 4-\( \text{CH}_2\text{CH}_3 \)). \( \delta_C \) (175 MHz; CDCl\(_3\)) : 217.3 (C-3), 138.4 (C-1’), 128.9 (C-2’), 128.0 (C-3’), 127.4 (C-4’), 81.3 (C-5), 75.6 (C-2), 67.5 (C-7), 50.8 (C-4), 48.1 (C-6), 18.3 (4-\( \text{CH}_2\text{CH}_3 \)), 16.2 (2-\( \text{CH}_3 \)), 11.1 (4-\( \text{CH}_2\text{CH}_3 \)). m/z (GCMS, EI), \( t_R = 7.86 \text{ min} \) : 248 (M\(^+\), 5%), 230 (M\(^+\)-H\(_2\)O, 10), 145 (90), 104 (100), 77 (Ph\(^+\), 20).
9.3 References

APPENDIX A: Crystal Structure of the ester acetal 151

2,5-diphenyl-[1,3]-dioxane-2-carboxylic acid methyl ester 151
Table 1 Crystal data and structure refinement for 07srv147

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<th>Identification code</th>
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<td>Formula weight</td>
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</tr>
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<td>Temperature/K</td>
<td>120(2)</td>
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</tr>
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</tr>
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<td>F(000)</td>
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<td>Crystal size/mm³</td>
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</tr>
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<tr>
<td>Index ranges</td>
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<td>Independent reflections</td>
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</tr>
<tr>
<td>Data/restraints/parameters</td>
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<td>Goodness-of-fit on F²</td>
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<tr>
<td>Final R indexes [I&gt;2σ (I)]</td>
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<tr>
<td>Final R indexes [all data]</td>
<td>R₁ = 0.0581, wR₂ = 0.1178</td>
</tr>
<tr>
<td>Largest diff. peak/hole / e Å⁻³</td>
<td>0.354/-0.252</td>
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Table 2 Atomic Coordinates (Å×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 07srv147. \( U_{eq} \) is defined as 1/3 of the trace of the orthogonalised \( U_{ij} \) tensor.

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<th>z</th>
<th>( U(eq) )</th>
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Table 3 Anisotropic Displacement Parameters (Å$^2 \times 10^3$) for 07srv147. The Anisotropic displacement factor exponent takes the form: $-2\pi^2 h^2a^2 U_{11}+...+2hka\times b\times U_{12}$

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Table 6 Torsion Angles for 07srv147.

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C4  O3   C2   O1  -55.51(12)
C4  O3   C2   C1  69.06(11)
C4  O3   C2   C11 -174.99(9)
C4  O3   C2   C1   55.27(12)
C4  C5   C6   O1  55.27(12)
C4  C5   C21  C22 -83.86(13)
C4  C5   C21  C26 93.04(16)
C5  C21  C22  C23 175.92(11)
C5  C21  C26  C25 -176.51(16)
C6  O1   C2   O3  58.22(12)
C6  O1   C2   C1  -66.03(11)
C6  O1   C2   C11 177.08(8)
C6  C5   C21  C22 154.56(11)
C6  C5   C21  C26 -28.54(18)
C21 C5   C6   O1  178.07(9)
Appendices

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å²×10^3) for 07srv147.

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APPENDIX B: Crystal Structure of the ester acetal **152** at 293K

2,5-diphenyl-[1,3]-dioxane-2-carboxylic acid methyl ester **152**
**Table 1 Crystal data and structure refinement for 07srv163**

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Table 2 Atomic Coordinates ($\text{Å} \times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{Å}^2 \times 10^3$) for 07srv163. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$ tensor.

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Table 3 Anisotropic Displacement Parameters (Å\(^2\)×10\(^3\)) for 07srv163. The Anisotropic displacement factor exponent takes the form: -2\(\pi^2\)[h\(^2\)a\(^*\)\(^2\)U\(_{11}\)+...+2hka\(^*\)b\(^*\)U\(_{12}\)]

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Table 6 Torsion Angles for 07srv163.

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APPENDIX C: Crystal Structure of the ester acetal 152 at 240K

2,5-diphenyl-[1,3]-dioxane-2-carboxylic acid methyl ester 152
Table 1 Crystal data and structure refinement for 07srv164

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Table 3 Anisotropic Displacement Parameters ($\text{Å}^2 \times 10^3$) for 07srv164. The Anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^* U_{11} + ... + 2hkabU_{12}]$

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Appendices

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APPENDIX D: Poster, Oral Presentations and Research Conferences attended by the author

- **July 2009:** Poster Presentation by the author
  15th IUPAC Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS 15), Glasgow, Scotland.

- **April 2009:** Oral Presentation by the author

- **March 2009:** Oral Presentation by the author
  SCI Postgraduate Meeting, University of Durham, England.

- **June 2008:** Oral Presentation by the author

- **April 2008:** Poster Presentation by the author
  RSC Organic Division, North East Regional Meeting, University of Newcastle, England.

- **January 2008:** Research Conference attended by the author
  Modern Aspects of Stereochemistry, University of Sheffield, England.

- **September 2007:** Research Conference attended by author
  RSC 22nd Postgraduate Heterocyclic Symposium, Organon, Scotland.

- **April 2007:** Research Conference attended by author

- **December 2006:** Research Conference attended by author
  Modern Aspects of Stereochemistry, University of Sheffield, England.

APPENDIX E: Scientific Papers Published