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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 acetals and ethyldiazoacetate. 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 1st October 2006 and 15th October 2009. It has not been submitted for any other degree and is the author's own work, except where acknowledged by reference.

Copyright:

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.

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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

α	Observed optical rotation in degrees
[α]	Specific rotation
δ / 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
cm^{-1}	Wavenumbers
CM	Complex mixture(s)
conc.	Concentrated
COSY	Correlation spectroscopy
d	Doublet (spectral)
DOSP	4-alkyl(C_{11}-C_{13})phenylsulfonyl-2R-pyrrolidinecarboxylate
ds	Diastereoselectivity
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane (CH_2Cl_2)
dd	Doublet of doublets
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

Abbreviations

eq	Equivalent
Et	Ethyl
Et_3N	Triethylamine
g	Gram
GC	Gas Chromatography
GC / MS	Gas Chromatography / Mass Spectroscopy
h	Hour(s)
hfacac	Hexafluoro acetylacetonate
hfb	heptafluorobutyramide
HMDS	bis(trimethylsilyl)amide
HMBC	Heteronuclear shift correlations *via* multiple bond connectivities
HPLC	High performance liquid chromatography
HSQC	Heteronuclear single quantum correlation
IBX	Iodoxybenzoic acid
i.e	*in extenso*
IR	Infra red
J / Hz	Coupling constant / Hertz
L.A	Lewis acid
LDA	Lithium diisopropylamide
Ln	n Ligands
m	Multiplet (spectral)
M	mol/l
Me	Methyl
MEPY	2-methyl-pyrrolidinecarboxylate
min	Minutes
mmol	Millimole(s)
m.p.	Melting point
MS	Mass spectrometry
MsN_3	Mesylazide
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
MTPA-Cl	α-methoxy-α-trifluoromethylphenylacetyl chloride
n-Bu	n-Butyl
NMO	N-methylmorpholine-N-oxide

NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
OAc	Acetate
oct	Octanoate
PDC	Pyridinium dichromate
pfb	Perfluorobutyrate
Ph	Phenyl
Piv	Pivaloyl (2,2-dimethylacetyl)
ppm	Part(s) per million
PTAD	1-adamantyl-N-phthalimidoacetate
PTTL	N-phthaloyl-*tert*-leucinate
q	Quartet (spectral)
rt	Room temperature
s	Singlet (spectral)
sec-Bu	sec-Butyl
SM	Starting material
t	Triplet (spectral)
TBAF	Tetrabutylammonium fluoride
TBDMSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
t-Bu	*tert*-Butyl
TBSP	1-(4-*tert*-butylphenyl)sulfonylpyrrolidinecarboxylate
Temp	Temperature
Tf	Triflate (trifluoromethanesulfonyl)
tfa	Trifluoroacetate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N',N',N',N'*-tetramethyl-1,2-ethylenediamine
TMS	Trimethylsilyl
tpa	Triphenylacetate
TPAP	Tetrapropyl ammonium perruthenate
UV	Ultraviolet

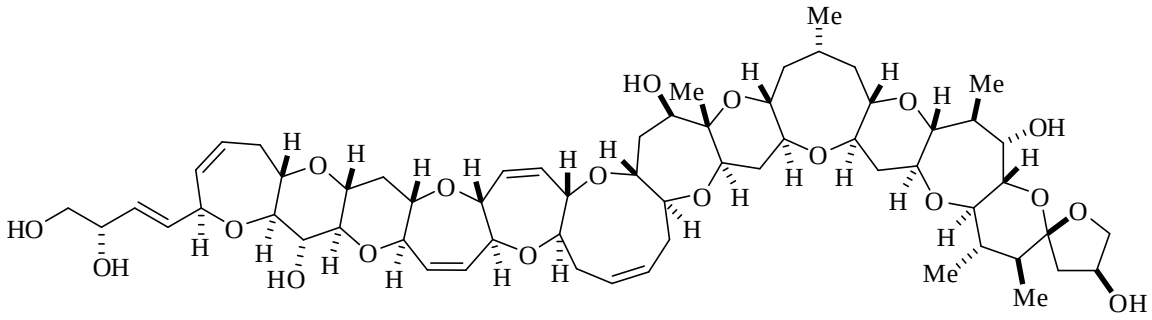
Abbreviations

1D	Unidimensional
2D	Bidimensional
18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane

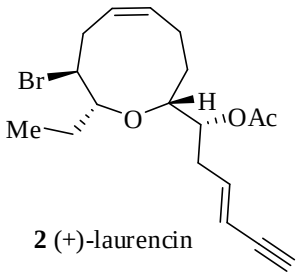
Contents

1.1 General Introduction

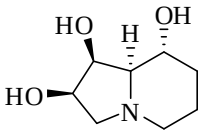
The unique biological activity of non-aromatic heterocycles and their derivatives play crucial roles in the modern day chemotherapy of a wide range of illnesses. This, when coupled with the range of intriguing structures for example **1**, **2** and **3** has provided a major synthetic goal for the organic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



1 ciguatoxin



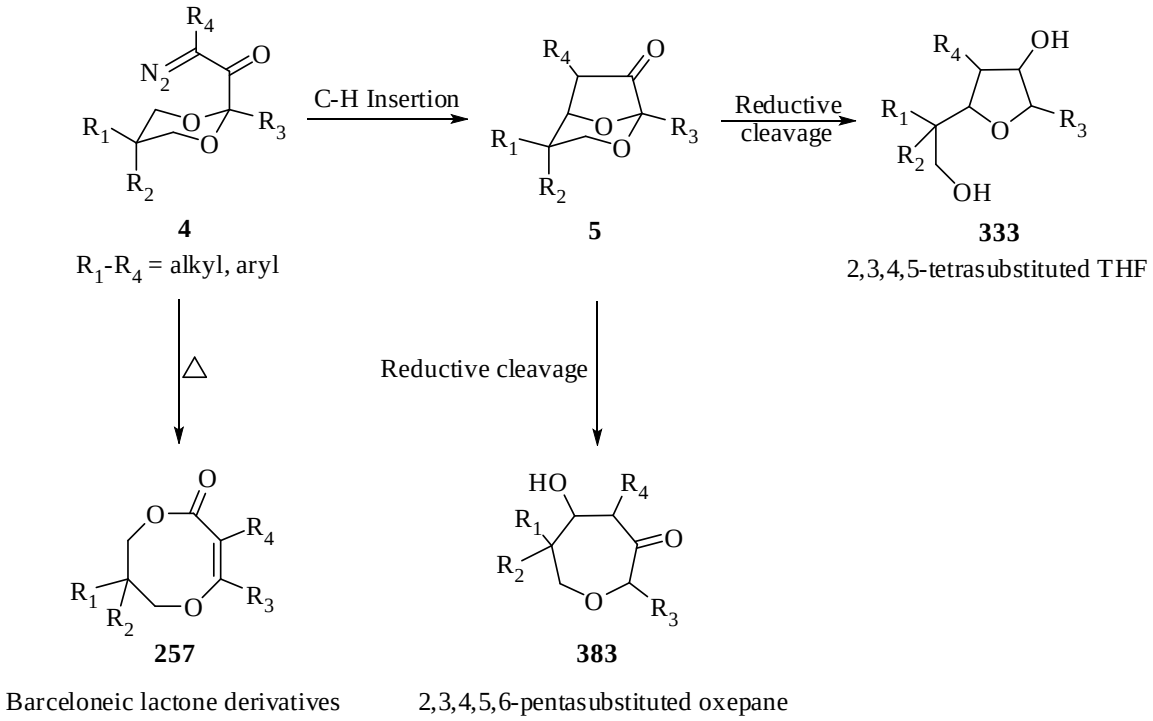
2 (+)-laurencin



3 (-)-swainsonine

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 **4** followed by either high temperature or stereoselective reductive cleavage of the resultant bicyclic acetals **5** (Scheme 1.2)



Scheme 1.2

Although several methods for the construction of 2,5-disubstituted and 2,3,5-trisubstituted THFs have been extensively documented,[2,3] fewer methods exist for the 2,3,4,5-tetrasubstituted THFs **333**.[4] Whilst, there is yet to be any reported synthesis for the barceloneic lactones **257** and 2,3,4,5,6-pentasubstituted oxepanes **383**.

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

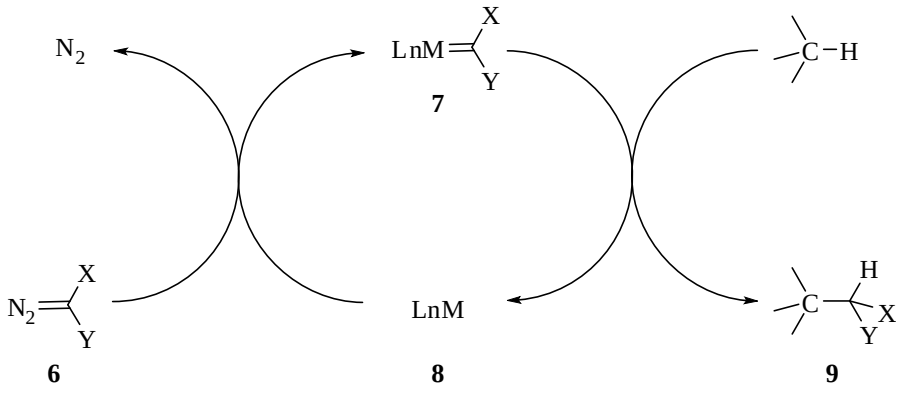
The activation of unfunctionalised C-H bonds for the formation of carbon-carbon bonds has been extensively studied over the past two decades.[5] However, C-H activation by metal-carbenoid induced C-H insertion is generally not included in reviews on C-H activation.

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.[6] 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).



Scheme 1.3

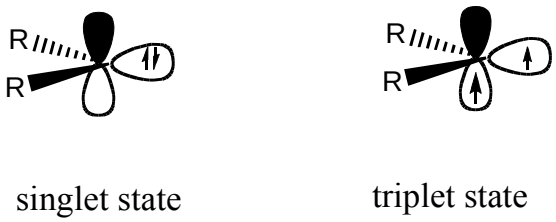
The cycle involves the decomposition of the diazo compound **6** by the metal complex **8** to generate molecular nitrogen and a high-energy carbenoid intermediate **7**. Subsequent C-H insertion gives the functionalised product **9** and regenerates the active catalyst.

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).



Scheme 1.4

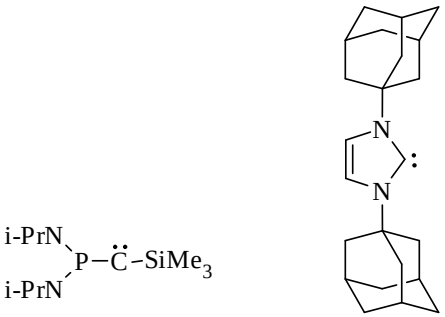
The difference in energy between singlet and triplet states is small (~32-42 kJ/mol for methylene carbene). The electronic properties of carbenes are affected by the nature of the substituents on the carbon atom. Substituents with π-donor character stabilise the *singlet* state by donating electron density into the vacant *p*-orbital on carbon. Thus, the carbene derived from dichloromethane ($:CCl_2$) is in a ground state *singlet* whereas methylene and phenylcarbene ($:CH_2$, PhCH:) 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.[7]

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-ylidene **11**[10], the first crystalline carbene, reported in 1991, which has found wide applications including complex formation (Scheme 1.5).



10 **11**

Scheme 1.5

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 σ-acceptor interactions and weak π-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.

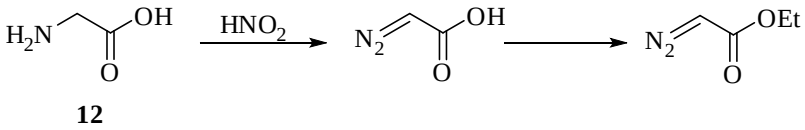
1.4 Metallocarbenes

1.4.1 Generation of metallocarbenes

Early investigations into diazo chemistry[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_2O, CuO, $CuSO_4$, CuCl and CuBr).[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, $Cu(acac)_2$).[13] In the late 1970s, Teyssie and co-workers[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 α-diazocarbonyl compounds.

1.5 Preparation of α-diazocarbonyl compounds

As stated in the preceeding 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 α-diazocarbonyl compound was the diazotisation of glycine **12** (Scheme 1.6)[15].



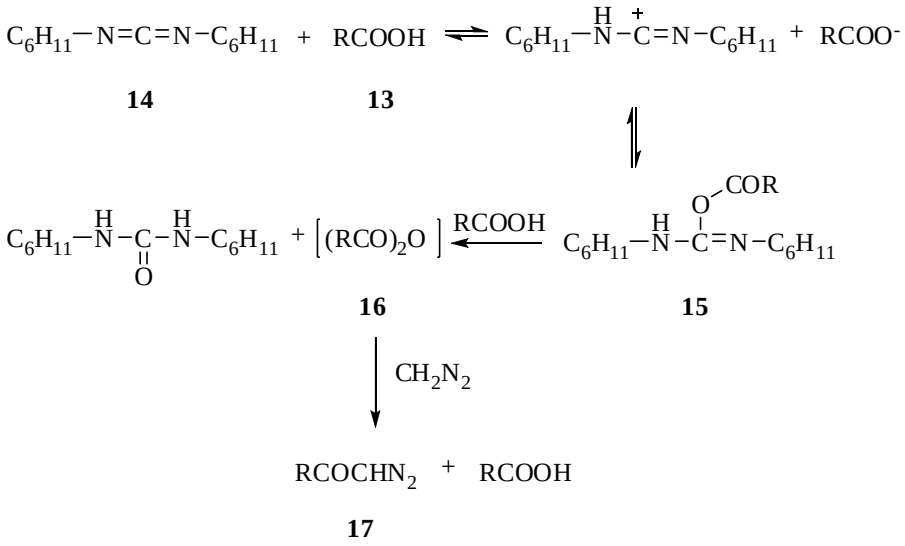
12

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 α-diazo 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 diazocarbonyls.

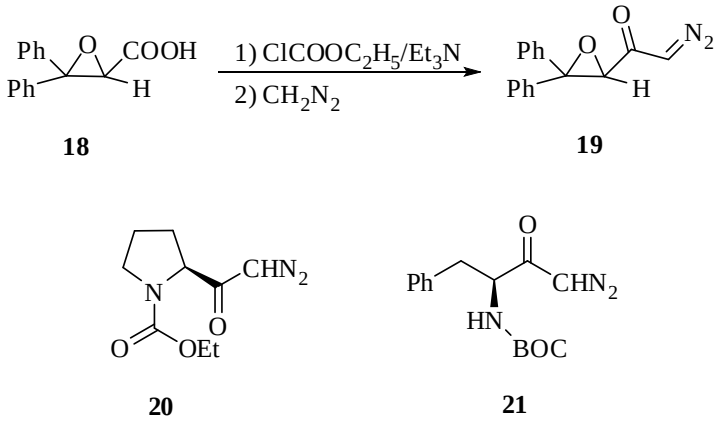
1.5.1 Acylation of diazoalkanes

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.[16] 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).[17]



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**[18] and also for the production of homochiral α-diazo ketones **20** and **21**[19] from *N*-protected amino acids (proline and phenylalanine) (Scheme 1.8).

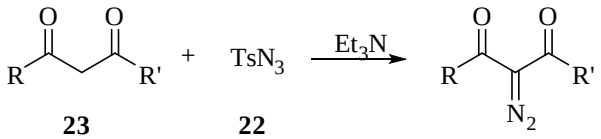


Scheme 1.8

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.[20] 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).[21]

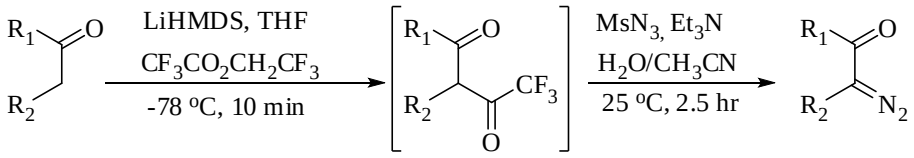


R, R'= alkoxy; R, R' = alkyl; R = alkyl, R' = alkoxy

Scheme 1.9

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

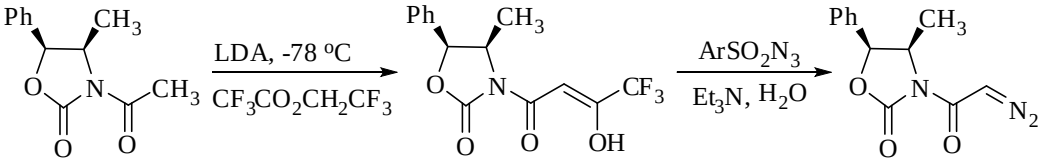
compounds. The diazotransfer to the reactive site of the former group activated by a single carbonyl generally results in a poor yield, however the efficiency can be improved by activation of the ketone precursor prior to diazotransfer. One generally accepted technique was developed by Danheiser,[22] 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 α-trifluoroacetyl derivative **25** prior to diazo transfer (Scheme 1.10).



24 **25** **26**

Scheme 1.10

Doyle[23] applied the strategy to achieve diazo transfer into a base sensitive N-acyloxazolidinone derivative **26** (Scheme 1.11).



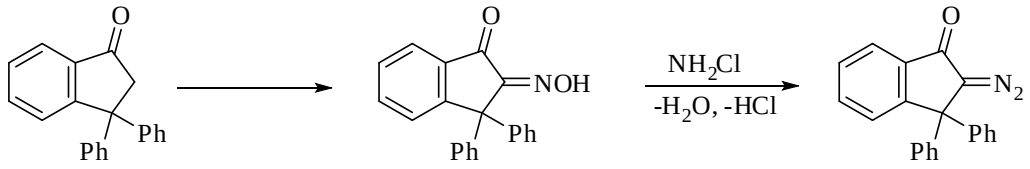
27 **28** **29**

Scheme 1.11

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

1.5.3 Other routes to α-diazocarbonyl compounds

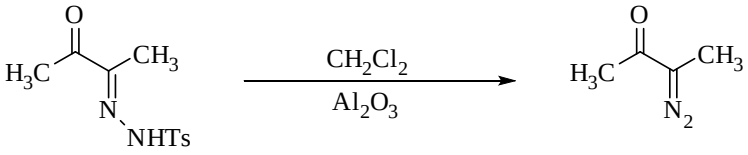
This brief section aims to highlight other less conventional methods to prepare α-diazo ketones including the Forster reaction, which involves oxime formation **31** at the α-methylene position of the ketone **30**, followed by reaction with chloroamine to give diazo ketone **32** (Scheme 1.12).[24]



30 **31** **32**

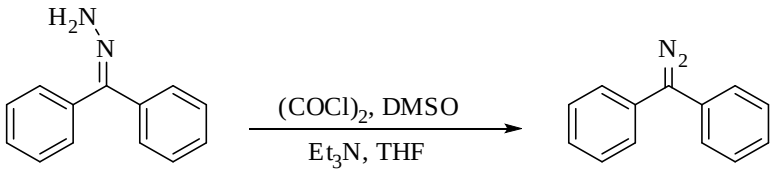
Scheme 1.12

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

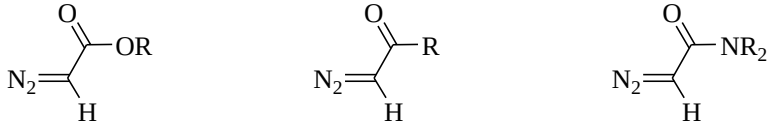
1.6 Classification of α-diazocarbonyl compounds

The stability and reactions of metallocarbenes (carbenoids) produced from the decomposition of α-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]

- 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).



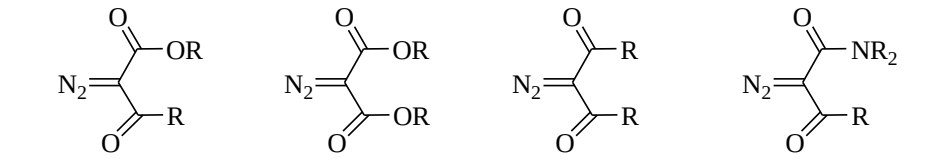
diazoacetate diazoketone diazoacetamide

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).



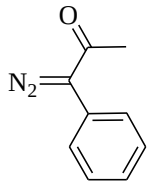
diazoacetoacetate diazomalonate diazodiketone diazoacetoacetamide

Scheme 1.16

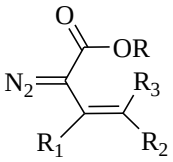
The second electron-withdrawing group gives added stabilization to the diazo compound, and therefore requires the use of active catalyst for the decomposition.[27] However, once formed the carbenoid is highly electrophilic and easily undergoes C-H activation.

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).



aryldiazoacetate



vinyldiazoacetate

Scheme 1.17

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

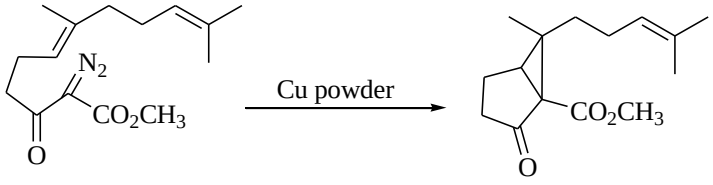
1.7 Diazocarbonyl compounds in synthesis

α-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 α-diazocarbonyl compounds.

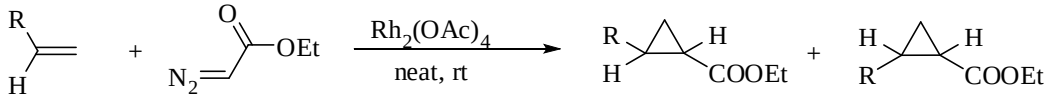
1.7.1 Cyclopropanation

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]



Scheme 1.18

Factors which impact on the diastereoselectivity and regioselectivity of cyclopropanation reaction includes sterics and the electronics of the substituents on the carbene and/or alkene, as well as the metal catalyst.[30] Thus, the use of the more hindered *t*-butyl substituent of **33** influences the diastereoselectivity and favours the formation of the *trans*-cyclopropane **35** (Scheme 1.19, Table 1.1).



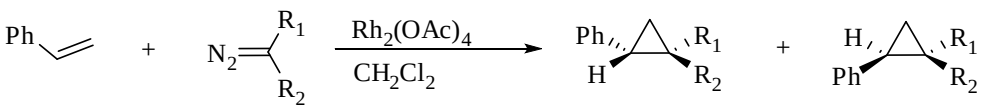
33 **34** **35** **36**

Scheme 1.19

Alkene	Yield (%)	*Trans/cis* ratio **35**/**36**
R=Ph	93	1.6
R=OEt	88	1.7
R=*t*-Bu	87	4.2

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).



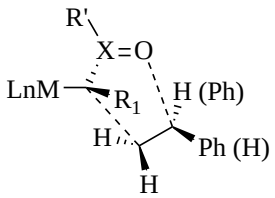
37 **38** **39**

Scheme 1.20

Entry	R_1	R_2	Yield (%)	Ratio **38**:**39**
1	H	Ph	38	23 : 77
2	H	COOEt	93	62 : 38
3	H	$CONMe_2$	74	69 : 31
4	H	NO_2	54	71 : 29

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).



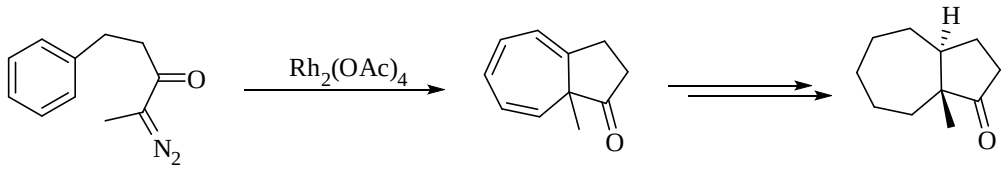
Scheme 1.21

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 $Rh_2(cap)_4$, $Rh_2(acam)_4$ > $Rh_2(OAc)_4$, $Rh_2(oct)_4$, $Rh_2(NHCOCF_3)_4$ > $Rh_2(tfa)_4$, $Rh_2(pfb)_4$.[31] 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. α,β-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.[32,33] 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]

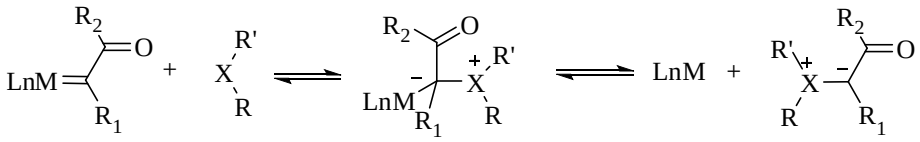


40 **41**

Scheme 1.22

1.7.3 Ylid formation and subsequent reactions

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



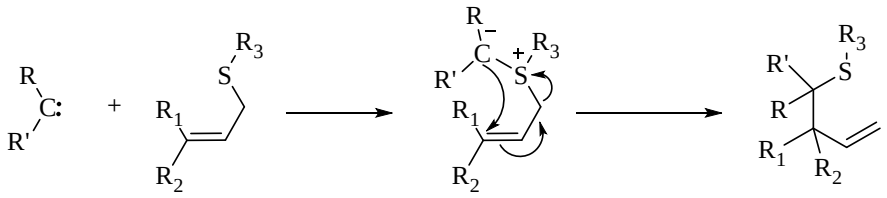
42 **43**

Scheme 1.23

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

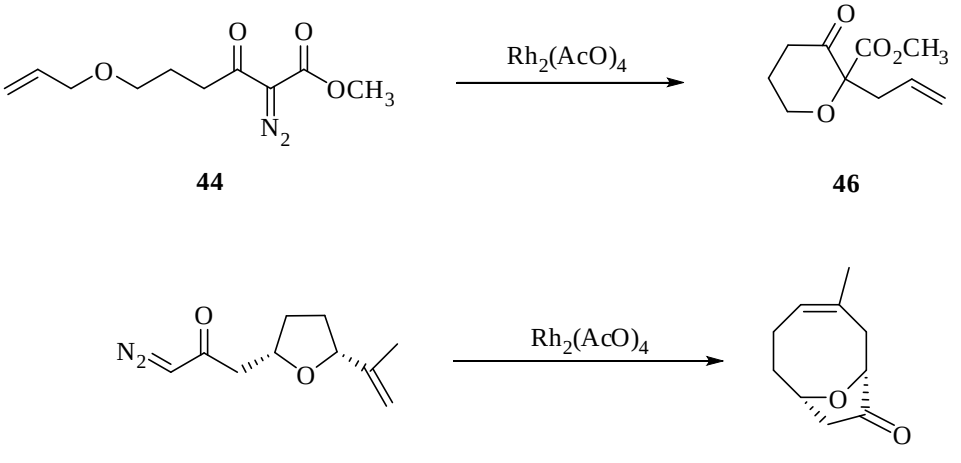
1.7.3.1 [2,3]-Sigmatropic rearrangements

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.[35] 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

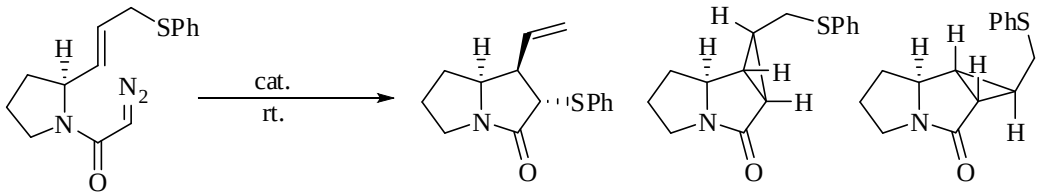
Copper catalysts were not particularly successful for this transformation due to the high temperature often required.[36] In contrast, diazo decomposition with rhodium (II) carboxylates which takes place under milder conditions has been successful for such transformations. Therefore, the tandem inter- 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).[37]



Scheme 1.25

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[38] and allylic substitution.[39]

The critical nature of catalyst choice is underscored by the following example, from studies by Chappie (Scheme 1.26, Table 1.3).[40]



48 **49** **50** **51**

Scheme 1.26

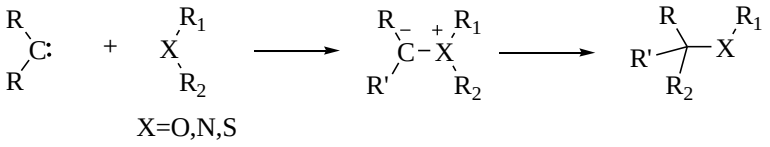
catalyst	Yield	**49**:**50**:**51**
$Rh_2(OAc)_4$	70	0 : 69 : 31
$Cu(hfacac)_2$	68	0 : 68 : 32
$Pd(OAc)_4$	78	0 : 78 : 27
$Rh_2(cap)_4$	71	90: 0 : 10

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 *anti* pyrrolidine **49**. In contrast using rhodium, copper and palladium based catalysts with electron withdrawing ligands produced only cyclopropane products **50** and **51**.

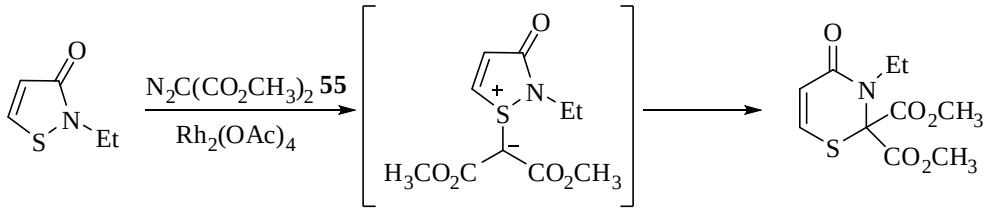
1.7.3.2 [1,2]-Sigmatropic rearrangements

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]



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).



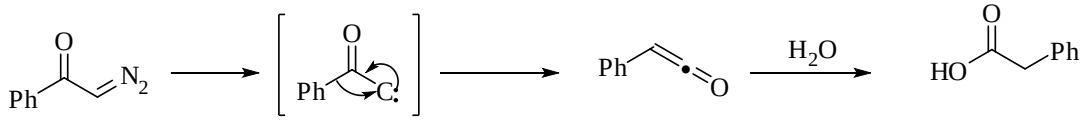
52 **53** **54**

Scheme 1.28

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

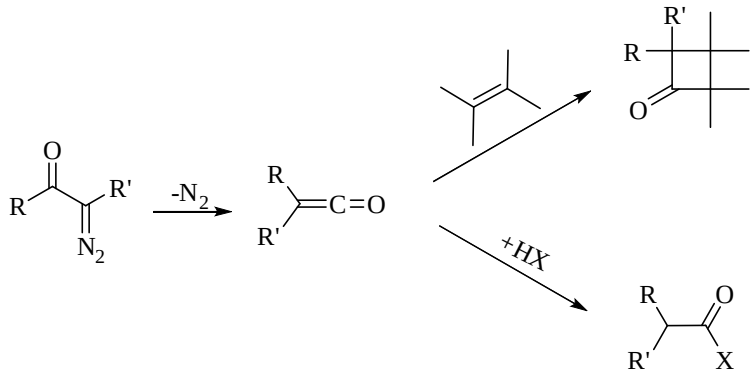
In simple terms, the Wolff rearrangement refers to a specific 1,2-rearrangement of a diazo ketone **56** following the loss of nitrogen to a ketene **57**, which then reacts with water giving the homologous acid **58** (Scheme 1.29).



56 α-ketocarbene ketene **57** **58**

Scheme 1.29

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).



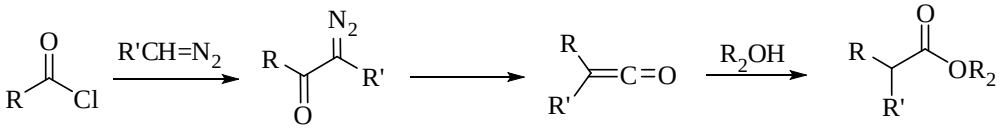
X=OH,OR,NH_2,NHR,NHOR,NR_2,SR

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.

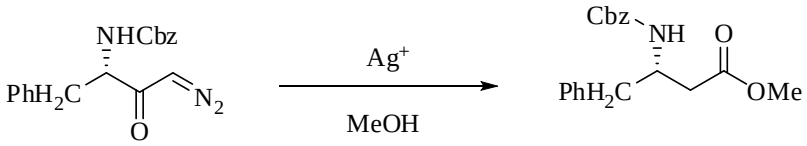
1.7.4.1 Arndt-Eistert homologation

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).



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).[43]



59 **60**

Scheme 1.32

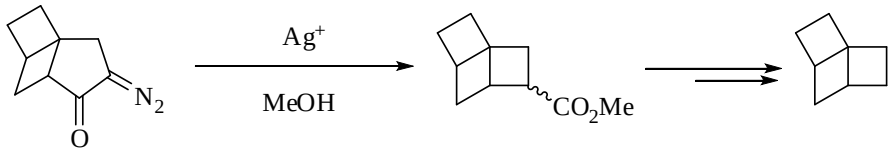
In general, the application to open chain diazo ester **61** and diazonamide **62** systems gives low yield due to the presence of less favoured alkoxy and amino migrating groups (Scheme 1.33).

61 **62**

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).[44]



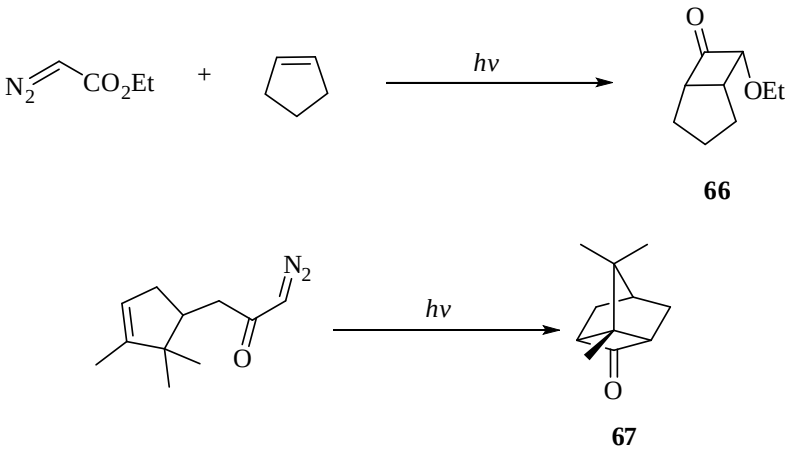
63 **64** **65**

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.[45]



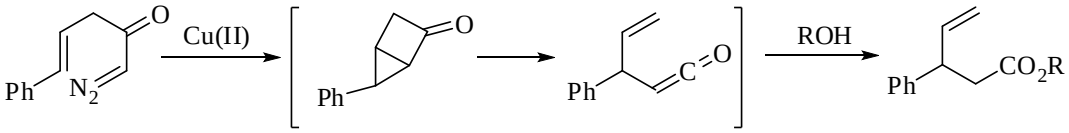
66

67

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).



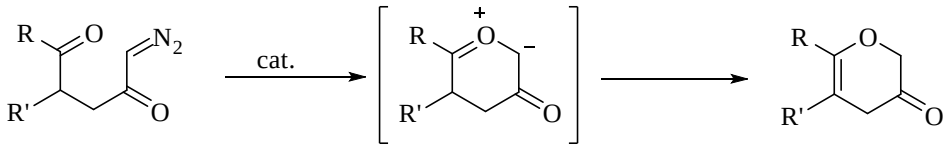
68 **69** **70** **71**

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 γ,δ-unsaturated carboxylic acid derivative **71**.[47]

1.7.5 Reactions with aldehydes and ketones

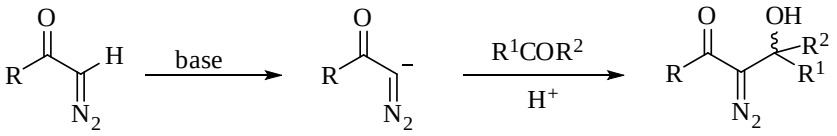
The carbon-oxygen double bond of a carbonyl forms carbonyl ylids **72** by donating electron density to the electron deficient carbenoid formed from a diazocarbonyl compound (Scheme 1.37).



72

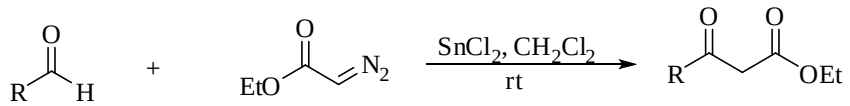
Scheme 1.37

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 β-dicarbonyl compounds. An application of the Lewis acid reaction to the synthesis of ester **78** is shown in Scheme 1.39.[48]



73 **74** **75**

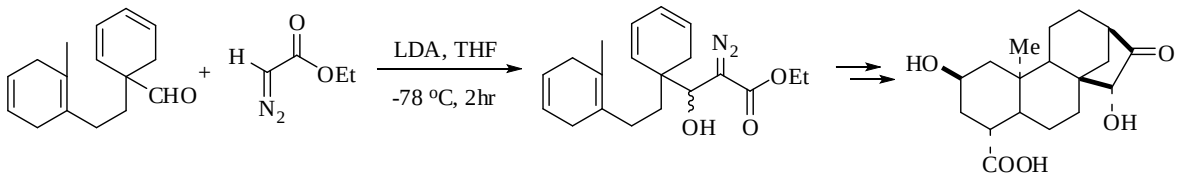
Scheme 1.38



76 **77** **78**

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.[49] A recent synthesis of (±)-atractyligenin **79** by Corey incorporates this methodology (Scheme 1.40).[50]



79

Scheme 1.40

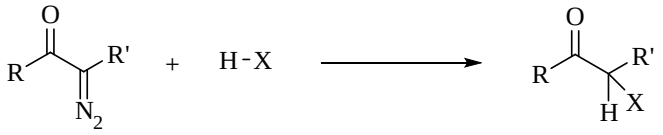
As earlier mentioned at the beginning of this section, the variety of transformations of diazocarbonyl compounds is enormous and may be difficult to cover in this thesis. Therefore, the last transformation to be discussed is the insertion reaction.

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.[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).



R/R' = alkyl, alkoxyl, aryl; X = O, S, N, Se, P, Halogen

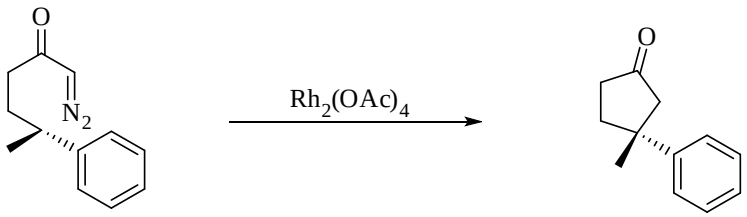
Scheme 1.41

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.[52] However, low yield and lack of chemical control limited their use.

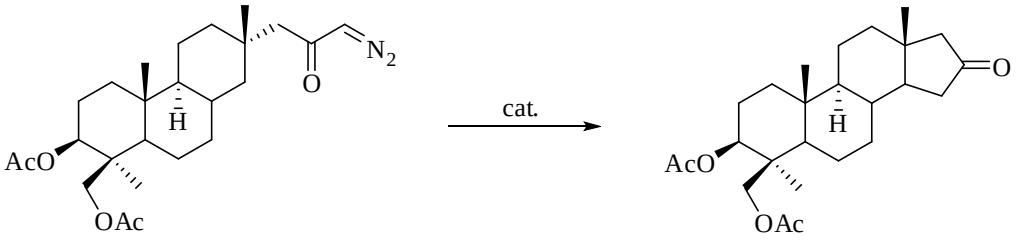
These limitations have been overcome by the use of metal catalyst particularly those of rhodium (II) carboxylates. These catalysts are useful for the catalytic decomposition of α-diazocarbonyl compounds leading to transition-metal carbenoid intermediates that can insert into a C-H bond. Studies have 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).



80 **81**

Scheme 1.42

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).[53]



82 **83**

Rh(II) catalyst = 59%

Cu(II) catalyst = 1%

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[54] and Padwa[55] on the reactivities *versus* selectivities of rhodium (II) catalysts resulted in the classification shown (Scheme 1.44).

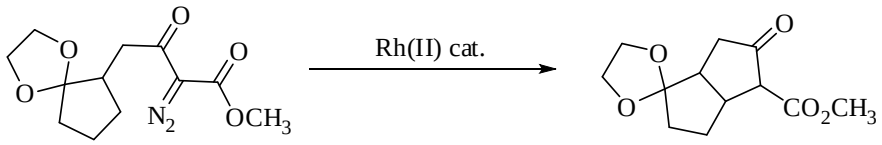
$$Rh_2(cap)_4 > Rh_2(acam)_4 > Rh_2(OAc)_4 > Rh_2(pfb)_4 > Rh_2(tfa)_4$$

increased reactivity for diazodecomposition

increased stereo- and regioselectivity

Scheme 1.44

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).

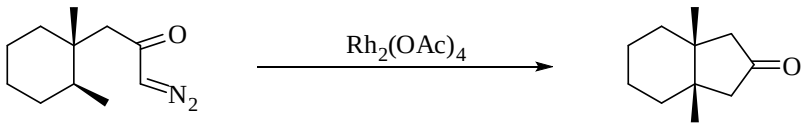


84 **85**

Scheme 1.45

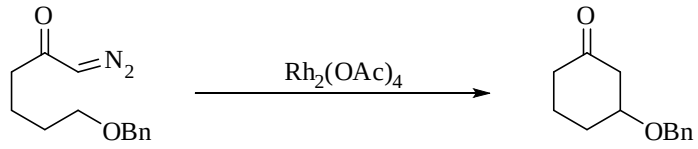
In the reaction, treatment of **84** with a Rh(II) catalyst afforded the five membered bicyclic cyclopentanone **85**, at the expense of the four membered ring (spiro product) and the six membered bicyclic product.

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^o-carbon > 2^o-carbon > 1^o-carbon > vinyl > aryl (Scheme 1.46).



Scheme 1.46

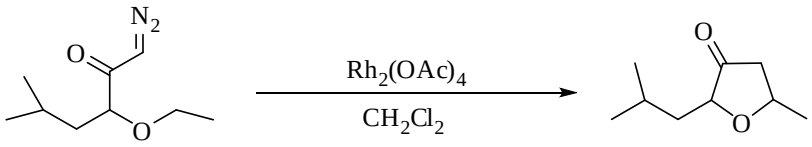
However, in cyclisation of heteroatom containing compounds exceptions do occur. The C-H insertion site is switched to favour specifically the C-H bond α to the heteroatom. In this case a different ring size than the expected five membered ring may be favoured (Scheme 1.47).



86 **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^{o}-carbon would become favoured over a 3^{o}-carbon in such heteroatom cyclisations (Scheme 1.48).



88 **89**

Scheme 1.48

Clearly, the oxygen atom in **88** activates the adjacent 2^{o}-carbon, favouring the formation of the furanone product **89**, as against the 3^{o}-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.

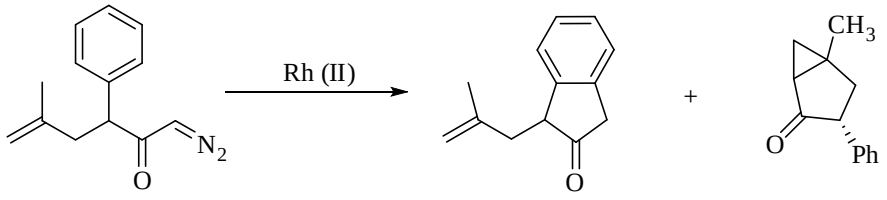
1.8 Selectivity in diazocarbonyl reactions

Extensive studies of dirhodium (II) catalyzed reactions of α-diazocarbonyl compounds demonstrate that chemoselectivity and therefore product yields are highly dependent on three

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.[60] 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 remarkeable, 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.[61] 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).



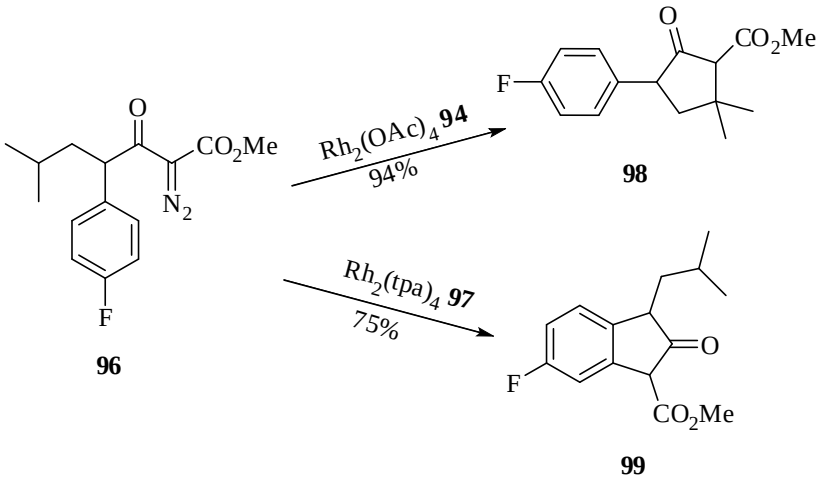
90 **91** **92**

$Rh_2(pfb)_4$ **93**	100	:	0
$Rh_2(OAc)_4$ **94**	52	:	48
$Rh_2(cap)_4$ **95**	0	:	100

Scheme 1.49

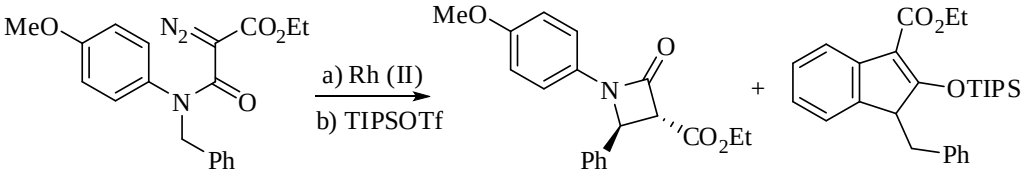
In this competitive insertion/cyclopropanation, the observed electrophilicity of the resultant carbenoids increases significantly of the order rhodium(II)caprolactam **95 <** rhodium(II)acetate **94 <** rhodium(II)perfluorobutyrate **93**. Interestingly, a complete reversal of reactivity was observed 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

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).



Scheme 1.50

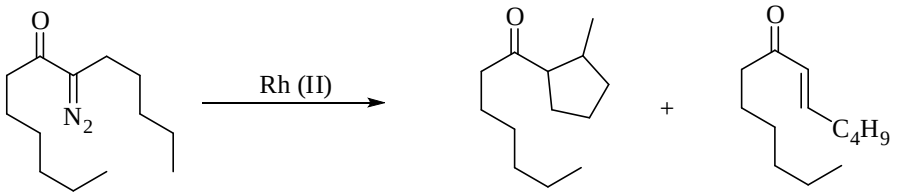
The reaction of **96** with $Rh_2(OAc)_4$ **94** gave exclusively **98** in 94% yield. However, when the $Rh_2(tpa)_4$ catalyst **97** was employed, **96** was observed to undergo an exclusive aryl C-H insertion reaction to give **99**. Moody, Padwa and co-workers have also investigated the effect of 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, $[Rh_2(NHCOC_3F_7)_4]$ **102**.[62] The latter catalyst afforded the aryl C-H insertion product exclusively which was isolated as the siloxyindole **101** (Scheme 1.51).



$Rh_2(OAc)_4$ **94**	21%	:	13%
$Rh_2(NHCOC_3F_7)_4$ **102**	0%	:	91%

Scheme 1.51

Taber's group has also noted the importance of the rhodium (II) catalyst ligand in the C-H insertion process.[63] They observed that strongly electron withdrawing ligands favour β-hydride elimination while C-H insertion is favoured by electron donating ligands (Scheme 1.52).



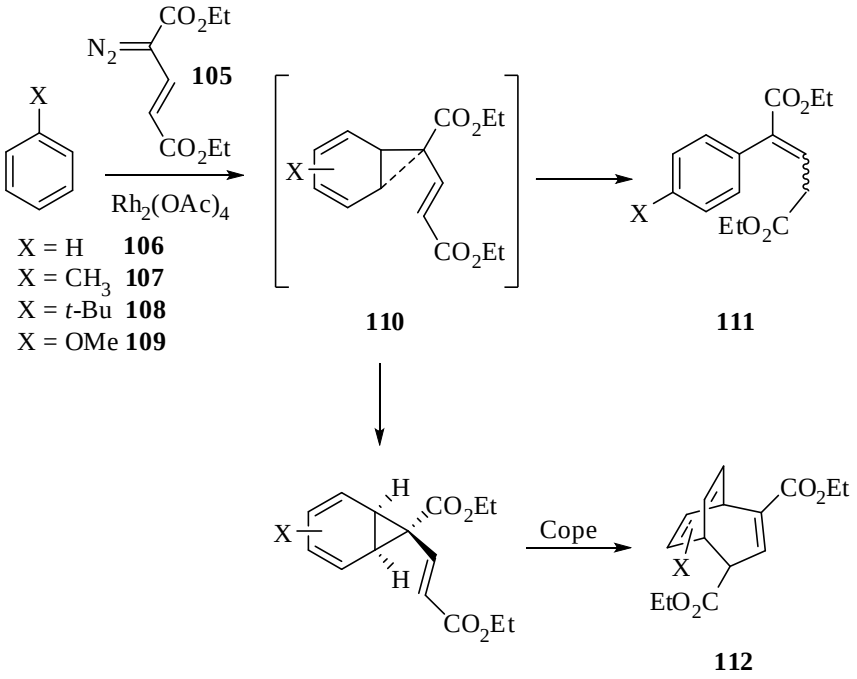
$Rh_2(OAc)_4$ **94**	70	:	30
$Rh_2(OBz)_4$ **103**	60	:	40
$Rh_2(tfa)_4$ **104**	38	:	62

Scheme 1.52

The more reactive rhodium carbenoid derived from the trifluoroacetate catalyst **104** favours the entropically less demanding pathway of β-hydride elimination.

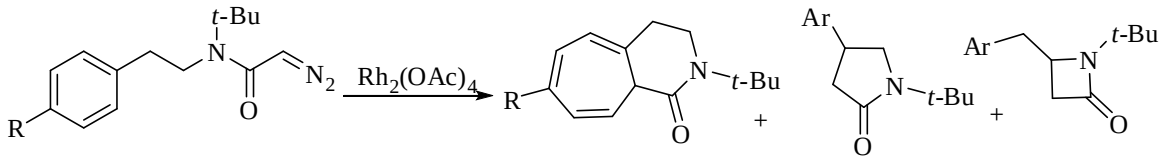
1.8.2 Nature of substrate and its effect on selectivity

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.[64] In their study of the reaction of vinyldiazoacetate **105** with benzene derivatives, they observed benzene **106**, toluene **107**, and *t*-butylbenzene **108** allowed access to bicycle [3.2.2]-nonatriene **112**. In contrast to anisole **109**, 1,2-dimethyoxy- and 1,2,3-trimethoxybenzene which afforded alkylation product **111**, presumably due to the greater stabilization of transition state **110** (Scheme 1.53).



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]



113 R = H, 85%	**116**	:	**117**	:	**118**
	68		32		0
114 R = OMe, 90%	**119**	:	**120**	:	**121**
	76		24		0
115 R = NO_2, 80%	**122**	:	**123**	:	**124**
	0		77		15

Scheme 1.54

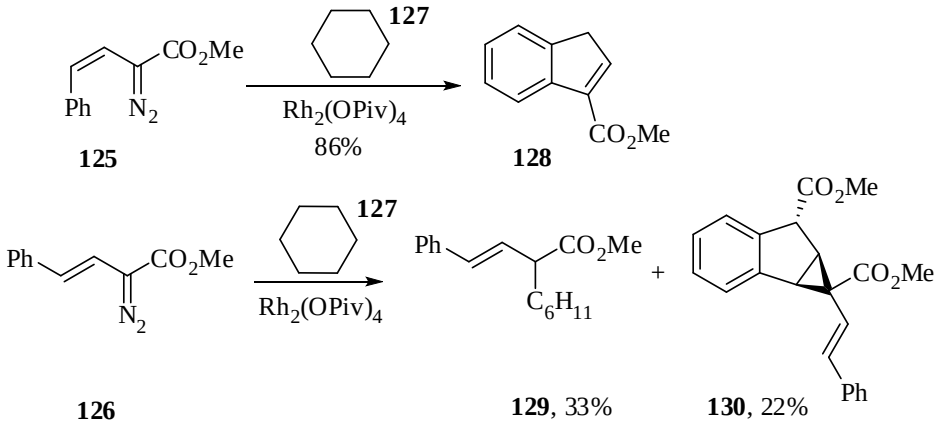
This yield improved to 3:1 when the more electron rich ring system **114** was used. In contrast, the electron deficient *p*-NO_2Ph system **115** shut down the Buchner reaction pathway, instead giving a mixture of C-H insertion products **123** and **124**.

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*-vinyldiazoacetate **126** (Scheme 1.55).[66]

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.



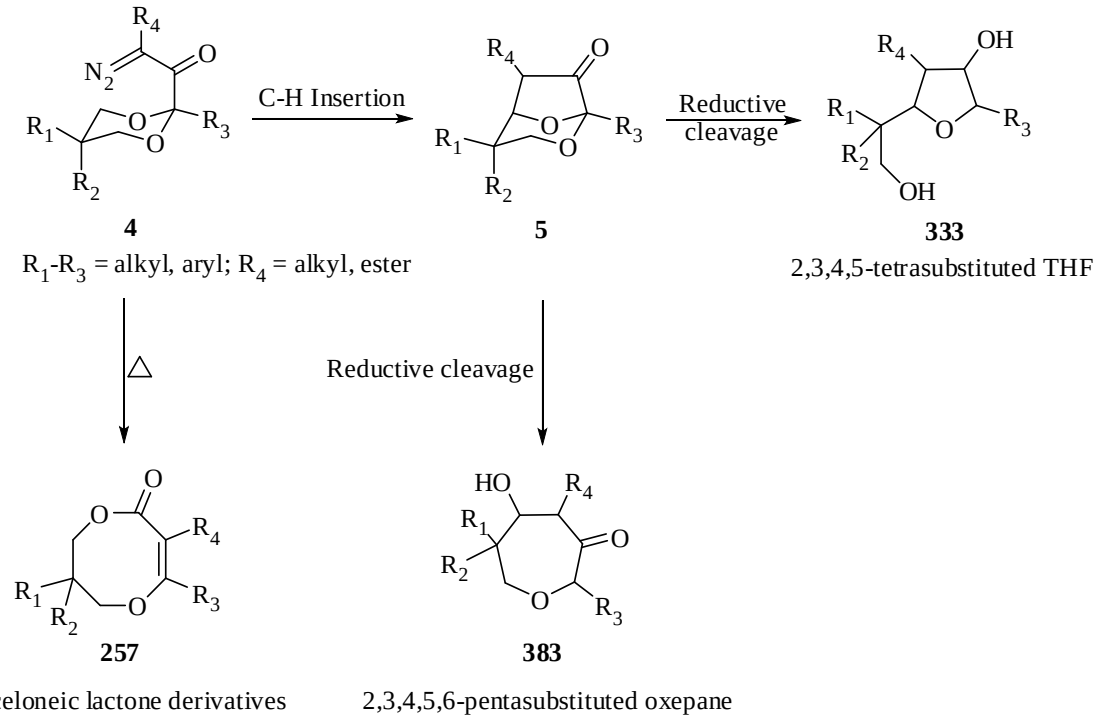
Scheme 1.55

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.

1.9 Aims of the project

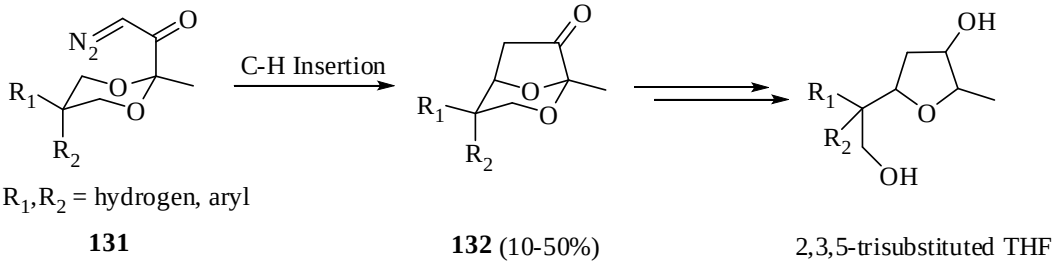
This introductory chapter has provided an insight into typical transformations of metallocarbenes initiated by rhodium (II) catalyst. In line with present research, emphasis was placed on intramolecular C-H insertion reactions. The intramolecular C-H insertion reaction has been shown to be synthetically 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).



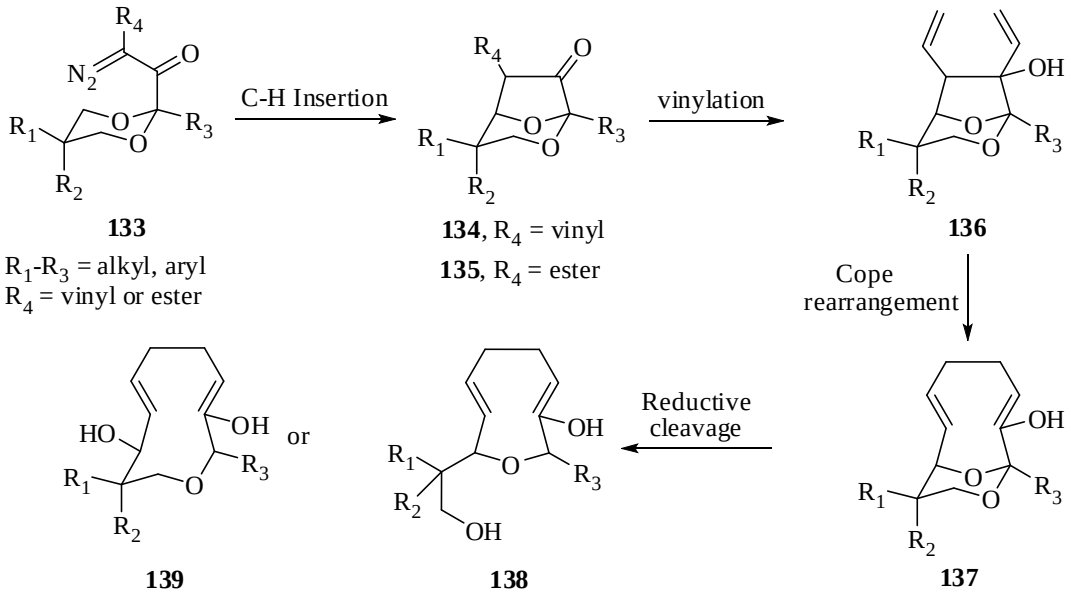
Scheme 1.56

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).



Scheme 1.57

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 R_4 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 R_4 respectively. It was hoped that such systems would allow for further transformation into macrocycles as illustrated using **134** (Scheme 1.58).



Scheme 1.58

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 arear for future exploration, the final Chapter will detail the experimental procedures and data obtained for the products synthesises.

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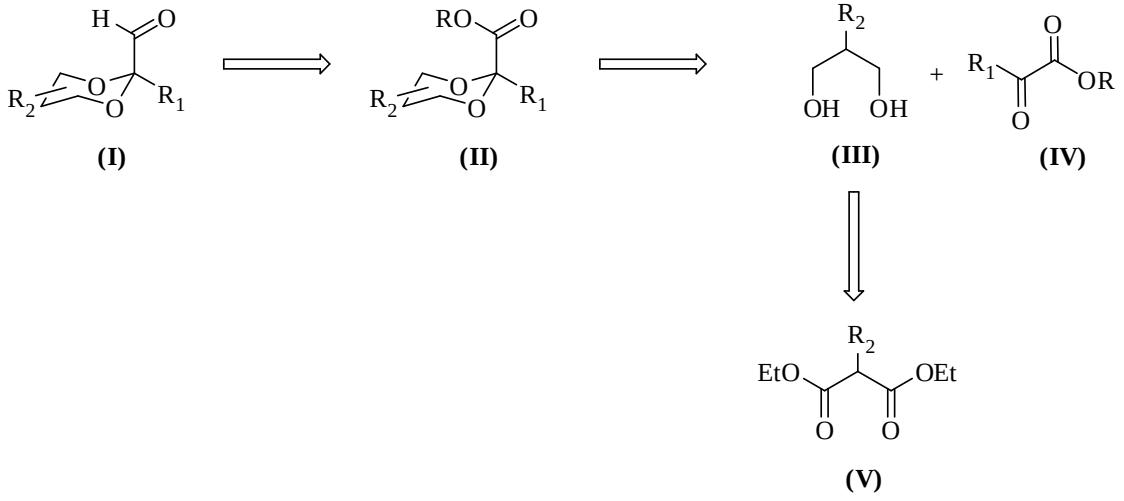
2.1 Introduction

As discussed in the preceeding 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).



(I) **(II)** **(III)** **(IV)** **(V)**

Scheme 2.1

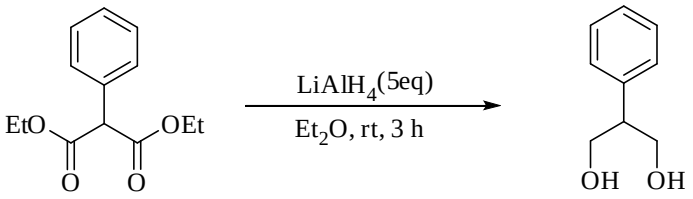
It was proposed that the aldehyde acetal **(I)** could be obtained from the ester acetal **(II)** by reduction of the ester. This in turn, may be obtained from ketalisation of pyruvate ester **(IV)** with diol **(III)**, prepared by reduction of the diethylmalonate **(V)**.

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 ($LiAlH_4$) is a valuable reagent employed widely for the reduction of esters. Consequently, a cooled suspension of $LiAlH_4$ (5 eq) in Et_2O at 0^oC 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).



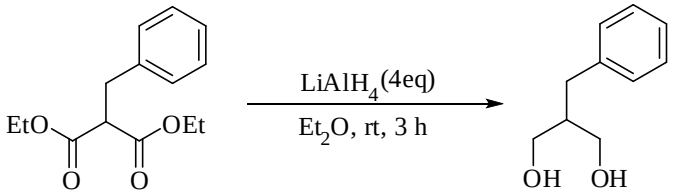
140 **141**, 60%

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 ^{13}C 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-CH_2 and 3-CH_2, 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 $LiAlH_4$ was carried out and diol **143** was obtained as a solid in high yield (Scheme 2.3).



142 **143**, 79%

Scheme 2.3

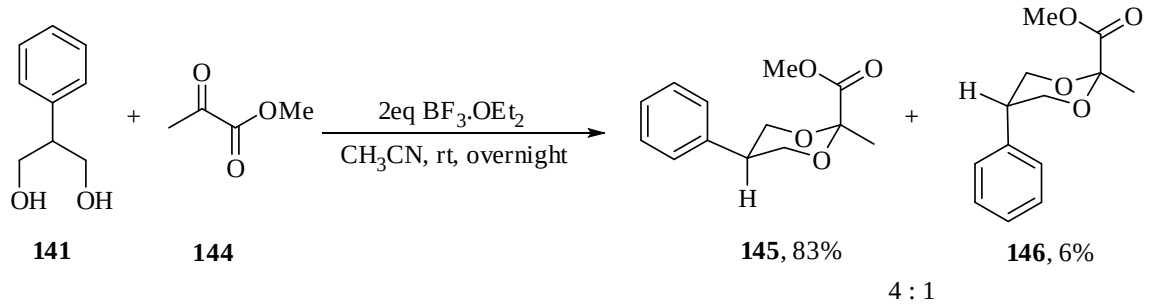
As before, evidence for the formation of diol **143** was confirmed by the IR spectrum with the broad signal at 3440-2980 cm^{-1} characteristic of alcohols and the absence of the signal attributed to the ester carbonyl at 1738 cm^{-1}. The ^1H NMR spectrum showed signals at 3.87 ppm and 3.75 ppm attributed to 2 x CH_2OH, 2.70 ppm attributed to 2-CH_2Ph together with a signal at 2.31 ppm attributed to the hydroxyl functionalities. Finally, the absence of the ester carbonyl signals in the ^{13}C 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 Ziegler[1] and Wardrop[2] 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 $BF_3.OEt_2$ and methyl pyruvate **144** in acetonitrile according to the published procedures (Scheme 2.4).



Scheme 2.4

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]

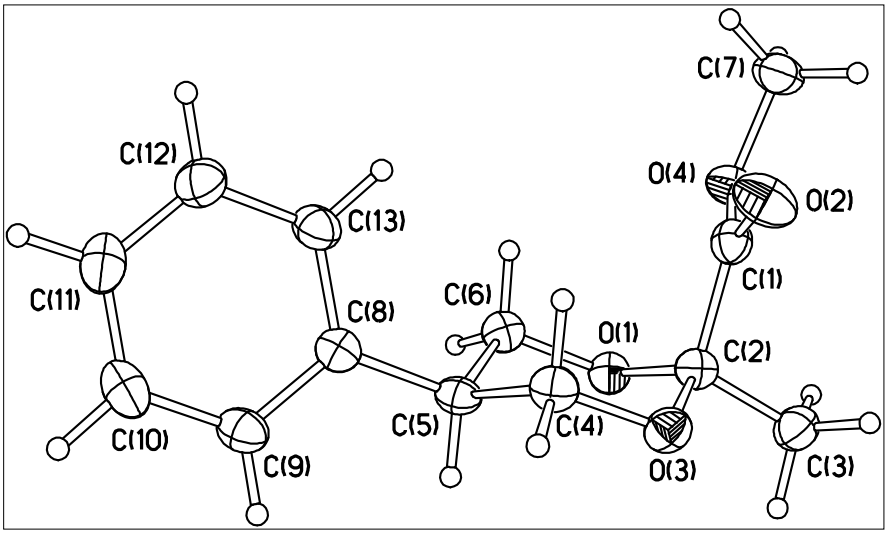


Figure 2.1

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).

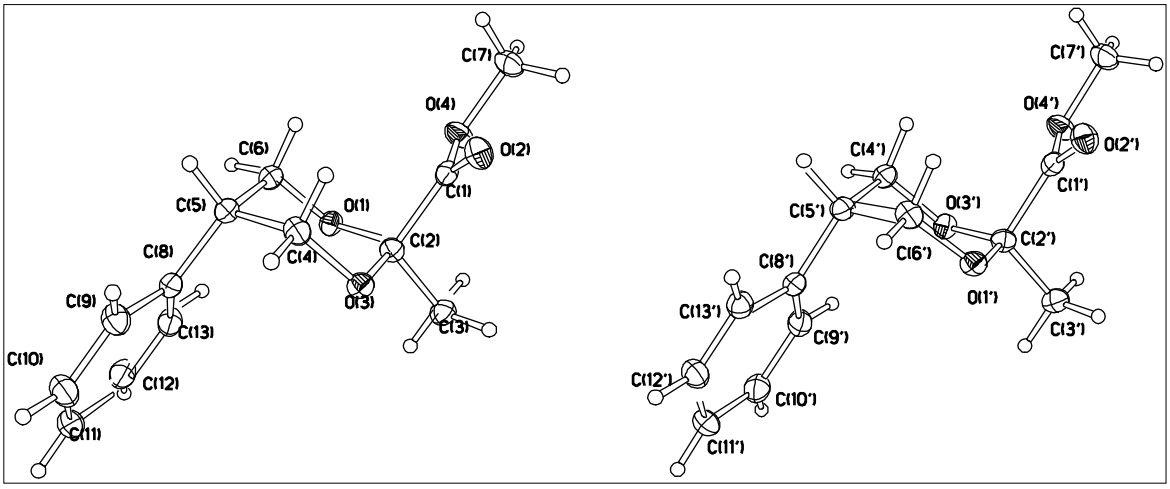
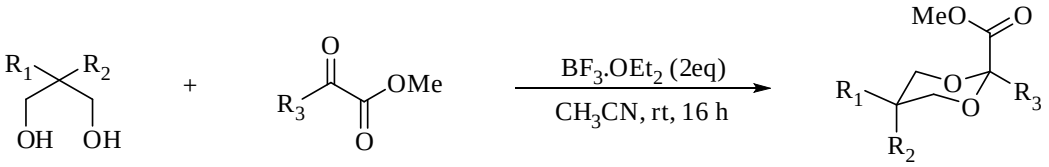


Figure 2.2

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).



155 **156** **145-154**

Scheme 2.5

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

Entry	Diol substituent	Pyruvate substituent	Ratio	Yield (%)	^{13}C and ^{1}H NMR (ppm)
1	R_1=Ph/H R_2=H/Ph	R_3=Me	4:1	89	**145** : 171.0 (CO), 98.1 (C-2), 3.95 (OMe) **146** : 170.3 (CO), 97.6 (C-2), 3.80 (OMe)
2	R_1=Bn/H R_2=H/Bn	R_3=Me	7:3	85	**147** : 171.2 (CO), 98.4 (C-2), 3.83 (OMe) **148** : 171.3 (CO), 98.7 (C-2), 3.81 (OMe)
3	R_1= CH_3/NO_2 R_2=NO_2/CH_3	R_3=Me	9:1	97	**149** : 169.7 (CO), 98.3 (C-2), 3.84 (OMe) **150** : 169.3 (CO), 98.5 (C-2), 3.84 (OMe)
4	R_1=Ph/H R_2=H/Ph	R_3=Ph	4:1	98	**151** : 169.9 (CO), 98.6 (C-2), 3.82 (OMe) **152** : 168.8 (CO), 98.4 (C-2), 3.78 (OMe)
5	R_1=Bn/H R_2=H/Bn	R_3=Ph	2:1	93	**153** : 169.8 (CO), 98.8 (C-2), 3.75 (OMe) **154** : 169.4 (CO), 98.9 (C-2), 3.73 (OMe)

Table 2.1

In all the compounds examined, mixtures of isomeric acetals were obtained and the nature of the groups R_1 and R_3 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 R_1 or R_2 group adopts the

preferential equatorial position. Similarly for the minor isomer, the larger R_1 or R_2 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 R_1 and R_2, 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).

Entry	R_1/R_2 group	R_3 group	^{1}H NMR of major isomer	^{1}H NMR of minor isomer
1	Ph	CH_3	4.10 (dd, *J* 11.7, 4.8, 4,6-***H***$_{eq}$) 3.95 (t, *J* 11.7, 4,6-***H***$_{ax}$)	4.25 (dd, *J* 12.1, 3.3, 4,6-***H***$_{eq}$) 4.10 (dd, *J* 12.1, 2.0, 4,6-***H***$_{ax}$)
2	Bn	CH_3	3.80 (dd, *J* 11.5, 4.4, 4,6-***H***$_{eq}$) 3.50 (t, *J* 11.5, 4,6-***H***$_{ax}$)	3.95-3.90 (m, 4,6-***H***$_{eq}$) 3.78 (d, *J* 11.0, 4,6-***H***$_{ax}$)
3	NO_2	CH_3	4.70 (d, *J* 13.3, 4,6-***H***$_{eq}$) 3.85 (d, *J* 13.3, 4,6-***H***$_{ax}$)	4.15 (d, *J* 11.7, 4,6-***H***$_{eq}$) 4.05 (d, *J* 11.7, 4,6-***H***$_{ax}$)
4	Ph	Ph	4.31 (dd, *J* 11.6, 4.8, 4,6-***H***$_{eq}$) 4.10 (t, *J* 11.6, 4,6-***H***$_{ax}$),	4.05 (t, *J* 11.8, 4,6-***H***$_{eq}$) 4.25 (dd, *J* 11.8, 4.5, 4,6-***H***$_{ax}$)
5	Bn	Ph	4.07 (dd, *J* 11.5, 4.4, 4,6-***H***$_{eq}$) 3.69 (2H, t, *J* 11.5, 4,6-***H***$_{ax}$)	3.78 (dd, *J* 11.9, 5.8, 4,6-***H***$_{eq}$) 4.05 (dd, *J* 11.9, 3.6, 4,6-***H***$_{ax}$)

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 R_3 = 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).

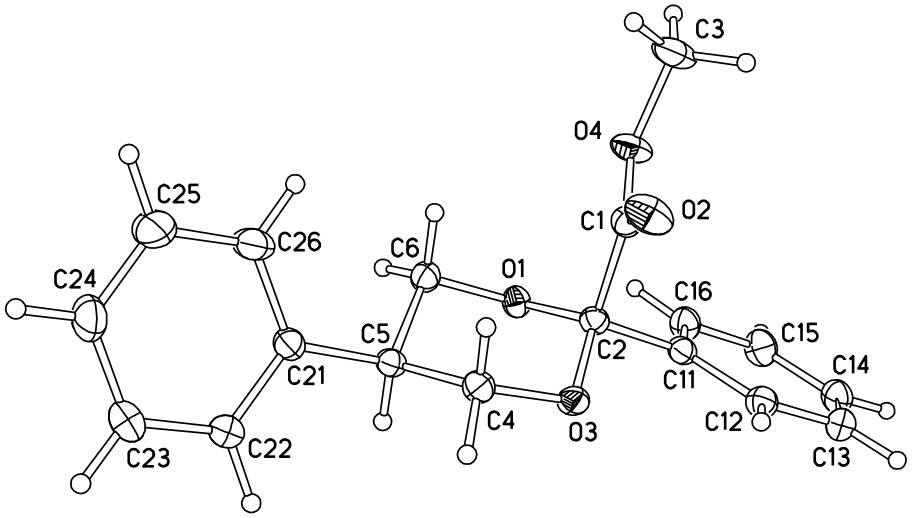
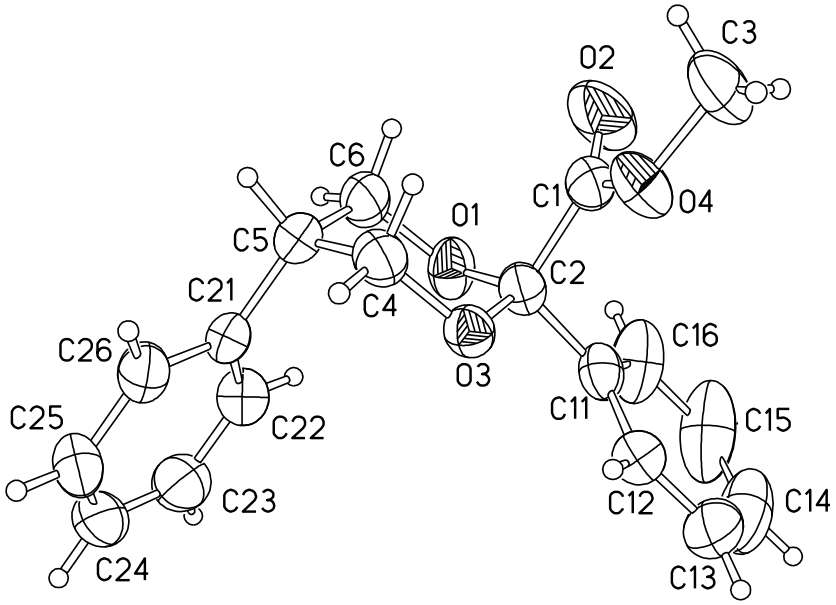


Figure 2.3

Pleasingly, and consistent with the reported phenyl series,[3] 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).



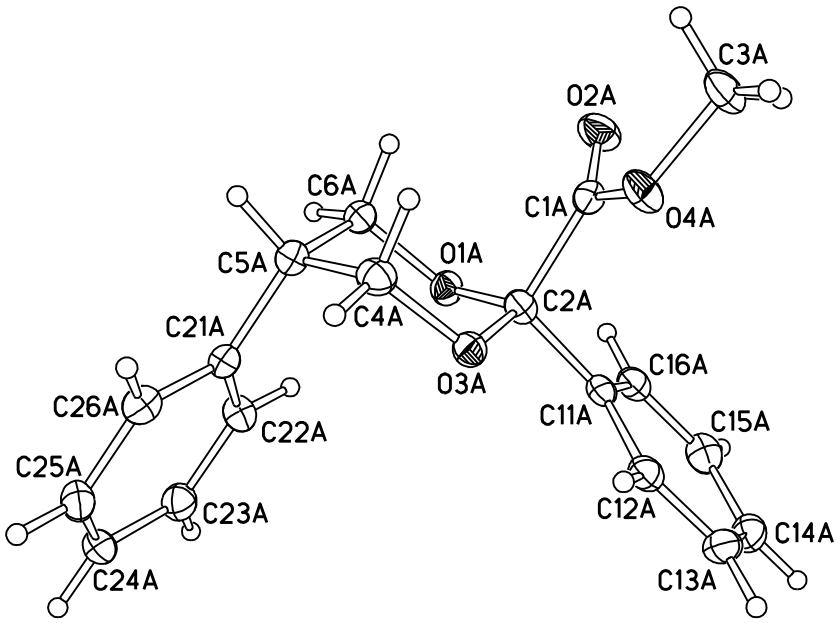
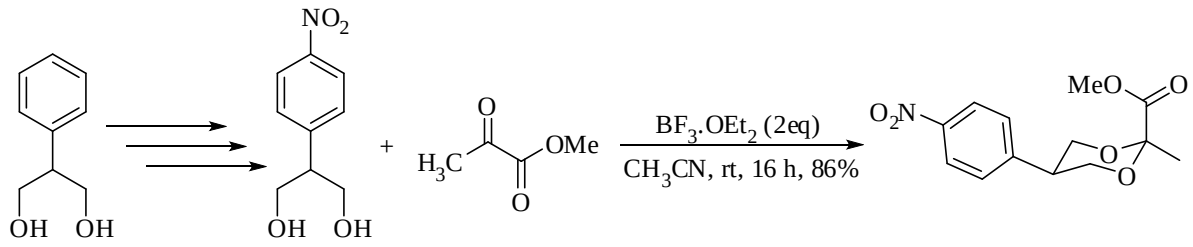


Figure 2.4

2.2.2.1 Nitration of ester acetals

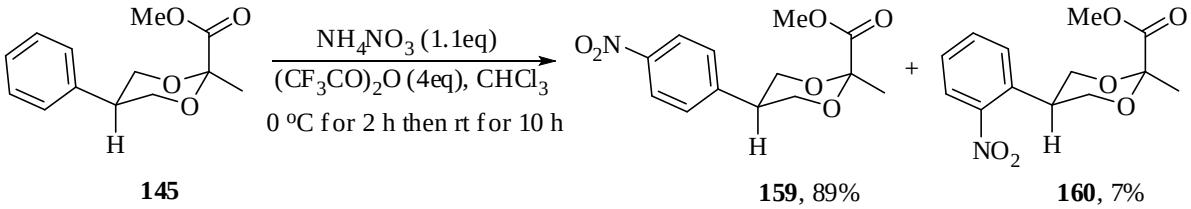
Having successfully prepared the ester acetals with varying electronics around the acetal core, it became apparent that a directing group on the aromatics may provide insights into their effects upon an eventual C-H insertion process. Towards this goal, it was decided to synthesise the nitrophenyl derivative **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).



141 **158** **144** **157**, 7:3

Scheme 2.6

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 nitration of **145** were explored (Scheme 2.7).



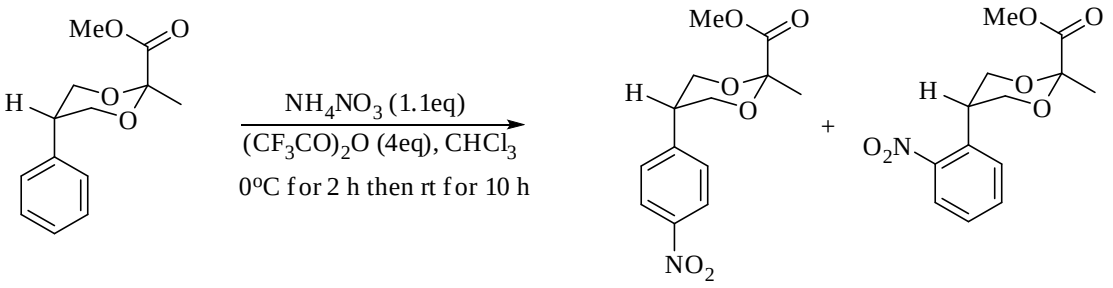
145 **159**, 89% **160**, 7%

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*-subtitution 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).



146

161, 86%

10:1

162, 8%

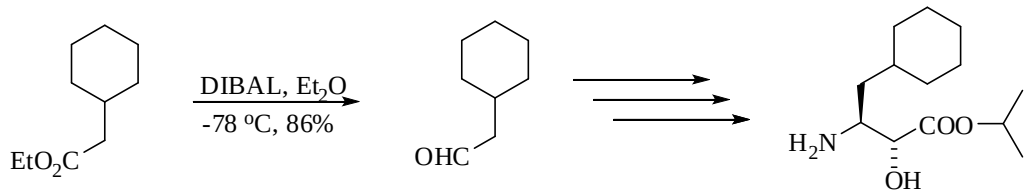
Entry	Isomers	^{13}C NMR (ppm)	^{1}H NMR (ppm)	IR (cm^{-1})
1	**161**	170.6 (CO), 98.3 (C-2), 3.85 (OMe)	8.12 (3'-H), 7.65 (2'-H)	1516, 1346 (NO_2)
2	**162**	170.6 (CO), 98.5 (C-2), 3.83 (OMe)	8.13 (6'-H), 7.89 (3'-H), 7.64 (5'-H), 7.43 (4'-H)	1511, 1339 (NO_2)

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

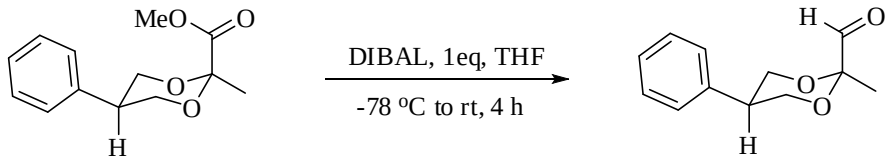
Diisobutylaluminium hydride (DIBAL) is a reagent that can be used to reduce esters to aldehydes. For example, Ito *et al* employed this reagent to reduce ester **163** to aldehyde **164** in the synthesis of cyclohexylnorstatine isopropyl ester **165** (Scheme 2.9).[6]



163 **164** **165**

Scheme 2.9

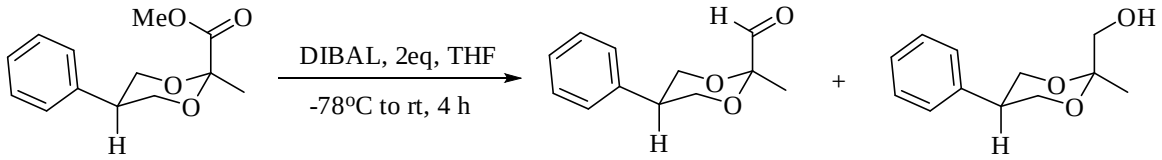
However, initial attempts to submit the ester acetal **145** for reduction using DIBAL resulted in incomplete conversion into the aldehyde acetal **176** and hence the low yield (11%) (Scheme 2.10).



145 **176**, 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).



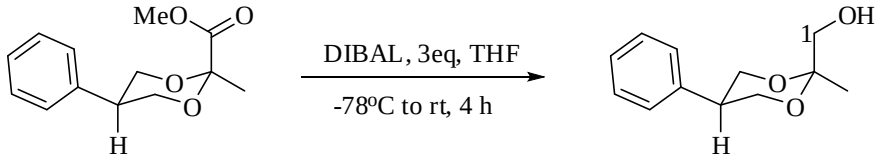
145 **176** **166**

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).

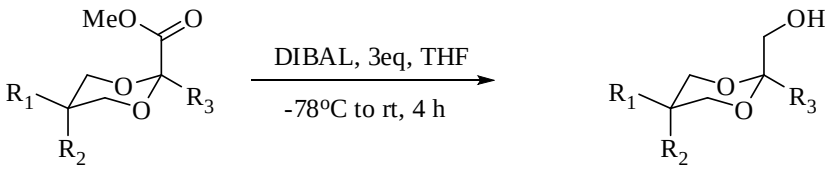


145 **166**, 95%

Scheme 2.12

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).



145, 146, 149-154, 159, 161 **166-175**

Scheme 2.13

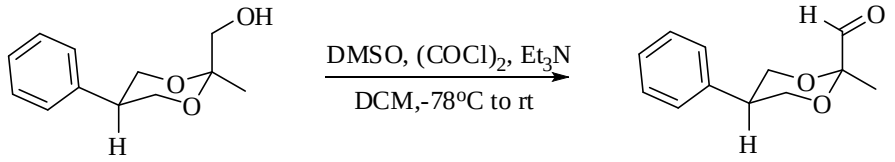
Entry	Substituents	Yield (%)	IR (cm^{-1})	^1H NMR (ppm)
1	R_1=Ph, R_2=H, R_3=CH_3	95	3390 (OH)	**166** : 3.73 (1-H_2), 1.83 (OH)
2	R_1=H, R_2=Ph, R_3=CH_3	98	3460 (OH)	**167** : 3.52 (1-H_2), 2.23 (OH)
3	R_1=Ph, R_2=H, R_3=Ph	100	3567 (OH)	**168** : 3.49 (1-H_2), 2.01 (OH)
4	R_1=H, R_2=Ph, R_3=Ph	100	3465 (OH)	**169** : 3.64 (1-H_2), 2.30 (OH)
5	R_1=Bn, R_2=H, R_3=Ph	92	3487 (OH)	**170** : 3.59 (1-H_2), 2.10 (OH)
6	R_1=H, R_2=Bn, R_3=Ph	92	3472 (OH)	**171** : 2.01 (OH)
7	R_1=*p*-NO_2Ph, R_2=H, R_3=CH_3	98	3470 (OH)	**172** : 3.67 (1-H_2), 1.84 (OH)
8	R_1=H, R_2=*p*-NO_2Ph, R_3=CH_3	95	3415 (OH)	**173** : 3.61 (1-H_2), 2.00 (OH)
9	R_1=CH_3, R_2=NO_2, R_3=CH_3	81	3312 (OH)	**174** : 3.65 (1-H_2), 1.72 (OH)
10	R_1=NO_2, R_2=CH_3, R_3=CH_3	83	3152 (OH)	**175** : 3.49 (1-H_2), 1.82 (OH)

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).

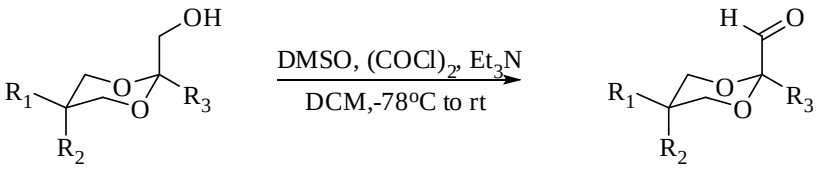


166 **176**, 95%

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 was as discussed above and is summarised in the table below (Scheme 2.15, Table 2.5).



166-175 **176-185**

Scheme 2.15

Entry	Substituent	Yield (%)	IR (cm^{-1})	^{1}H and ^{13}C NMR (ppm)
1	R_1=Ph, R_2=H, R_3=CH_3	95	1744 (CHO)	**176** : 9.63 (CHO), 201.4 (CHO)
2	R_1=H, R_2=Ph, R_3=CH_3	94	1747 (CHO)	**177** : 9.55 (CHO), 199.2 (CHO)
3	R_1=Ph, R_2=H, R_3=Ph	95	1729 (CHO)	**178** : 9.54 (CHO), 197.6 (CHO)
4	R_1=H, R_2=Ph, R_3=Ph	98	1727 (CHO)	**179** : 9.35 (CHO), 192.3 (CHO)
5	R_1=Bn, R_2=H, R_3=Ph	91	1736 (CHO)	**180** : 9.42 (CHO), 196.0 (CHO)
6	R_1=H, R_2=Bn, R_3=Ph	94	1733 (CHO)	**181** : 9.30 (CHO), 193.6 (CHO)
7	R_1=*p*-$NO_2C_6H_4$, R_2=H, R_3=CH_3	88	1737 (CHO)	**182** : 9.63 (CHO), 200.2 (CHO)
8	R_1=H, R_2=*p*-$NO_2C_6H_4$, R_3=CH_3	80	1741 (CHO)	**183** : 9.61 (CHO), 199.5 (CHO)
9	R_1=CH_3, R_2=NO_2, R_3=CH_3	79	1741 (CHO)	**184** : 9.52 (CHO), 198.6 (CHO)
10	R_1=NO_2, R_2=CH_3, R_3=CH_3	86	1759 (CHO)	**185** : 9.40 (CHO), 196.7 (CHO)

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 acetals, alcohol acetals 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

2.5 References

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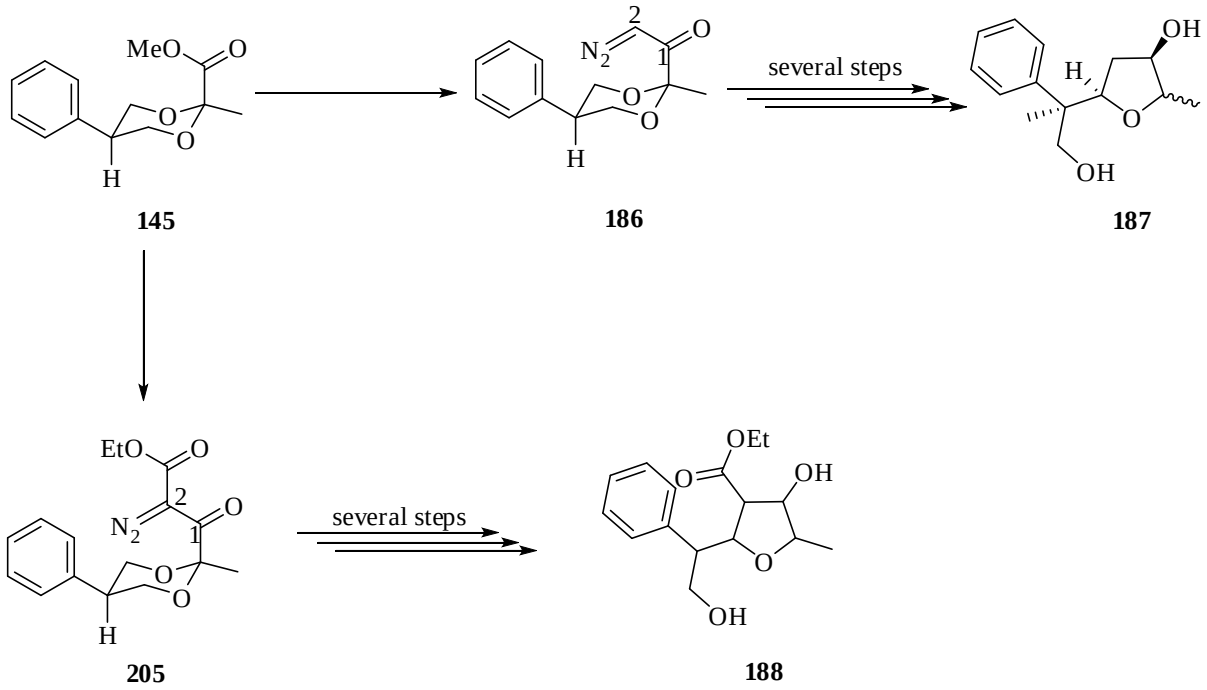
3.1 Introduction

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).

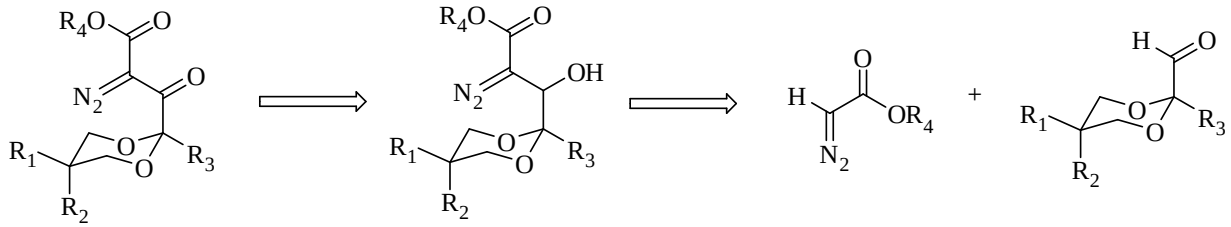


Scheme 3.1

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).



(I) **(II)** **(III)** **(IV)**

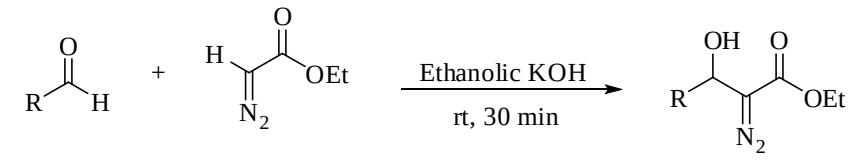
Scheme 3.2

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 *α*-diazo-*β*-hydroxy esters **191** using various aldehydes **189** and ethyl diazoacetate **190** (Scheme 3.3).



R = alkyl, aryl — 80-90%

189 **190** **191**

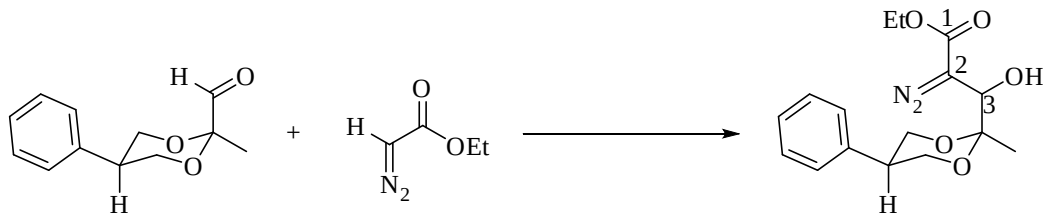
Scheme 3.3

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^{o}C followed by the addition of the aldehyde acetal **176**.

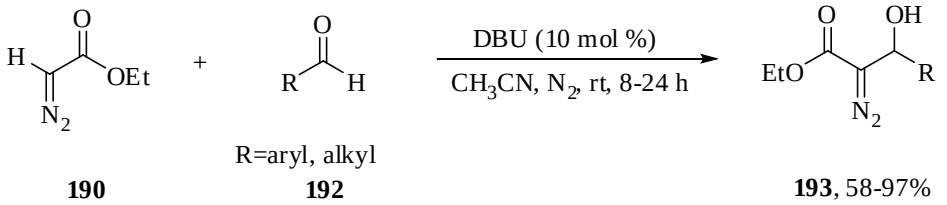


176 **190** **194**

Scheme 3.4

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 ethyldiazoacetate (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).



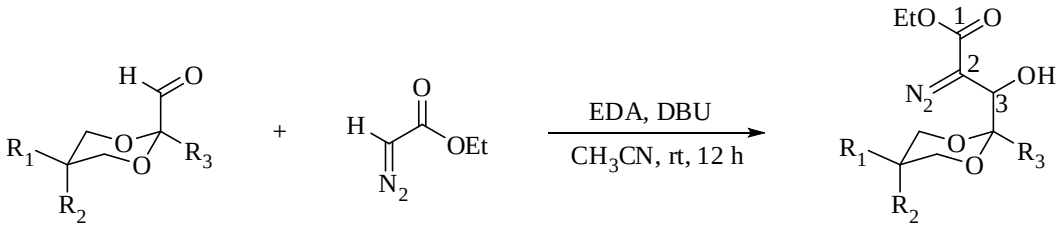
Scheme 3.5

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-OC*H*$_2$CH$_3$ and 1-OCH$_2$C*H*$_3$ 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_2O). 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 withe signals at 67.8 ppm, 60.8 ppm and 14.4 ppm corresponding to *C*-3, 1-O*C*H$_2$CH$_3$ and 1-OCH$_2$*C*H$_3$ 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 3520-3410cm^{-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).



176-180, 182, 184 **190** **194-200**

Scheme 3.6

Entry	Substituents	Yield (%)	IR (cm^{-1})	^{13}C and ^{1}H NMR (ppm)
1	R_1=Ph, R_2=H, R_3=CH_3	86	2096 (CN_2)	**194** : 166.4 (CO), 2.84 (OH) 1.28 (OCH_2CH_3)
2	R_1=H, R_2=Ph, R_3=CH_3	79	2103 (CN_2)	**195** : 166.7 (CO), 3.07 (OH) 1.29 (OCH_2CH_3)
3	R_1=Ph, R_2=H, R_3=Ph	80	2114 (CN_2)	**196** : 166.1 (CO), 3.04 (OH) 1.09 (OCH_2CH_3)
4	R_1=H, R_2=Ph, R_3=Ph	79	2103 (CN_2)	**197** : 166.0 (CO), 3.11 (OH) 1.11 (OCH_2CH_3)
5	R_1=Bn, R_2=H, R_3=Ph	64	2098 (CN_2)	**198** : 166.0 (CO), 3.30 (OH) 1.20 (OCH_2CH_3)
6	R_1=*p*-$NO_2C_6H_4$, R_2=H, R_3=CH_3	94	2099 (CN_2)	**199** : 166.4 (CO), 1.29 (OCH_2CH_3)
7	R_1=CH_3, R_2=NO_2, R_3=CH_3	96	2107 (CN_2)	**200** : 166.2 (CO), 2.83 (OH) 1.29 (OCH_2CH_3)

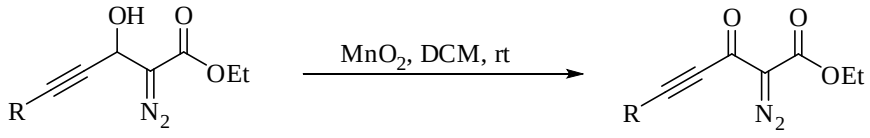
Table 3.1

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.

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

3.2.2 Oxidation of diazoketol acetals

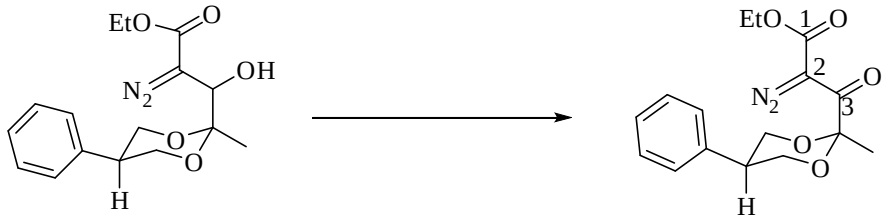
Deng in a recent study showed that mangenese (IV) oxide (MnO_2) can be conveniently used to oxidise *α*-diazo-*β*-hydroxycarbonyls such as **201** to the corresponding *α*-diazo-*β*-dicarbonyl products **202** in very good yields (Scheme 3.7).[10]



201 R=aryl, alkyl **202**, 88-92%

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.



194 **205**

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).

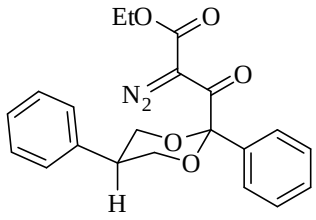
Entry	MnO_2 (eq)	Time (h)	No of Portions	Yield (%)
1	10	10	2	7
2	10	16	2	22
3	10	24	3	60
4	10	48	3	80
5	30	24	3	60

Table 3.2

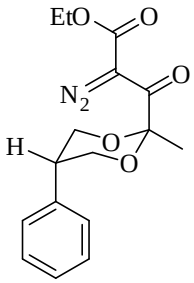
The best yield of 80% (entry 4) was obtained when 10 eq of MnO_2 was added in three portions over 48 hours. This result indicates the time dependence of the oxidation, as using the same 10 eq for a shorter time period afforded lower yields (entries 1-3). An increase to 30eq had no affect on the yield obtained (entries 5 *vs* 3).

Evidence for the formation of the diazodiketone acetal **205** was obtained from IR, ^{1}H NMR and ^{13}C 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 ^{1}H 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 ^{13}C NMR spectrum showed a signal at 188.6 ppm attributed to the carbonyl at *C*-3, further confirming the formation of the diazodiketone.

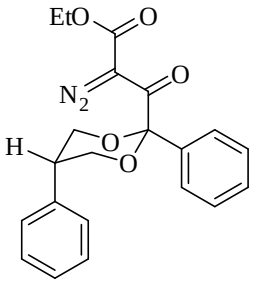
Similarly, acceptable results were obtained for the independent oxidations that resulted in the isolation of the diazodiketones **206**, **210** and **211** (Figure 3.1).



206, 66%



210, 75%

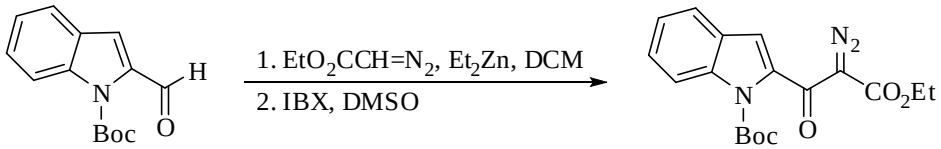


211, 62%

Figure 3.1

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]

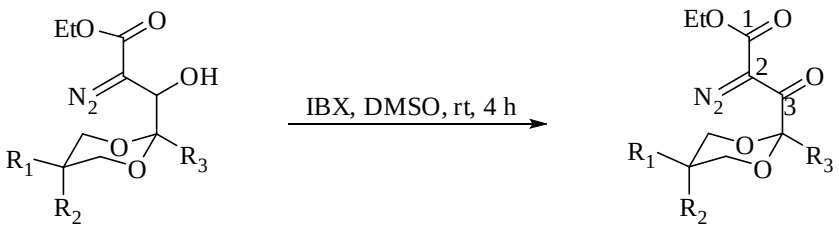


203 **204**, 71% (2 steps)

Scheme 3.9

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).



194, 196, 198-200 **205-209**

Scheme 3.10

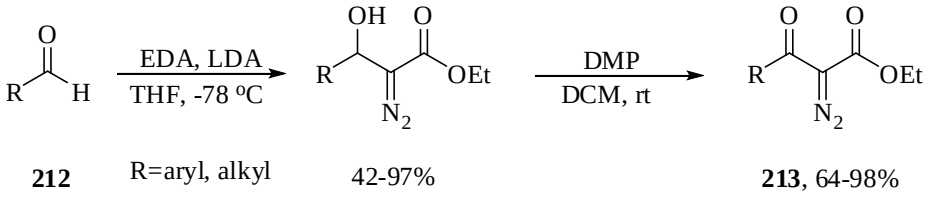
Entry	Substituents	Yield (%)	IR (cm^{-1})	^{13}C (ppm)
1	R_1=Ph, R_2=H, R_3=CH_3	90	1732 (CO)	**205** : 188.6 (CO)
2	R_1=Ph, R_2=H, R_3=Ph	93	1727 (CO)	**206** : 186.2 (CO)
3	R_1=Bn, R_2=H, R_3=Ph	100	1735 (CO)	**207** : 186.3 (CO)
4	R_1=*p*-$NO_2C_6H_4$, R_2=H, R_3=CH_3	100	1723 (CO)	**208** : 188.1 (CO)
5	R_1=CH_3, R_2=NO_2, R_3=CH_3	86	1735 (CO)	**209** : 186.8 (CO)

Table 3.3

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.[11] The first step of this involved the LDA assisted condensation of ethyldiazoacetate with aldehydes **212** at -78 ^oC followed subsequently by a Dess-Martin periodinane (DMP) oxidation (Scheme 3.11).



212 R=aryl, alkyl 42-97% **213**, 64-98%

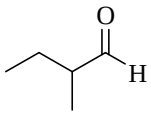
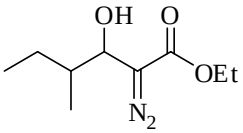
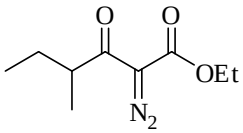
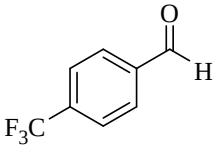
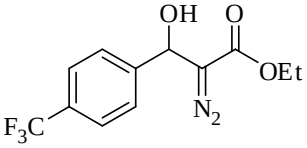
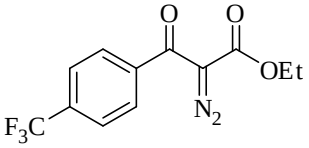
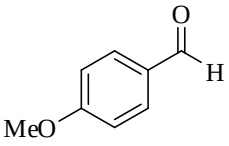
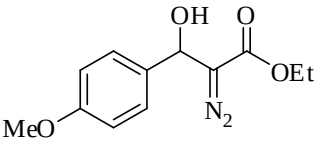
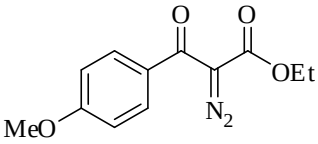
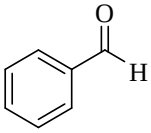
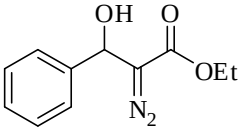
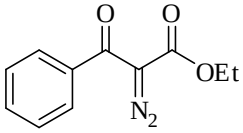
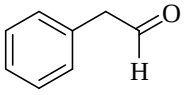
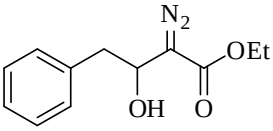
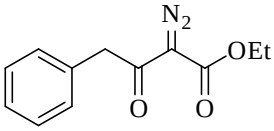
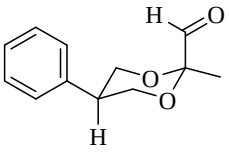
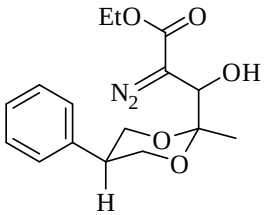
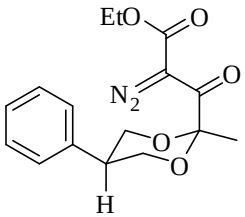
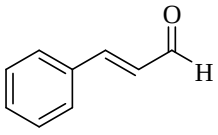
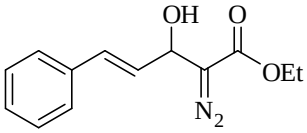
Scheme 3.11

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 *α*-diazo-*β*-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).

Entry	Aldehyde substrate	α-Diazo-β-hydroxyl compound[a]	Diazoacetoacetate derivative[a]	Overall yield (%)
1	 **214**	 **220** : 95 %	 **226** *:* 80 %	74
2	 **215**	 **221** : 93 %	 **227** : 100 %	93
3	 **216**	 **222** : 32 % (85 %)[c]	 **228** : 93 %	30
4	 **217**	 **223** : 81 %	 **229** : 96 %	78
5	 **218**	 **224** : 67 %	 **230** : 64 %	43
6	 **176**	 **194** : 86%	 **205** : 90%	77
7	 **219**	 **225** : 0%	-	-

[a] Yields after column chromatographic purification.
[c] The yield is based on recovered starting material.
nd 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.

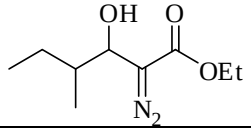
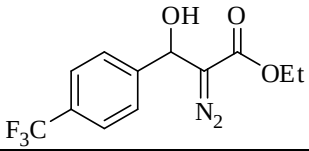
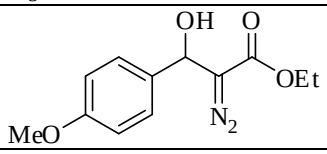
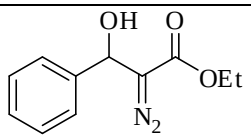
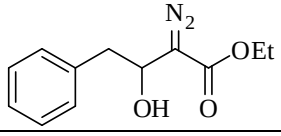
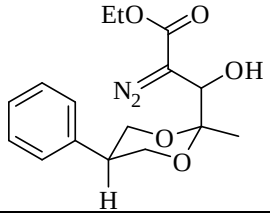
Entry	*α*-Diazo-*β*-hydroxyl compound	IR (cm^{-1})	^{13}C and ^{1}H NMR (ppm)
1		2089 (CN_2)	**220** : 166.8 (CO), 71.1 (CN_2), 2.50 (OH), 1.28 (OCH_2CH_3)
2		2092 (CN_2)	**221** : 166.0 (CO), 77.2 (CN_2), 2.90 (OH), 1.31 (OCH_2CH_3)
3		2091 (CN_2)	**222** : 166.4 (CO), 62.5 (CN_2), 2.96 (OH), 1.30 (OCH_2CH_3)
4		2093 (CN_2)	**223** : 166.3 (CO), 66.4 (CN_2), 2.96 (OH), 1.30 (OCH_2CH_3)
5		2091 (CN_2)	**224** : 166.3 (CO), 65.9 (CN_2), 2.51 (OH), 1.27 (OCH_2CH_3)
6		2096 (CN_2)	**194** : 166.4 (CO), 57.9 (CN_2), 2.84 (OH), 1.28 (OCH_2CH_3)

Table 3.5

Likewise, key evidence for the formation of the diazoacetoacetates **205**, **226-230** are summarised in Table 3.6 below.

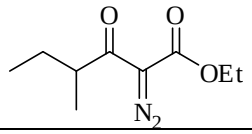
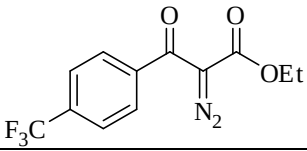
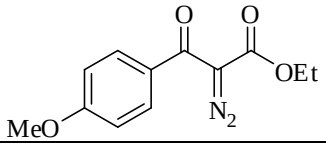
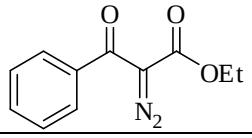
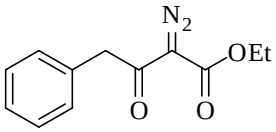
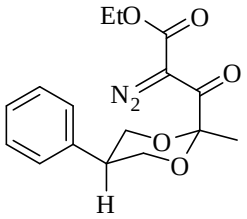
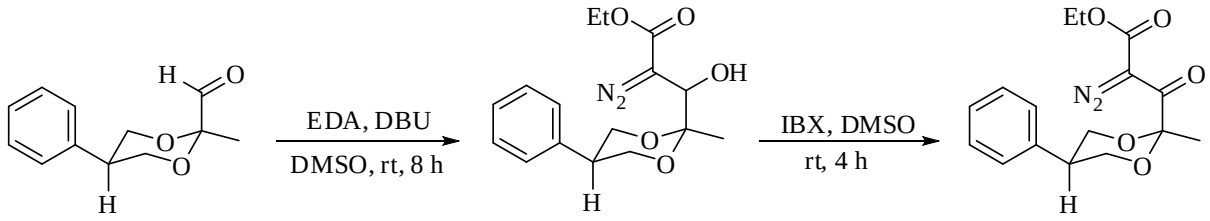
Entry	Diazoacetoacetate derivative	IR (cm^{-1})	^{13}C NMR (ppm)
1		2130 (CN_2)	**226** : 196.7 (CO)
2		2146 (CN_2)	**227** : 186.0 (CO)
3		2139 (CN_2)	**228** : 185.3 (CO)
4		2139 (CN_2)	**229** : 186.8 (CO)
5		2133 (CN_2)	**230** : 190.2 (CO)
6		2127 (CN_2)	**205** : 188.6 (CO)

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

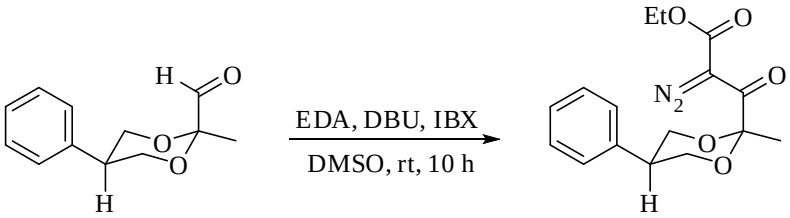
one-pot method. The key parameter in this development would be the choice of a suitable common solvent. Initial attempts at dissolving IBX in acetonitrile, the solvent employed for the initial aldol condensation, indicated its limited solubility. Therefore the use of DMSO was explored. Pleasingly, aldehyde 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).



176 **194** **205**, 91%

Scheme 3.12

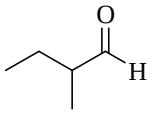
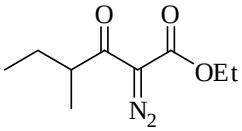
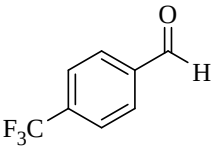
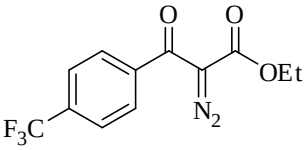
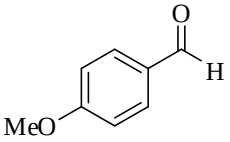
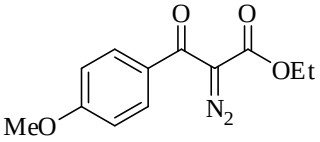
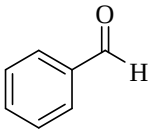
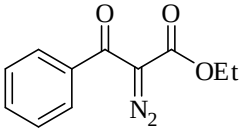
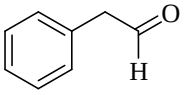
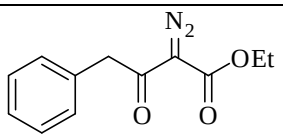
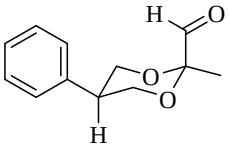
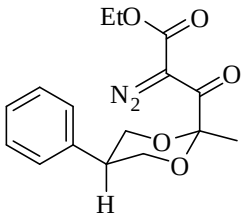
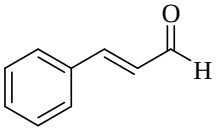
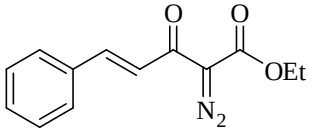
Analytical and spectroscopic data obtained were in agreement with that previously obtained. Pleased with this result and having established the compatibility of all the reagents, it was decided to examine the possibility of further telescoping the procedure by adding the oxidant at the outset of the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



176 **205**, 89%

Scheme 3.13

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[a]
1	 **214**	 **226** *:* 74 %
2	 **215**	 **227** : 100 %
3	 **216**	 **228** : 50 %
4	 **217**	 **229** : 80 %
5	 **218**	 **230** : 52 %
6	 **176**	 **205** : 89%
7	 **219**	 **231** : 60%

[a] Yields after column chromatographic purification.

Table 3.7

The diazoacetoacetate 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 diazoacetoacetates in moderate to good yield. As before, satisfactory analytical and spectroscopic data were obtained for the products.

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 MnO_2 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

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4.1 Introduction

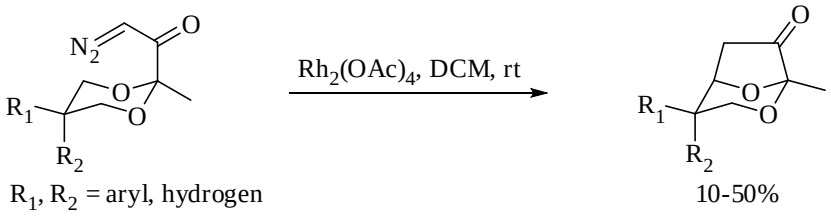
The preceeding chapter discussed the preparation of a range of diazodiketone acetals, representative of the acceptor-acceptor substituted class of carbenoids.

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[1] 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).



R_1, R_2 = aryl, hydrogen

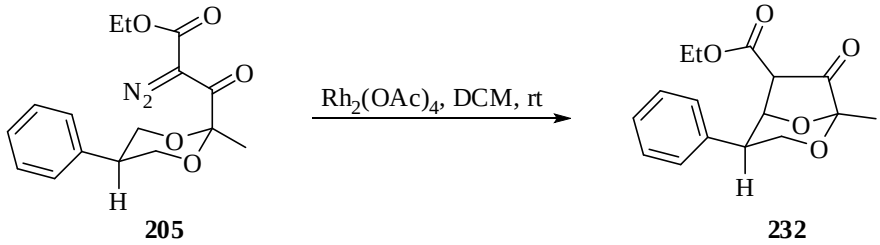
131

10-50%

132

Scheme 4.1

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 bicyclicketone 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.



205 **232**

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.

Entry	Catalyst loading (mol%)	Rate of addition	Solvent	Temp. (^oC)	Yield (%)
1	1	over 24 hours	CH_2Cl_2	Room temp	SM
2	2	over 24 hours	CH_2Cl_2	Room temp	SM
3	5	over 24 hours	CH_2Cl_2	Room temp	SM
4	5	over 24 hours	CH_2Cl_2	Reflux	SM + CM
5	5	over 24 hours	Toluene	Reflux	SM + CM
6	5	3 portions	Toluene	Reflux	SM + CM
7	5	over 24 hours	Benzene	Reflux	SM + CM

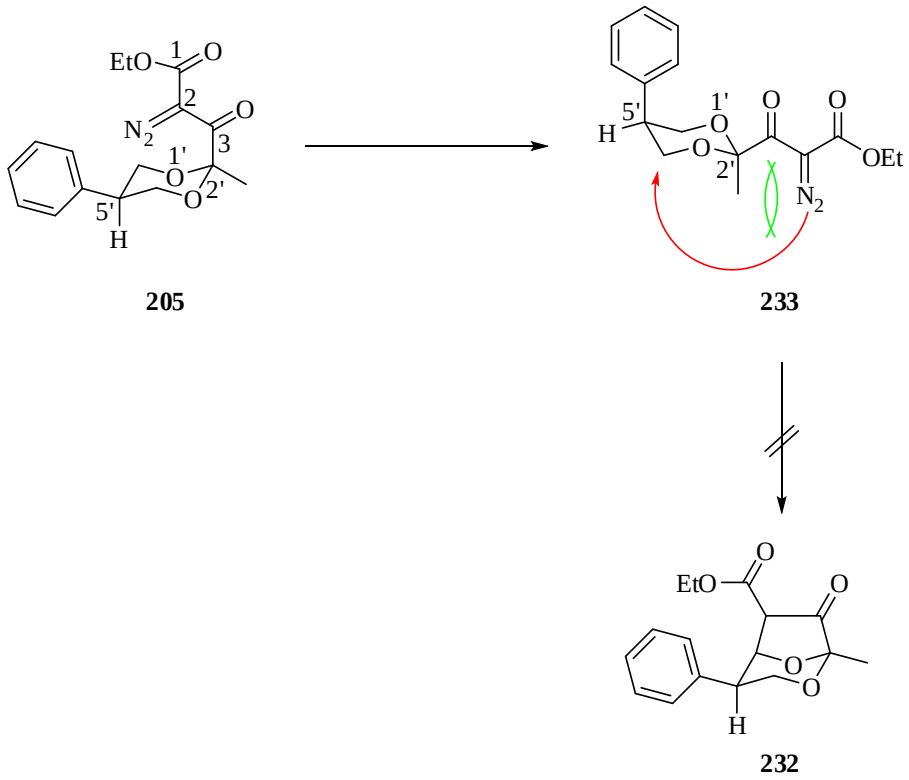
SM = Starting material; CM = Complex mixture

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;

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.

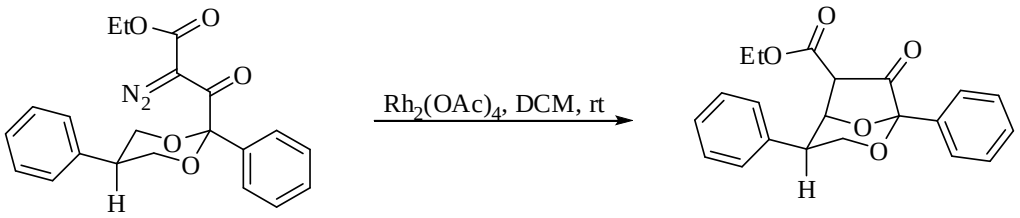
2. Although 1,3-dioxanes-2-carboxylic acid derivatives display a pronounced preference (~3 to 4 kcal/mol) for an axially oriented 2-carboxylate group[2], the bulkiness of this derivative in diazodiketone acetal **205** may have caused a ring inversion or 'flip', leading to an orientation that places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



Scheme 4.3

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.



206 **234**

Scheme 4.4

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

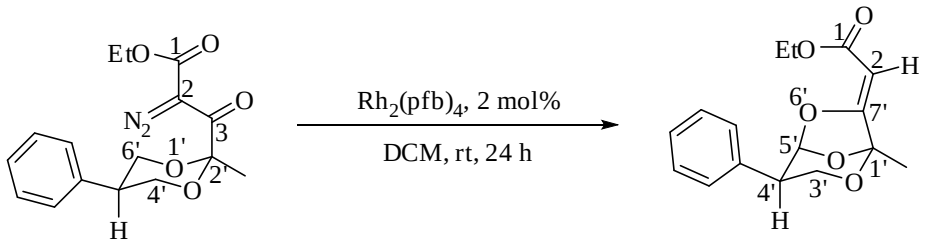
From an extensive literature survey, it was established that C-H insertions of diazocarbonyl compounds can show high levels of chemoselectivity that varies according to the nature of the catalyst employed.[3] Therefore it was decided to evaluate the use of rhodium (II) catalyst with differing electron demands of the ligands. Rhodium (II) octanoate [$Rh_2(oct)_4$] and rhodium (II) heptafluorobutyrate [$Rh_2(pfb)_4$] catalysts were investigated because they represented both ends of the rhodium (II) catalysts reactivity/selectivity spectrum.[4,5] According to the spectrum, $Rh_2(oct)_4$ catalyst bearing electron donating ligands is noted to show low reactivity but high selectivity while $Rh_2(pfb)_4$ 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 $Rh_2(oct)_4$ catalyst resulted in recovery of the starting material (entry 1 & 2,

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).

Entry	Catalyst	Cat. loading (mol%)	Temp. (^oC)	Solvent	Rate of addition of SM	Yield (%)
1	$Rh_2(oct)_4$	2	rt	DCM	Over 24h	SM
2	$Rh_2(oct)_4$	2	Reflux	DCM	Over 24h	SM + CM
3	$Rh_2(pfb)_4$	2	rt	DCM	Over 24h	20

SM = Starting material; CM = Complex mixture

Table 4.2



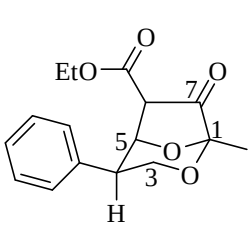
205 **235**, 20%

Scheme 4.5

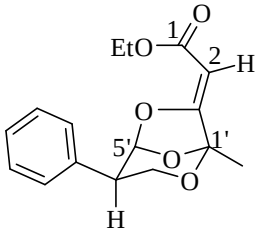
Evidence for the formation of the trioxabicyclic product **235** was obtained from the IR, ^1H NMR and ^{13}C NMR spectra. Comparison of the IR spectrum of **205** with that of product **235** showed the disappearance of the signal at 2127 cm^{-1} attributed to the diazo functionality (C=N_2) and the appearance of a signal at 1705 cm^{-1} assigned to the enol ether. The ^1H 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.



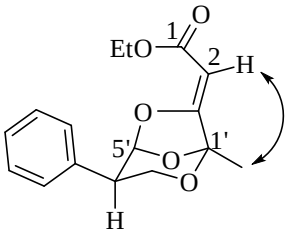
232



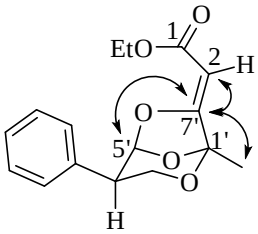
235

Figure 4.1

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'.



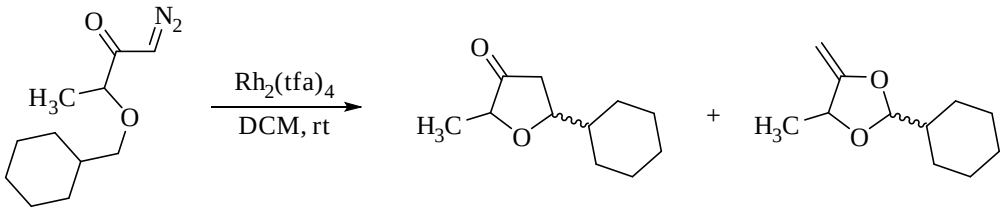
235, A



235, B

Figure 4.2

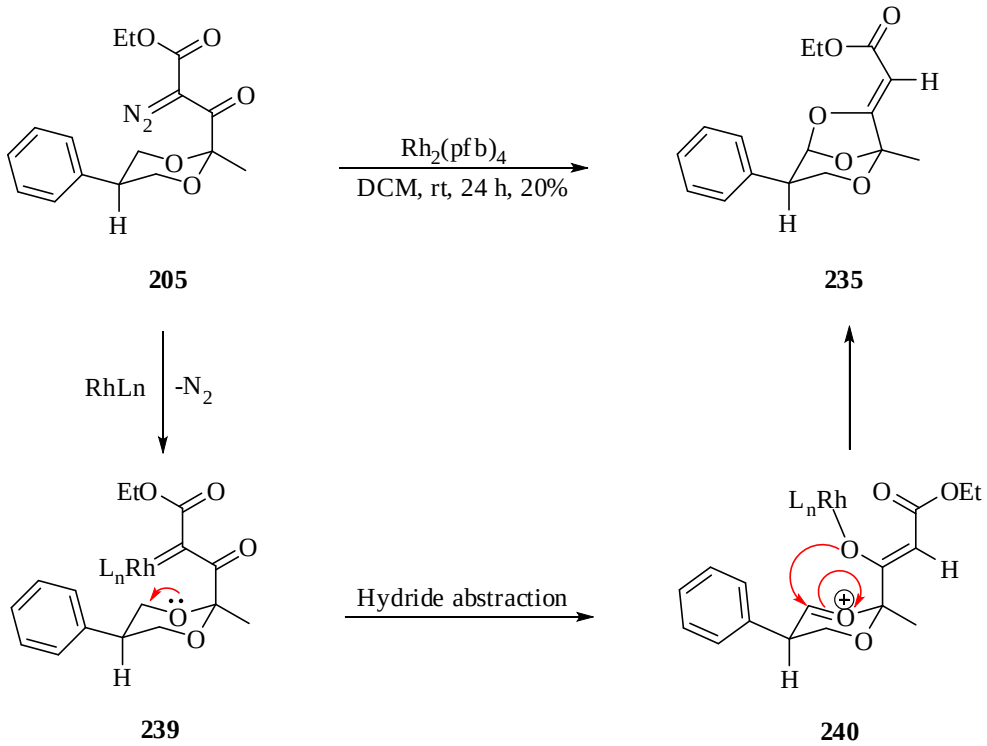
The trioxabicyclic ester **235** is however not an entirely strange product. Its formation by an O-H insertion is due to the highly electron withdrawing nature of the perfluorobutyrate ligands and hence confirmed that generation of the intermediate carbenoid was accessible. Clark and co-workers recently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



236 **237**, 35% **238**, 40%

Scheme 4.6

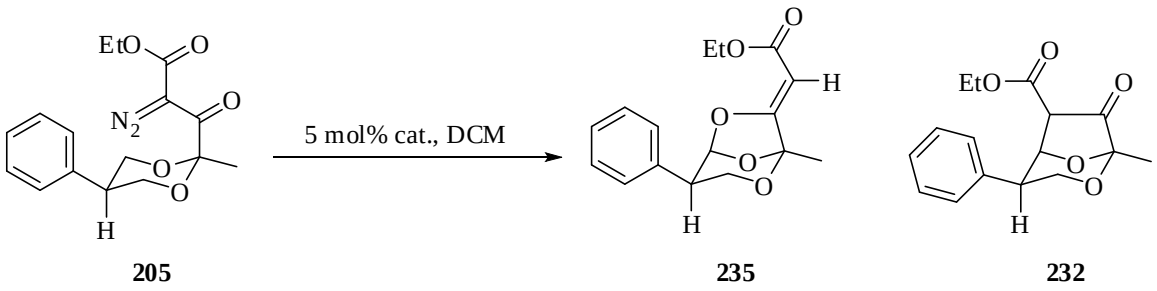
The generally accepted mechanistic rationale for the formation of **235** is shown below (Scheme 4.7).



Scheme 4.7

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.



205 **235** **232**

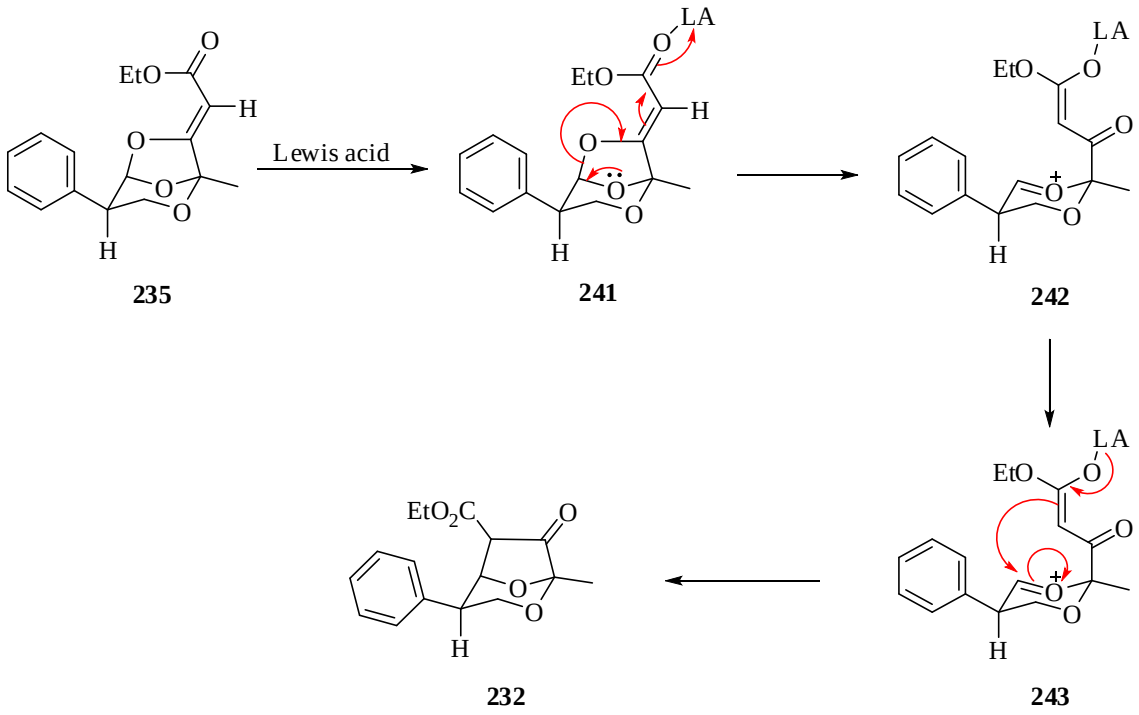
Scheme 4.8

Entry	Catalyst	Temp.	Outcome
1	$Pd(OAc)_2$	rt	**205**
2	$Pd(acac)_2$	rt	**205**
3	$Cu(acac)_2$	rt	**205**
4	$Cu(hfacac)_2$	rt	**205**
5	$Cu(hfacac)_2$	35 ^oC	**205** + decomposition
6	$Rh_2(DOSP)_4$	rt	**235**
7	$Rh_2(MEPY)_4$	rt	**205**
8	$Rh_2(tfa)_4$	rt	**205**

Table 4.3

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).



235 **241** **242** **243** **232**

Scheme 4.9

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.

Entry	Catalyst	Cat. loading (mol%)	Temp. (^oC)	Solvent	Rate of addition of SM	Yield (%)
1	$Rh_2(pfb)_4$	2	rt	DCM	Over 24h	20
2	$Rh_2(pfb)_4$	2	Reflux	DCM	Over 24h	9
3	$Rh_2(pfb)_4$	2	rt	DCM	Instant	27
4	$Rh_2(pfb)_4$	5	rt	DCM	Over 24h	30
5	$Rh_2(pfb)_4$	5	rt	DCM	Instant	40

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 $BF_3.OEt_2$, $TiCl_4$ and $Sc(OTf)_3$ were screened. In a typical experiment, a solution of the trioxabicycle **235** (1 eq) in DCM was cooled to -78 ^oC 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.

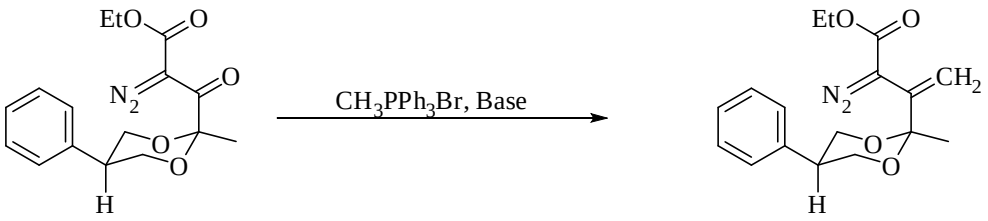
Following work-up and purification, the $BF_3.OEt_2$ and $Sc(OTf)_3$ mediated reactions gave only starting material **235**. However the ^1H NMR spectrum of the crude $TiCl_4$ mediated reaction was more promising as it showed complete consumption of starting material but analysis was difficult owed to 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).



205 **244**

Scheme 4.10

The first attempt was to evaluate the Wittig reaction in the methylenation step. Thus, a solution of methyltriphenylphosphonium bromide (CH_3PPh_3Br) in THF was cooled to 0 ^oC 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.

Entry	Reaction conditions	Result
1	LDA, CH_3PPh_3Br, THF, 0 ^oC	SM recovered
2	*n*-BuLi, CH_3PPh_3Br, THF, 0 ^oC	Complex mixture
3	NaH, CH_3PPh_3Br, DMSO, rt	SM recovered

SM = Starting material

Table 4.5

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.

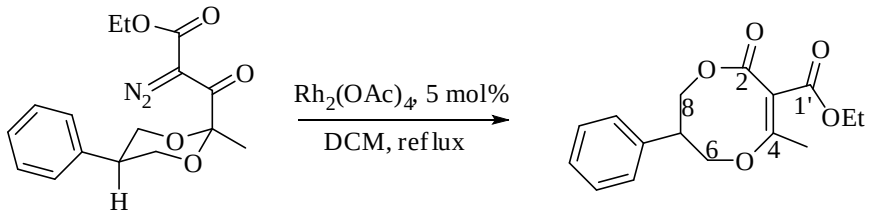
Since efforts to obtain product **244** by preforming the Wittig reagent were unsuccessful, it was decided to attempt the methylenation reaction using the commercially available Tebbe's reagent.

Thus, a solution of Tebbe's reagent in toluene was added to a solution of diazodiketone acetal **205** in THF at 0 ^{o}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 sterics 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).



205 **248**, 3%

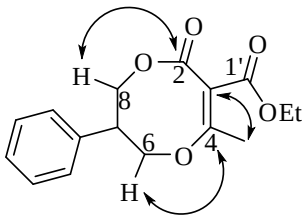
Scheme 4.11

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.

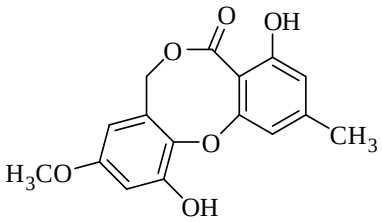
Stronger evidence for such a proposal came from careful analysis of correlations in the various 2D NMR experiments undertaken. Notably, a significant NOESY correlation was observed between 1'-OCH_2CH_3 and the 4-CH_3 signal, consistent with a *cis* alkene and thereby confirming the cyclic nature of the 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).



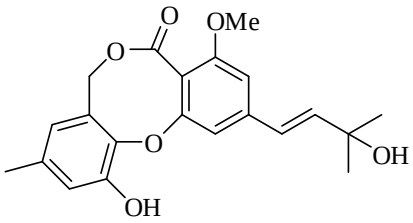
248

Figure 4.3

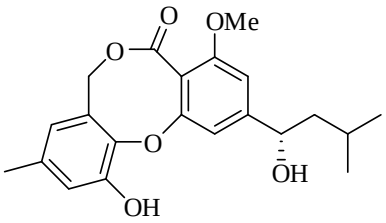
A search of various databases revealed that this structure was novel with the closest analogue being found in the fungal natural products barceloneic lactone **245**, isolated from a fungus of the genus *Phoma* in a screen for protein-farnesyl tranferase (PFT-ase) inhibitors,[9] and penicillide **246** and dehydropeniccilide **247**, found in the ascomycetous fungus *Talaromyces derxii*,[10] Figure 4.4.



245



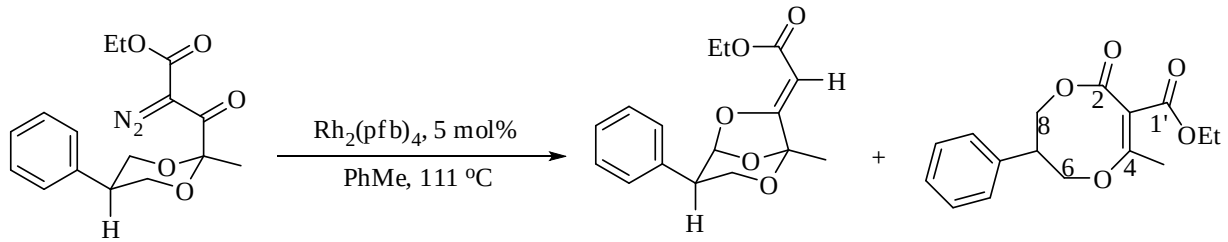
246



247

Figure 4.4

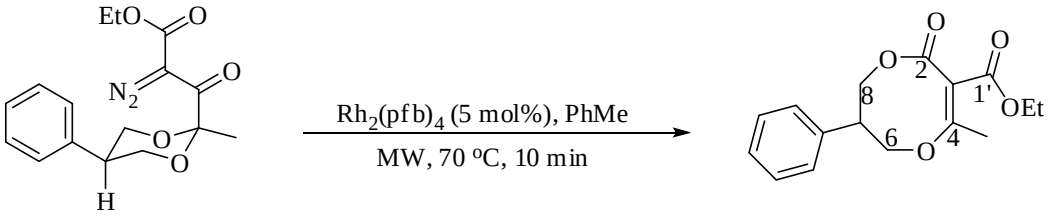
Since synthetic approaches to these compounds have not been reported, it was considered that a brief examination of the scope and mechanism of this rearrangement was merited. Further attempts to perform the reaction at a higher temperature and for a shorter period of time necessitated the search for 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 $Rh_2(pfb)_4$ in toluene afforded a mixture of **235** (45%) and **248** (22%) (Scheme 4.12).



205 **235**, 45% **248**, 22%

Scheme 4.12

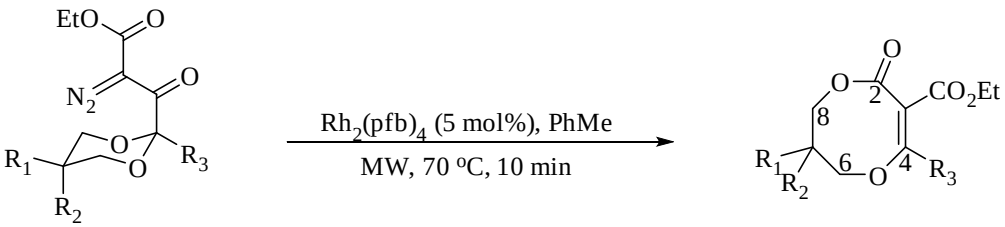
The formation of **235** (as a result of the electron withdrawing ligands on $Rh_2(pfb)_4$ catalyst) represented a background reaction occurring prior to reaching the critical reaction temperature for the rearrangement. This was confirmed by repeating this process in a microwave reactor (Scheme 4.13).



205 **248**, 40%

Scheme 4.13

Under these conditions, a cleaner reaction with no evidence for the formation of **235** could be achieved at much lower reaction temperatures (70 ^{o}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).



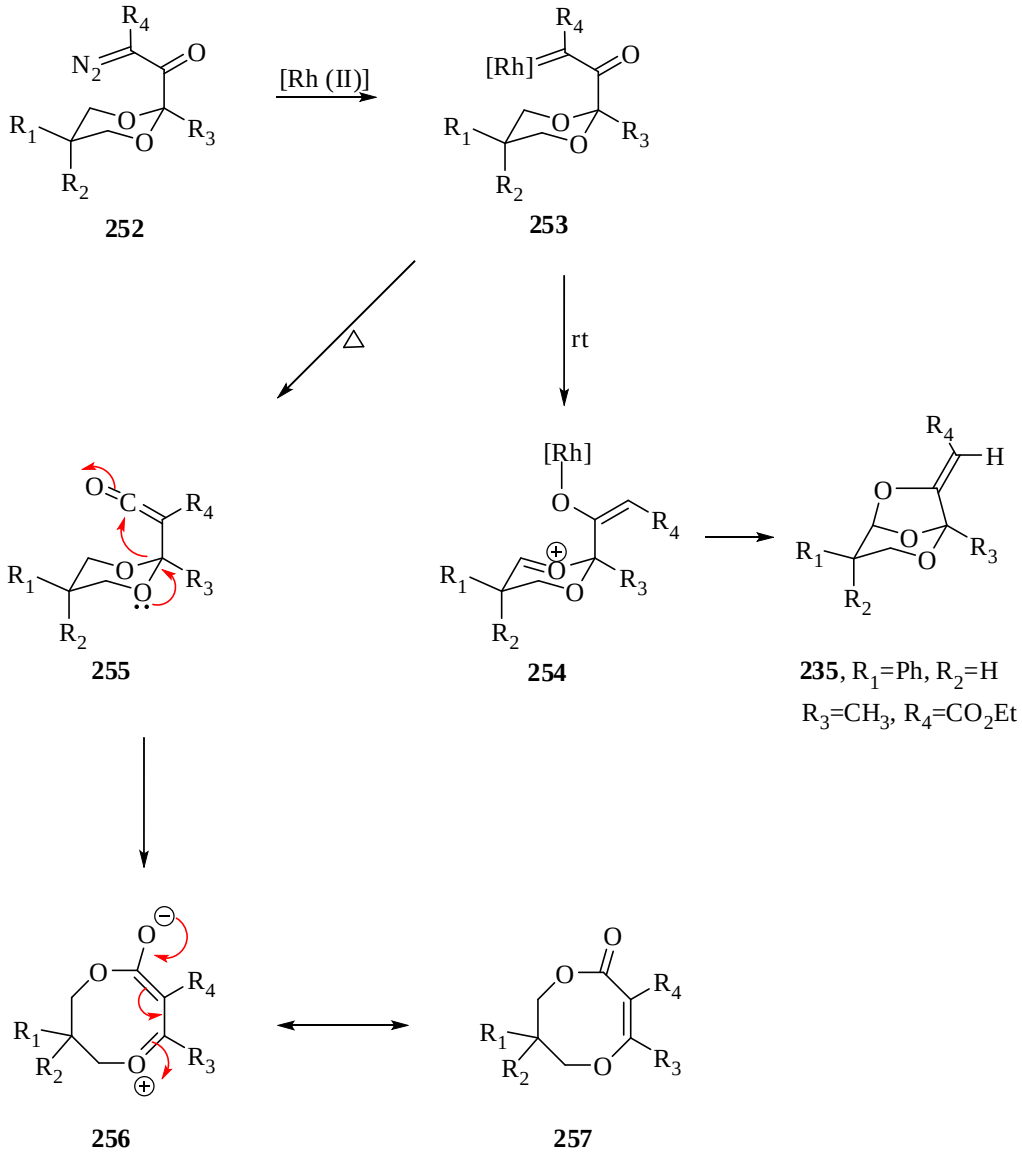
205, 206, 208, 209 **248-251**

Scheme 4.14

Entry	Substituents	Yield (%)	IR (cm^{-1})	^{13}C and ^{1}H NMR (ppm)
1	R_1=Ph, R_2=H, R_3=CH_3	40	1606 (C=C)	**248** : 168.5 (C-4), 168.1 (C-2), 2.29 (4-CH_3)
2	R_1=Ph, R_2=H, R_3=Ph	28	1606 (C=C)	**249** : 168.3 (C-4), 168.1 (C-2)
3	R_1=*p*-$NO_2C_6H_4$, R_2=H, R_3=CH_3	47	1608 (C=C)	**250** : 168.7 (C-4), 167.9 (C-2), 2.43 (4-CH_3)
4	R_1=CH_3, R_2=NO_2, R_3=CH_3	30	1607 (C=C)	**251** : 167.4 (C-4), 165.9 (C-2), 2.21 (4-CH_3)

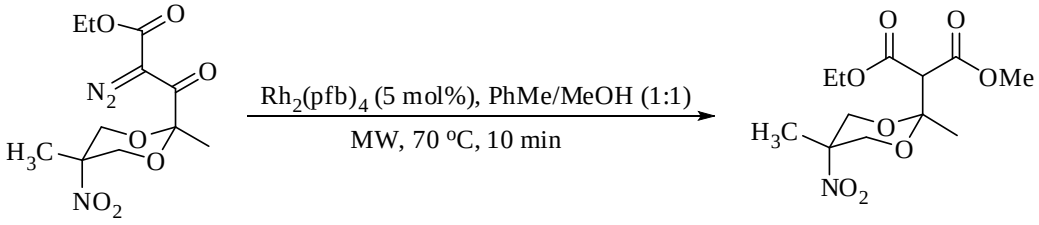
Table 4.6

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 occurs leading to the ketene **255**.[11] In the absence of the stabilising group (alkene or ester unit) this is unstable and undergoes decomposition at these high temperatures, *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**.



Scheme 4.15

In support of such a hypothesis, heating of diazodiketone acetal **209** with $Rh_2(pfb)_4$ 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).



209 **258**, 18%

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.

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.

4.4 References

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11 . For a similar example of Wolff rearrangement occurring at elevated temperatures see: Boukraa, M.; Dayoub, W.; Doutheau, A. *Lett. Org. Chem.* **2006**, 3, 204.

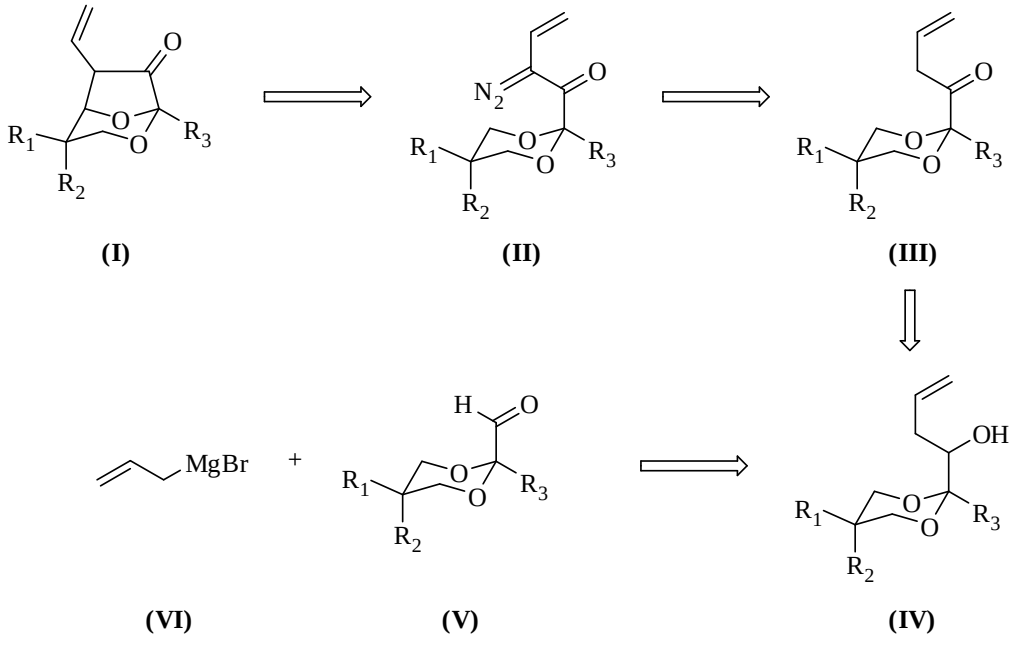
5.1 Introduction

As efforts, discussed in the preceeding 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).



Scheme 5.1

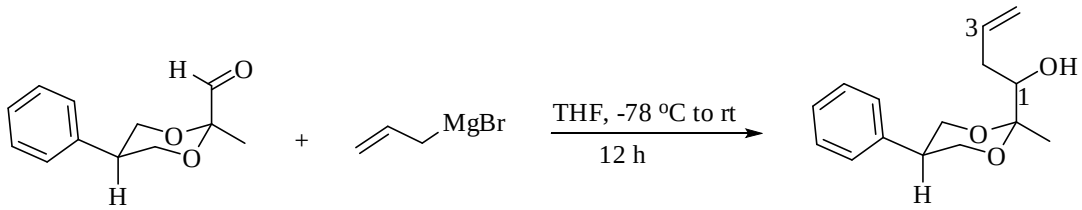
The synthetic plan involved four key steps. It was proposed that the bicyclic vinylketone acetal **(I)** would be obtained from a Rh (II) catalysed C-H insertion reaction from the

vinyldiazoketone 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 ^{o}C (Scheme 5.1). The product was isolated in excellent yield (94%) as a racemic mixture at carbon 1.



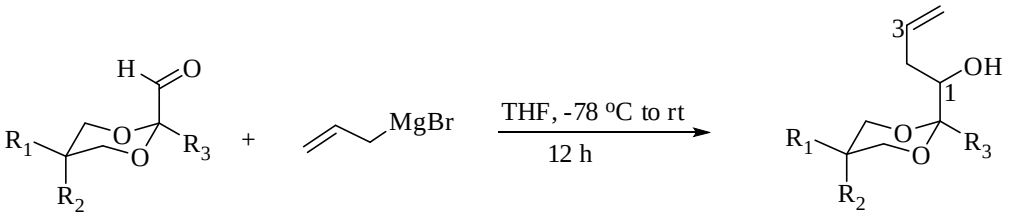
176 **259**, 94%

Scheme 5.1

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

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).



178-180, 182, 184 **259-263**

Scheme 5.2

Entry	Substituent	Yield (%)	IR (cm^{-1})	^{1}H and ^{13}C NMR (ppm)
1	R_1=Ph, R_2=H, R_3=CH_3	94	3390 (OH) 1641 (C=C)	**259** : 4.12 (1-H), 70.8 (C-1)
2	R_1=H, R_2=Ph, R_3=CH_3	92	3437 (OH) 1641 (C=C)	**260** : 3.60 (1-H), 76.5 (C-1)
3	R_1=Ph, R_2=H, R_3=Ph	72	3521 (OH) 1641 (C=C)	**261** : 3.72 (1-H), 77.2 (C-1)
4	R_1=H, R_2=Ph, R_3=Ph	65	3503 (OH) 1640 (C=C)	**262** : 3.69 (1-H), 77.3 (C-1)
5	R_1=Bn, R_2=H, R_3=Ph	81	3560 (OH) 1641 (C=C)	**263** : 3.68 (1-H), 77.5 (C-1)
6	R_1=*p*-NO_2Ph, R_2=H, R_3=CH_3	nd	-	-
7	R_1=CH_3, R_2=NO_2, R_3=CH_3	nd	-	-

nd = not determined

Table 5.1

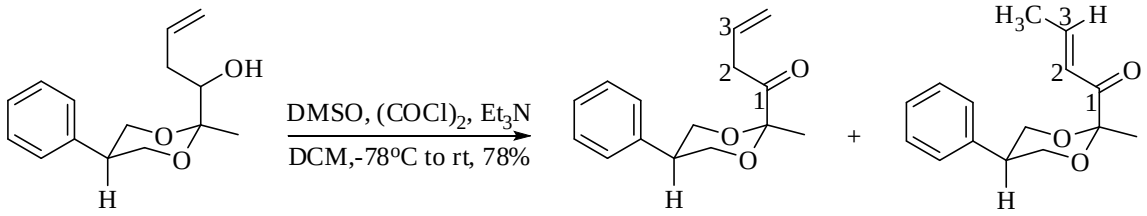
In most of the cases studied, the allylalcohol acetals **259-263** were obtained in good yields from the corresponding aldehydes with the exception of aldehydes **182**, **184** bearing electron

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).



259 **264** **268**

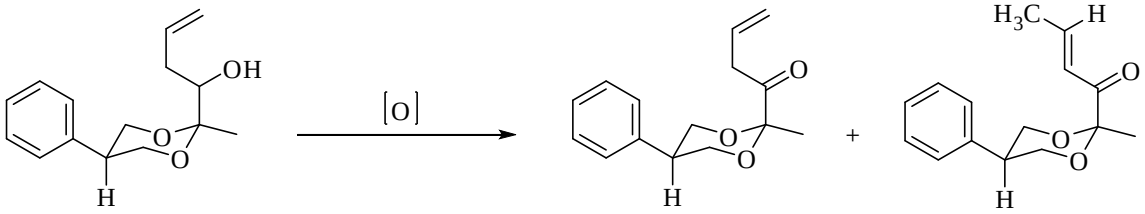
1:10

Scheme 5.3

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).



259 **264** **268**

Scheme 5.4

Entry	Reaction condition	Results
1	IBX, DMSO, rt, 4 h	SM + complex mixture
2	NMO, TPAP, DCM, rt, 24 h	SM recovered
3	PDC, 4Å mol. sieves, DCM, rt, 4 h	76%, 11:1 (**264**:**268**)

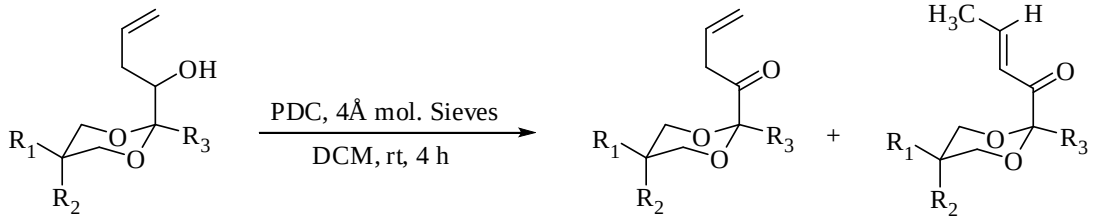
SM = starting material

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 allyalcohol 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).



259-261, 263 **264-267** **268-271**

Scheme 5.5

Entry	Substituents	Ratio	Yield (%)	IR (cm^{-1})	^{13}C and ^{1}H NMR (ppm)
1	R_1=Ph, R_2=H R_3=CH_3	11:1	76	1728 (CO)	**264** : 208.1 (CO), 3.41 (2-H_2)
2	R_1=H, R_2=Ph R_3=CH_3	12:1	69	1729 (CO)	**265** : 206.0 (CO), 3.49 (2-H_2)
3	R_1=Ph, R_2=H R_3=Ph	13:1	68	1730 (CO)	**266** : 205.6 (CO), 3.29 (2-H_2)
4	R_1=Bn, R_2=H R_3=Ph	13:1	71	1738 (CO)	**267** : 204.5 (CO), 3.33 (2-H_2)

Table 5.3

In all the examined compounds, mixtures of isomeric ketone acetals were obtained and the nature of the substituents (R_1 and R_3) 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

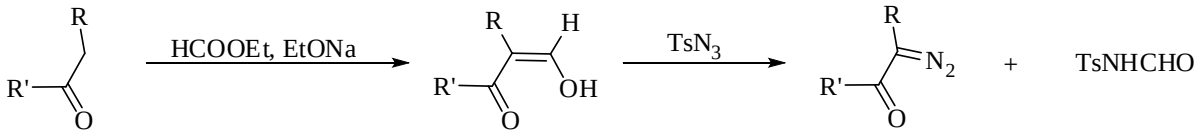
5.2.3.1.1 Introduction

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 α-methylene proton of an acceptor (usually a carbonyl group).

Two main classes of acceptors based on the acidity of the α-methylene proton are known;

- Simple ketone enolates

In this case, the diazo transfer process is not very efficient and often gives poor yields.[1] However, diazo transfer can be achieved by an indirect deformylative diazo-transfer (Scheme 5.6).[2]

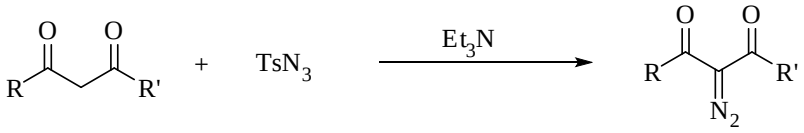


272 R, R'=alkyl **273** **274**

Scheme 5.6

- β-Keto esters, β-diketones, malonic esters

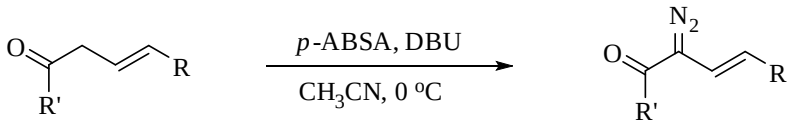
In these cases, the enhanced reactivity of the α-methylene position permits diazo transfer and the substrates are readily converted into 2-diazo-1,3-dicarbonyl compounds by the standard Regitz procedure (Scheme 5.7).[3]



275 R, R'=aryl, alkyl **276**

Scheme 5.7

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

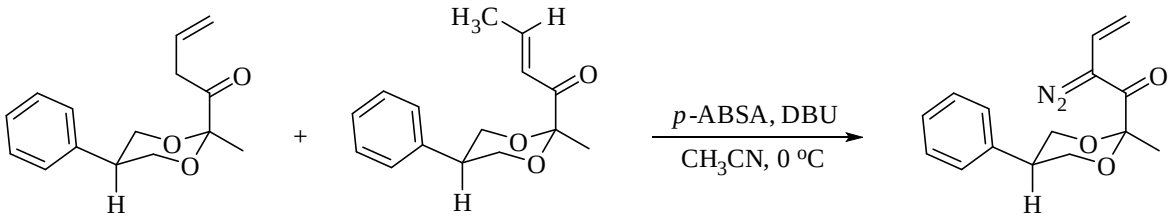


277 R, R'=aryl, alkyl **278**, 84-86%

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_3CN at 0 ^oC.



Scheme 5.9

Initial attempts using *p*-ABSA (1 eq) and DBU (1.5 eq) led to the formation of the desired vinyldiazoketone 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_3N) for the *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 vinyldiazoketone 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 vinyldiazoketone 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_3N) 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 ^oC and subsequently warmed-up to room temperature, higher ratios of product **279** were obtained (entry 8, 10-12). Gratifingly, 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).

Entry	Diazo transfer reagent	Base	Temp. (^oC)	Yield (%)	Ratio[a] **279**:**268**
1	*p*-ABSA (1 eq)	DBU (1.5 eq)	0	43	5:1
2	*p*-ABSA (1.5 eq)	DBU (1eq)	0	nd	5:1
3	MsN_3[5] (1.5 eq)	DBU (1eq)	0	nd	1:3
4	*p*-ABSA (1.75 eq)	DBU (1.25 eq)	0	nd	2.5:1
5	MsN_3 (1.75 eq)	DBU (1.25 eq)	0	nd	1:3.5
6	*p*-ABSA (1.5 eq)	LiHMDS (1 eq)	0	nd	**268** + decomp
7	*p*-ABSA (1.5 eq)	Et_3N (1 eq)	0	Quantitative	0:100
8	*p*-ABSA (1 eq)	DBU (1eq)	rt	30	15:1
9	*p*-ABSA (1.5 eq)	DBU (1 eq)	rt	40	ND
10	*p*-ABSA (5 eq)	DBU (1.25 eq)	rt	43	25:1
11	*p*-ABSA (1.5 eq)	DBU (1.25 eq)	0 to rt	85	33:1
12	*p*-ABSA (2 eq)	DBU (1.25 eq)	0 to rt	86	38:1
13	*p*-ABSA (2 eq)	DBU (3.5 eq)	0 to rt	90	100:0
14	*p*-ABSA (1 eq)	DBU (4 eq)	0 to rt	90	100:0
15	*p*-ABSA (1 eq)	DBU (4 eq)	rt	90	100:0

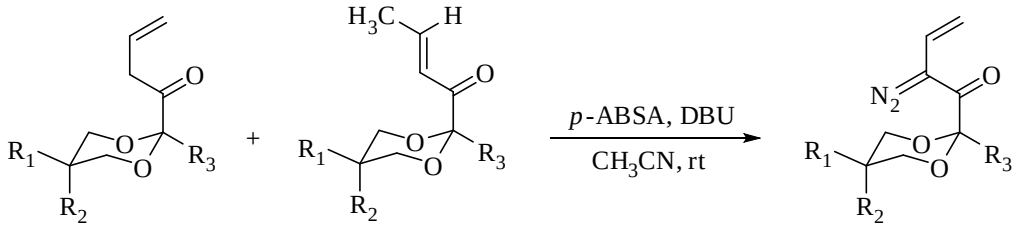
[a] = ratios are from ^1H NMR integration, nd = not determined, decomp = decomposition

Table 5.4

Evidence for the formation of the vinyldiazoketone acetal **279** was provided by the IR, ^1H 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 ^1H NMR spectrum which showed the disappearance of the signal at 3.41 ppm confirmed the diazo transfer exclusively into the kinetically favoured α-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 vinyldiazoketone acetals **279-282** was as discussed above and is summarised in the table below (Scheme 5.10, Table 5.5).



264-271 **279-282)**

Scheme 5.10

Entry	Substituents	Yield (%)	IR (cm^{-1})	^{13}C (ppm)
1	R_1=Ph, R_2=H R_3=CH_3	90	2082 (CN_2)	**279** : 66.7 (CN_2)
2	R_1=H, R_2=Ph R_3=CH_3	72	2088 (CN_2)	**280** : 68.6 (CN_2)
3	R_1=Ph, R_2=H R_3=Ph	69	2081 (CN_2)	**281** : 69.1 (CN_2)
4	R_1=Bn, R_2=H R_3=Ph	71	2083 (CN_2)	**282** : 77.2 (CN_2)

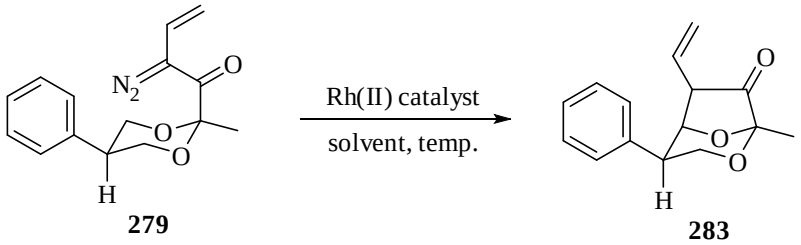
Table 5.5

In all of the cases studied, the vinyldiazoketone 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 vinyldiazoketone 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 vinyldiazoketone 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).



279 **283**

Scheme 5.11

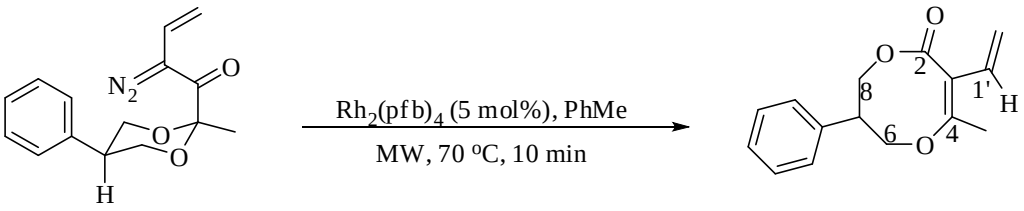
Disappointingly, initial attempts which involved the use of 1 mol% $Rh_2(OAc)_4$ at room temperature did not afford the desired bicyclic vinyl ketone acetal **283**. Further attempts to increase the catalyst loading gradually to 10 mol% had no effect on the outcome of the reaction. (Table 5.6, entry 2-4).

Entry	Catalyst	Catalyst loading	Solvent	Temp. (^oC)	Results
1	$Rh_2(OAc)_4$	1 mol %	DCM	Rt	SM recovered
2	$Rh_2(OAc)_4$	2 mol %	DCM	Rt	SM recovered
3	$Rh_2(OAc)_4$	5 mol %	DCM	Rt	SM recovered
4	$Rh_2(OAc)_4$	10 mol %	DCM	Rt	SM recovered

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 vinyldiazoketone **279** (Scheme 5.12).

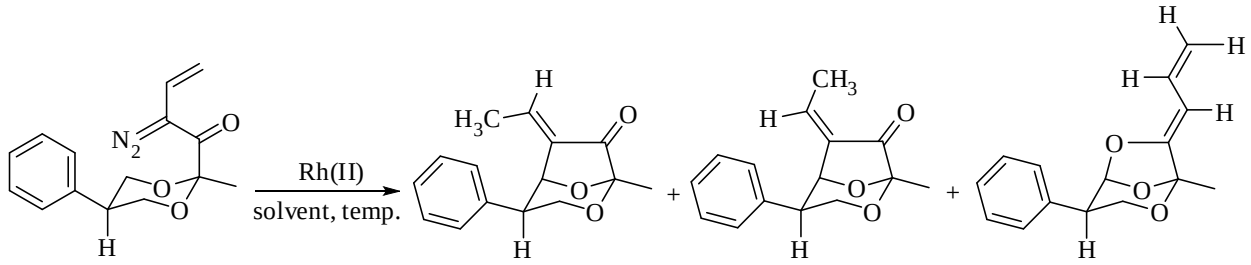


279 **284**, 45%

Scheme 5.12

Following the reaction of **279** with 5 mol% $Rh_2(pfb)_4$ under microwave conditions, the barceloneic lactone derivative **284** was isolated in 45% yield. Evidence for the formation of **284** was provided by the IR, ^1H 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 ^1H 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.

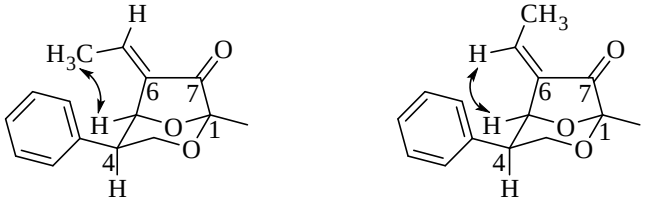
The formation of **284** confirmed the accessibility of the carbenoid from **279** under the influence of a rhodium (II) catalyst. Intrigued by this, it was decided to explore this catalyst system further. Thus, a solution of **279** was slowly added to $Rh_2(pfb)_4$ catalyst in DCM at room temperature. 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.



279 (*E*) **285** (*Z*) **286** **287**

Scheme 5.13

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-CHC*H*$_3$ protons while in **286**, there was a significant correlation between the 5-*H* and the 6-C*H*CH$_3$ protons (Figure 5.1).



(*E*) **285** (*Z*) **286**

Figure 5.1

Pleased with this outcome, efforts were then directed towards the exclusive formation of the C-H insertion products by a careful screening of Rh (II) catalyst systems, the results obtained are summarised below (Table 5.7).

Irrespective of the solvent and Rh (II) catalyst system, conducting the reaction under forcing conditions surpresses 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]-(2*S*)-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.[6] The specific rotation, $[\alpha]^{28.1}_D$ for the enriched mixture was +24.0^o obtained at a concentration of 0.8 g/ml in $CDCl_3$.

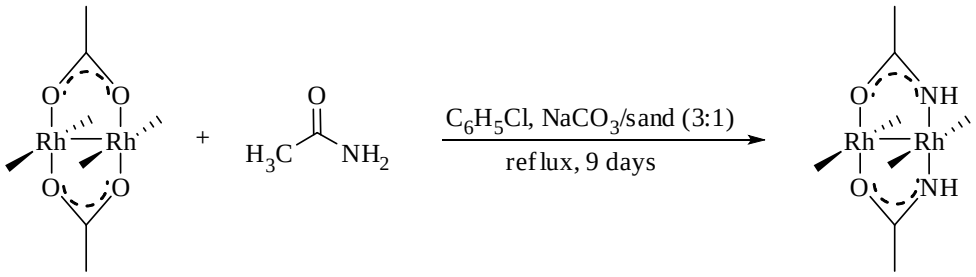
Entry	Solvent	Temp (^{o}C)	Catalyst	Catalyst Loading (mol%)	Yield **287** (%)	Yield **285+286** (%)	Ratio[d] **285:286**	Yield **284** (%)	Method
1	DCM	reflux	$Rh_2(OAc)_4$	1	0	30	ND	38	b[e]
2	DCM	reflux	$Rh_2(OAc)_4$	5	0	7	5:1	25	a
3	C_6H_6	reflux	$Rh_2(OAc)_4$	1	0	ND	1:1	4	a
4	C_6H_6	reflux	$Rh_2(OAc)_4$	5	0	trace	ND	45	b[f]
5	C_6H_6	reflux	$Rh_2(OAc)_4$	5	0	-[c]	-	16	b[g]
6	DCM	reflux	$Rh_2(pfb)_4$	5	0	trace	ND	14	a
7	C_6H_6	reflux	$Rh_2(OAc)_4$	5	0	10	3:1	20	a
8	C_6H_6	rt	$Rh_2(pfb)_4$	5	5	10	ND	0	a[n]
9	C_6H_6	rt	$Rh_2(pfb)_4$	5	10	40	3:1	0	b[g]
10	DCM	rt	$Rh_2(OAc)_4$	5	0	0	-	0	b[g]
11	DCM	rt	$Rh_2(pfb)_4$	5	10	30	3:1	0	b[g]
12	C_7H_8	rt	$Rh_2(pfb)_4$	5	10	33	2:1	0	b[g]
13	C_7H_8	0	$Rh_2(pfb)_4$	5	9	30	2:1	0	b[g]
14	C_7H_8	rt	$Rh_2(pfb)_4$	5	11	22	ND	0	b[g]
15	C_7H_8	rt	Rh_2(*S*-TBSP)$_4$	5	0	30	96:4	0	b[g]

(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

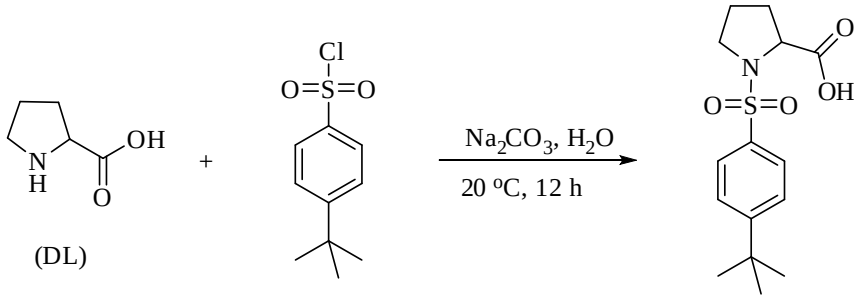
Pleased with this result, attention turned to explore this catalyst system further. However, due to its high commercial cost (£66.40 per 100mg, Aldrich), and the intention to gain insight of potential asymmetry induction, it was decided to investigate the achiral (racemic) catalyst system (±)-$Rh_2(TBSP)_4$. 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 $Rh_2(acam)_4$ **290** by exchanging the acetate ligands in **288** for acetamides **289** (Scheme 5.14).[7]



288 **289** **290,** 85%

Scheme 5.14

Based on this precedent, preparation of the (±)-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).



(DL)

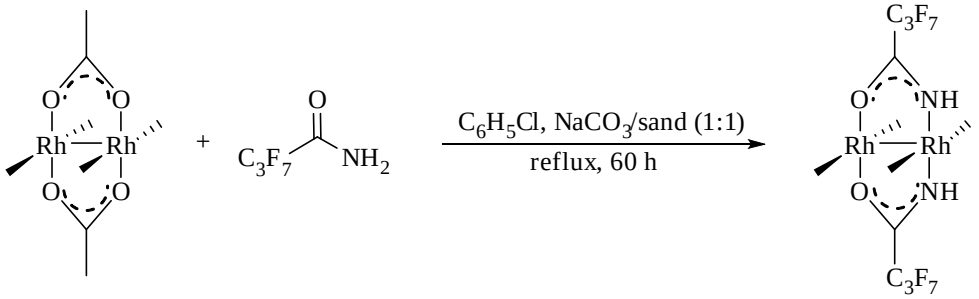
291 **292** **293,** 70%

Scheme 5.15

Thus, 4-*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}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 $Rh_2(OAc)_4$. Thus, a mixture of **293** and $Rh_2(OAc)_4$ in chlorobenzene was refluxed in a Soxhlet extraction apparatus for six days. Following the removal of chlorobenzene by distillation, a mixture containing mainly residual $Rh_2(OAc)_4$, 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 $Rh_2(pfb)_4$ 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 $Rh_2(hfb)_4$ (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 $Rh_2(hfb)_4$ following the same high temperature ligand exchange reaction between $Rh_2(OAc)_4$ **288** and the commercially available heptafluorobutyramide **294** was conducted (Scheme 5.16).

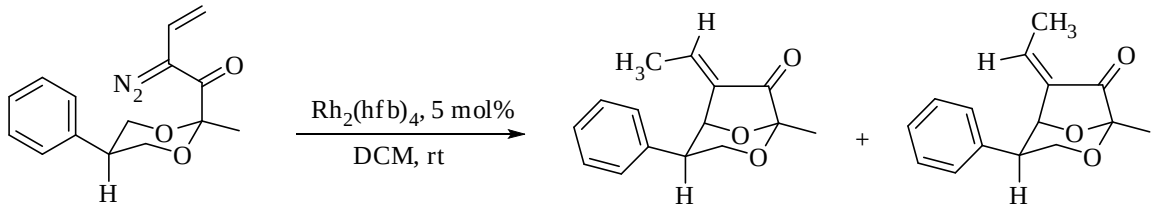


288 **294** **295**, 85%

Scheme 5.16

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).



279 (*E*) **285** 3:1 (*Z*) **286**

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).

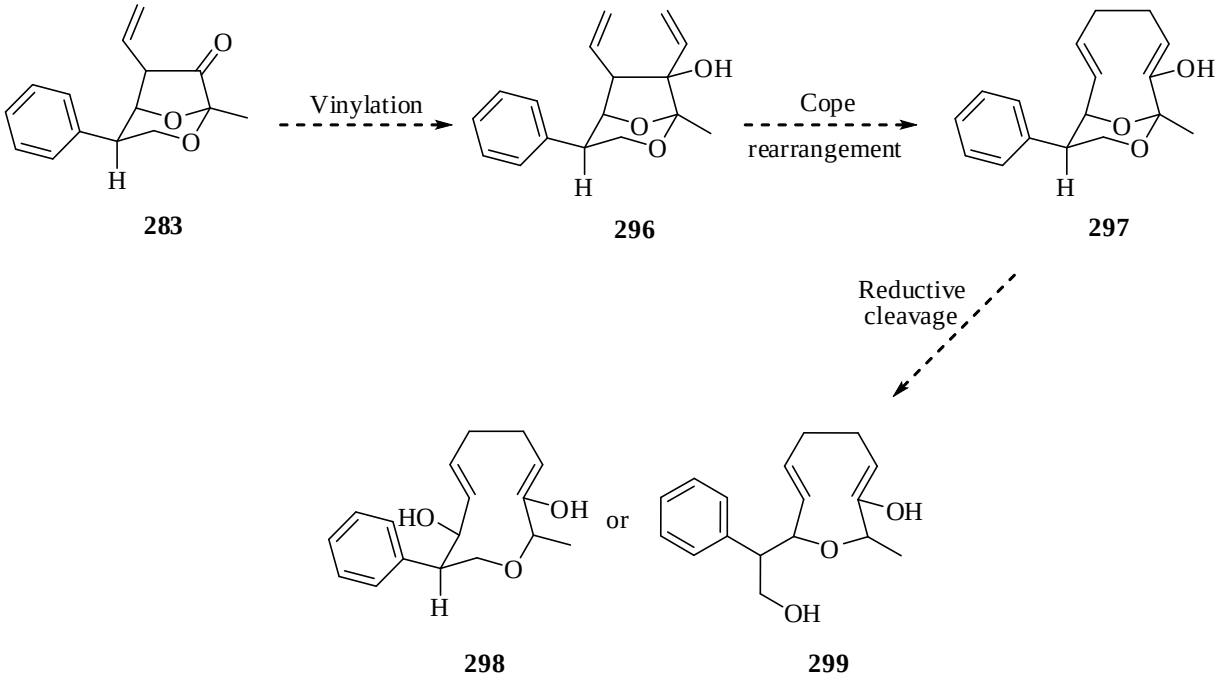
Entry	Solvent	Yield (%)	Ratio (*E* **285**:*Z* **286**)
1	DCM	15	3:1
2	C_7H_8	30	3:1
3	C_6H_6	40	3:1

Table 5.8

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.

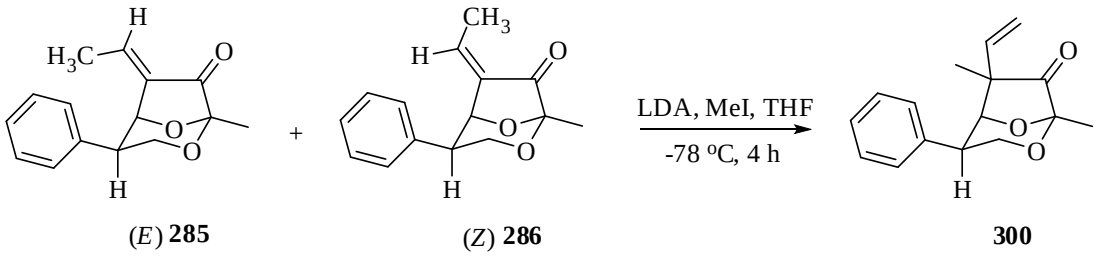
5.2.4.2 Attempted deconjugation of bicyclic ketones

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).



Scheme 5.18

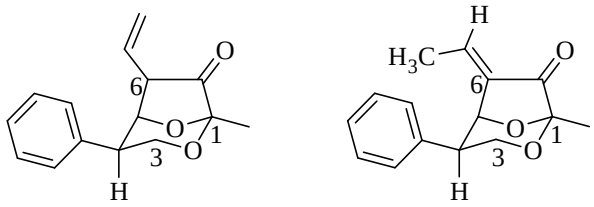
The first step in this sequence involved a 1,2 addition to the ketone of **283** which was proposed to suffer from a competing 1,4 addition in enone mixtures **285** and **286**. Therefore, it was decided to isomerise the enone mixtures to the vinyl ketone **283** or its analogues. Initial attempt involved the use of lithium diisopropylamide (LDA) and methyl iodide at low temperature (Scheme 5.19).



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

conducting these trials, the ^{1}H NMR spectrum of the crude reaction mixture involving the $Rh_2(hfb)_4$ catalysed decomposition of vinyldiazoketone 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-C*H*CH_2, 6-CH_2C*H*$_2$ and 6-CHC*H*$_2$ respectively in **283**. Moreover, there was no evidence for the proton at 6.28 ppm attributed to 6-C*H*CH_3 in the ^{1}H NMR spectrum of the enone compound **285** (Figure 5.2).



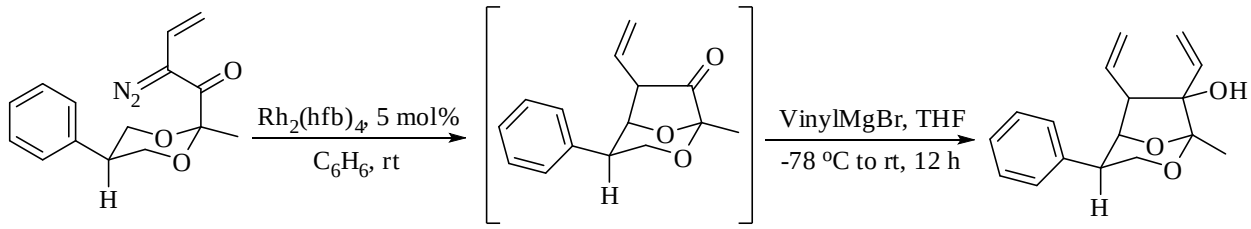
283 (*E*) **285**

Figure 5.2

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 bicyclicvinyl 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).



279 **283** **296**

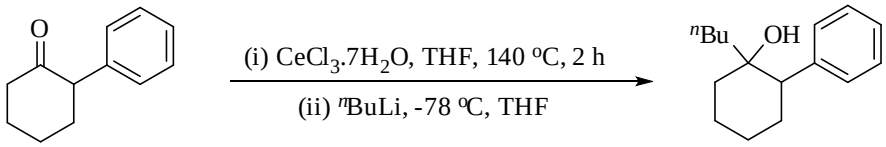
Scheme 5.20

Thus, to a solution of vinylmagnesium bromide in THF at -78 ^{o}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 ^{o}C and then at 90 ^{o}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 ^{o}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 ^{o}C.[8] 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 α-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.[9] 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 α,β-unsaturated substrates which present problems with the addition of simple organometallics are almost completely surpressed (Scheme 5.21).



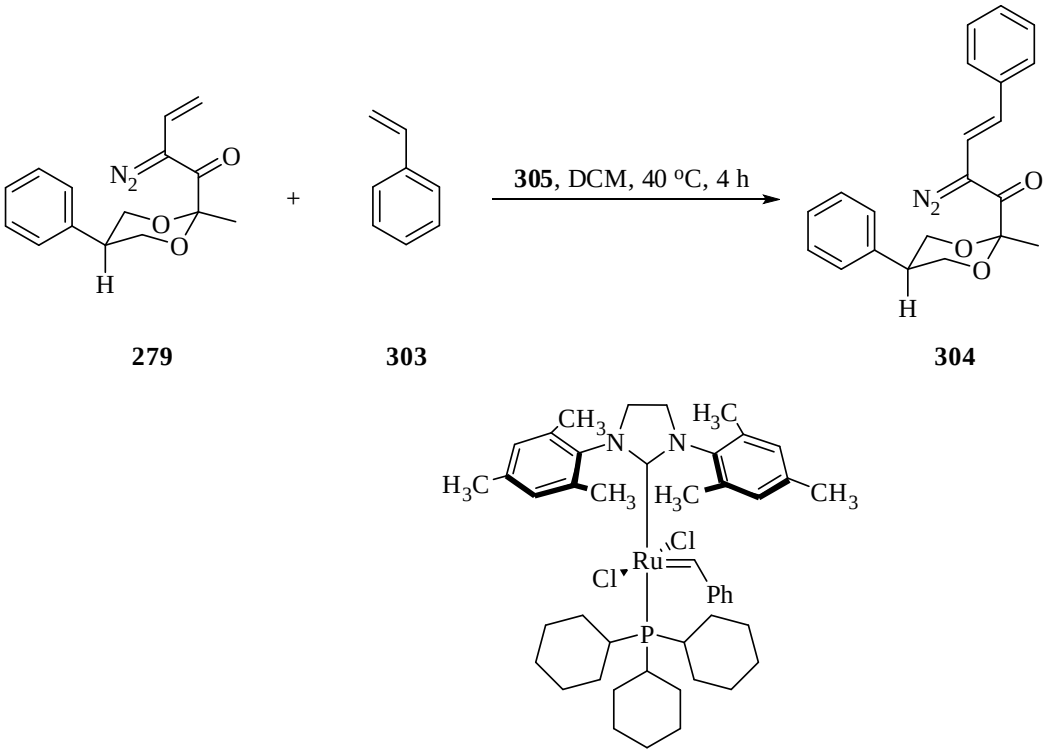
301 **302**, 86%
ds=20:1

Scheme 5.21

Based on this precedent, it was decided to explore this procedure in the conversion of **283** to **296**. Thus, a sonicated $CeCl_3.7H_2O$ solution in THF was added to a stirred solution of vinyllithium (prepared in the same manner as before) at -78 ^oC. 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 α-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).

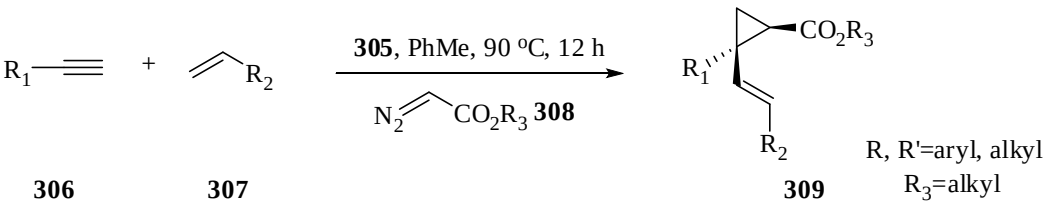


279 **303** **304**

305 = 2nd gen. Grubbs' catalyst

Scheme 5.22

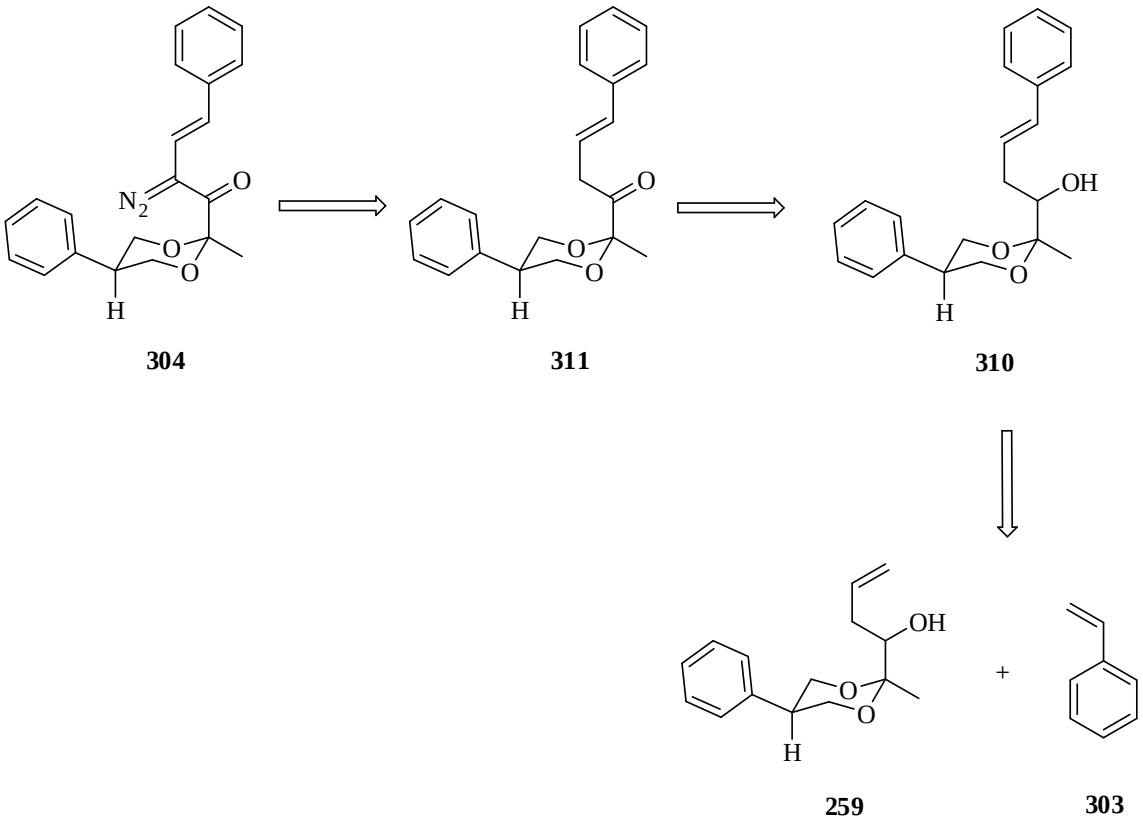
Thus, to a homogenous mixture of **279** and styrene **303** in DCM at 40 °C was added Grubbs' catalyst. Disappointingly, a complex mixture of products which proved difficult to identify was obtained together with recovered starting material **279** (10%). Curiously, not even the reduced form of the 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).[10]



306 **307** **309**

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.

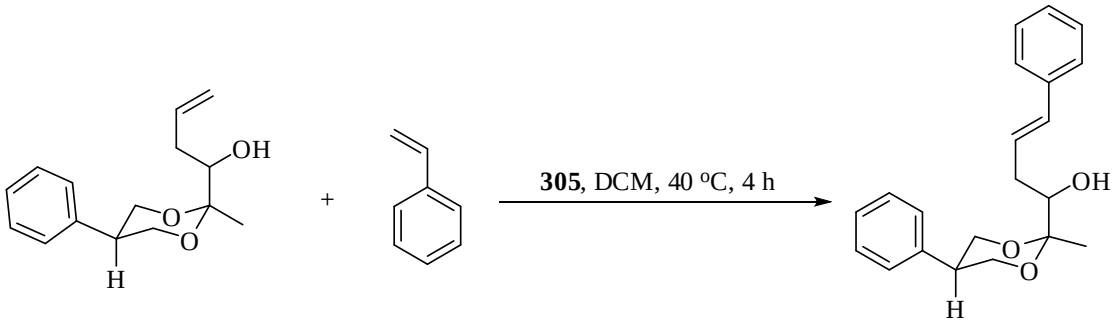


304 **311** **310** **259** **303**

Scheme 5.24

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).



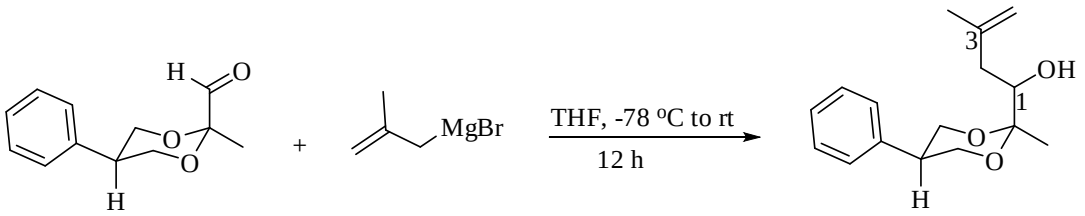
259 **303** **310**, 85%

Scheme 5.25

Thus, Grubbs' catalyst **305** was added to a mixture of allylalcohol acetal **259** and styrene **303** in DCM at 40 ^{o}C. Following work-up and purification using the Diver protocol,[11] 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).

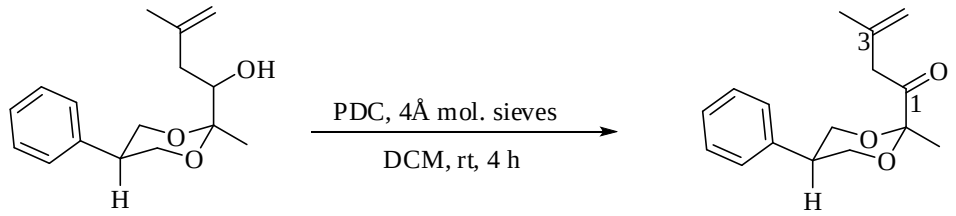


176 **312** **313**, 61%

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).

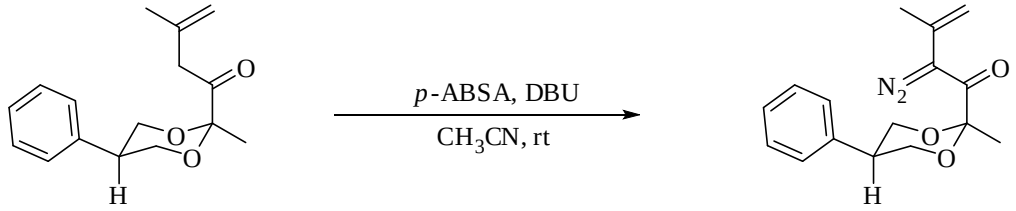


313 **314**, 66%

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).

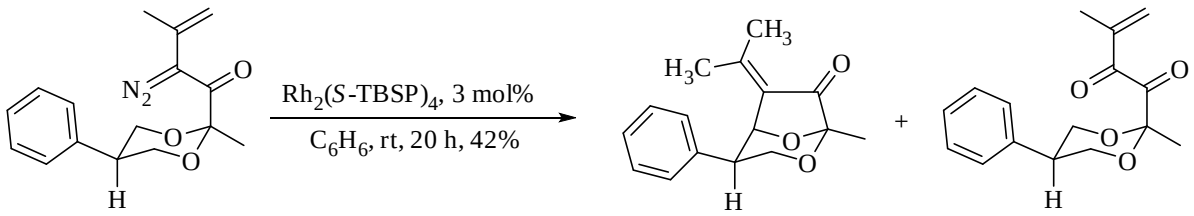


314 **315**, 57%

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 Rh_2(*S*-TBSP)$_4$ as the catalyst (Scheme 5.29).



315 **316** **317**

(2:1)

Scheme 5.29

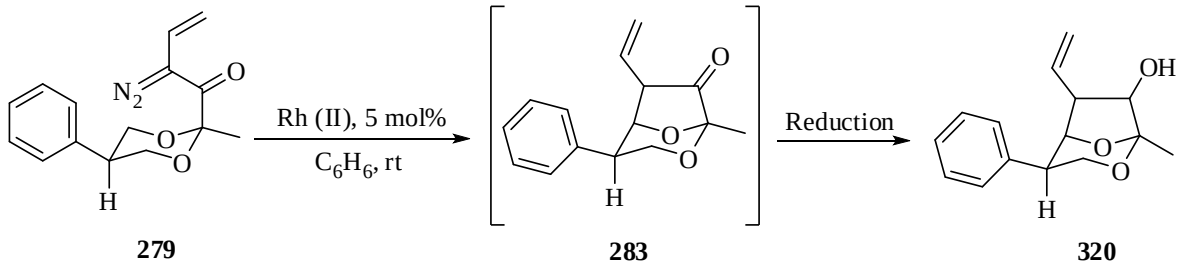
Thus, a solution of diazoketone acetal **315** was slowly added to a dilute solution of the catalyst at room temperature. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated the presence of two acetal products **316** and **317** in ratio 2:1, which subsequently proved inseparable 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 vinyldiazoketone **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

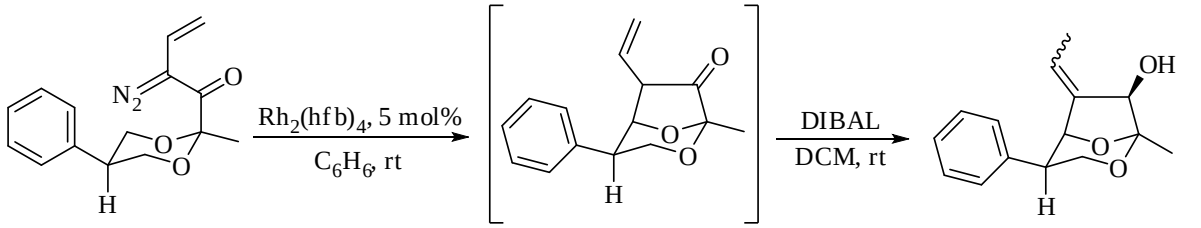
Having tried to prevent the isomerisation process unsuccessfully, it was decided to explore the possibility of selectively reducing the carbonyl functional group in **283** without affecting the alkene bond to give **320** (Scheme 5.30).



279 **283** **320**

Scheme 5.30

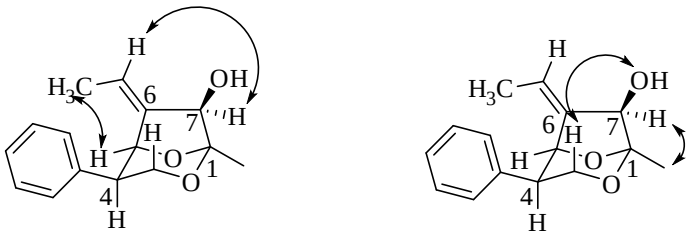
Initial attempts involved investigating the use of diisobutylaluminiumhydride (DIBAL) as a suitable reagent for the reduction. Thus, following the same procedure as earlier described for the Rh (II) catalysed decomposition of **279**, the resulting crude reaction mixture containing **283** was added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



279 **283** **318, 319** (42%)
E/*Z*=1:1

Scheme 5.31

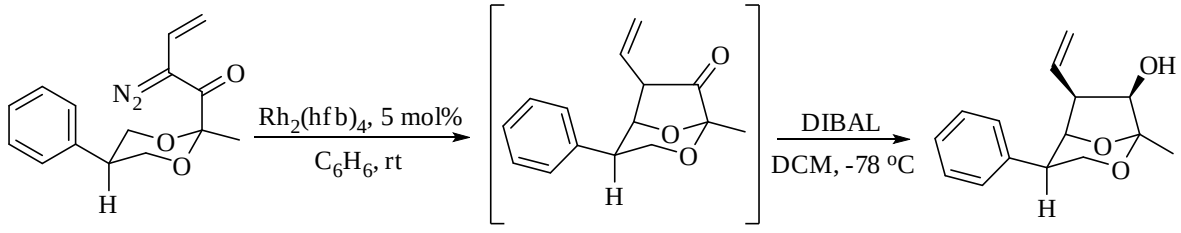
Following work-up and purification, an isomeric mixture of bicyclic enols **318** and **319** were obtained in overall moderate yield (40%) in the ratio 1:1. As before, evidence for the formation of the bicyclic enols obtained from analytical and spectroscopic data was satisfactory. The stereochemistry 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-CHC*H*$_3$ and 5-*H*, 6-C*H*CH$_3$ 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-C*H*$_3$ and 7-*H* protons (Figure 5.3, B) and was in agreement with previous observations involving a similar study by Garbi.[13]



319, A **319, B**

Figure 5.3

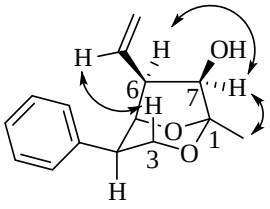
The formation of the enols was preceeded by isomerisation to the conjugated enone followed by a 1,2 reduction of the ketone to an alcohol. The isomerisation was thought to be a result of conducting the reaction at room temperature which favoured the Lewis acid (DIBAL) mediated isomerisation to the thermodynamically 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 ^{o}C (Scheme 5.32).



279 **283** **320**, 41%

Scheme 5.32

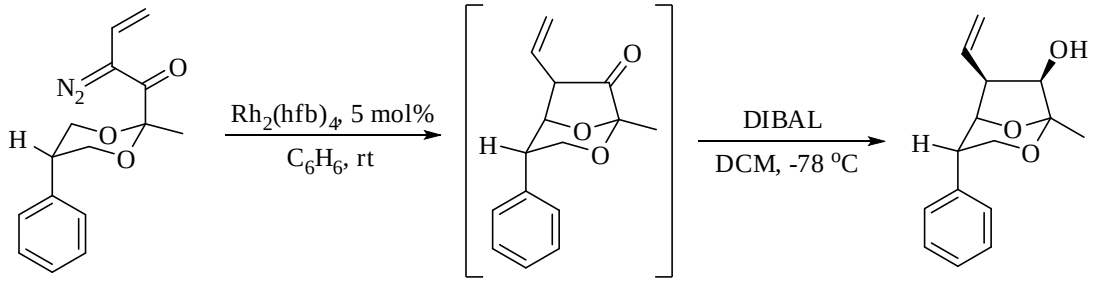
Gratifyingly, the reaction proceeded uneventfully and the desired bicyclic alcohol **320** was isolated in good overall yield (41%) as a single product. Evidence for the formation of bicyclic alcohol **320** was obtained from the IR and ^{1}H NMR spectra. The IR spectrum showed the appearance of the 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-C*H*=CH$_2$ proton gave a strong correlation to the axial 3-*H* proton, which implied that the 6-C*H*=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-C*H*$_3$ protons (Figure 5.4).



320

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).



280 **321** **322**, 35%

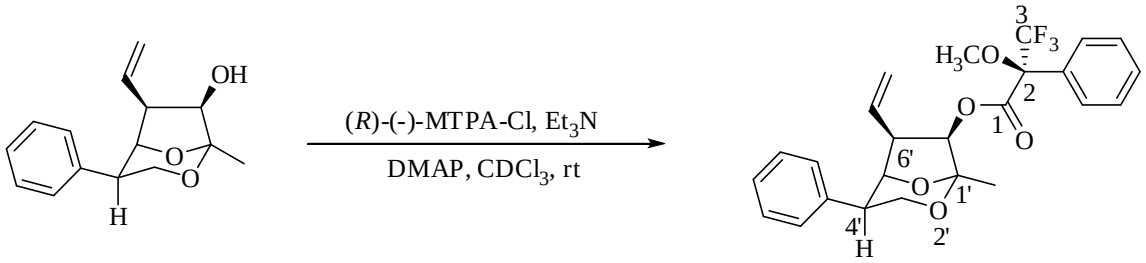
Scheme 5.33

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 vinyldiazoketone 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 ($[\alpha]^{28.1}_D$ = + 24.0^o), 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).



320

323, 324 (60%)
1:1

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.[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_3N 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 ^1H NMR spectrum confirmed, as expected the formation of the diastereoisomers in the ratio 1:1 (Figure 5.5).

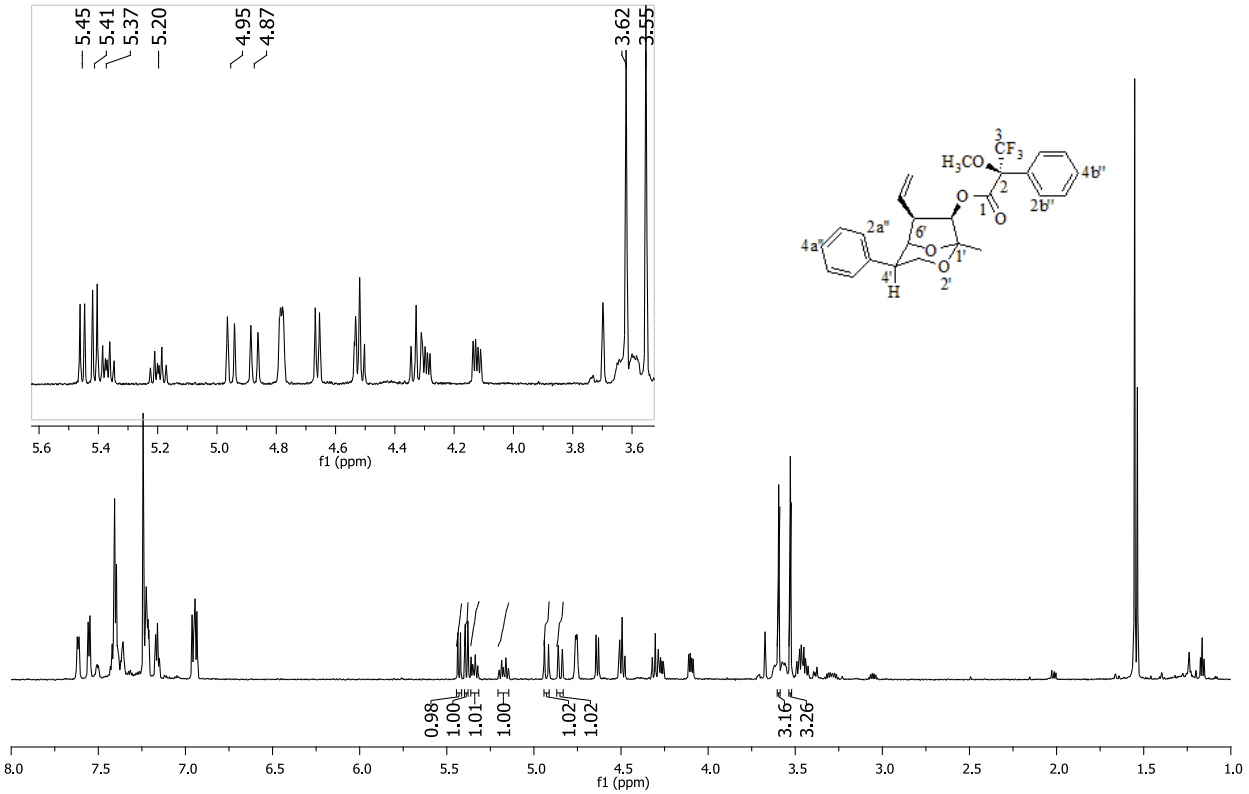


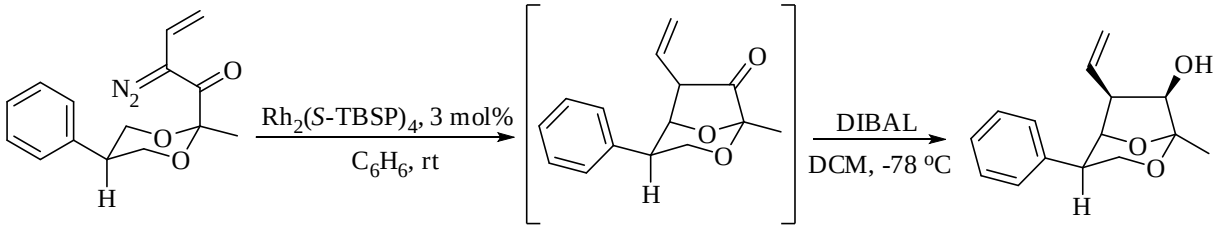
Figure 5.5

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=C*H*H 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

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 Rh_2(*S*-TBSP)$_4$ catalyst to induce asymmetry, having had success previously with this catalyst system in the diazo decomposition of vinyldiazoketone acetal **279**. Thus, following the same two step diazo decomposition and reduction but using Rh_2(*S*-TBSP)$_4$ catalyst and DIBAL in successions, the vinyldiazoketone acetal **279** was converted into the bicyclic alcohol **320** in a good overall yield of 45% (Scheme 5.35).



279 **283** **320**, 45%

$[\alpha]^{20.1}_{D} = -31.2^{o}$

Scheme 5.35

In a similar manner, the vinyldiazoketone **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, $[\alpha]^{20.1}_{D}$ of the product **320** obtained at a concentration of 0.4 g/ml in $CDCl_3$ was -31.2^{o}. 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).

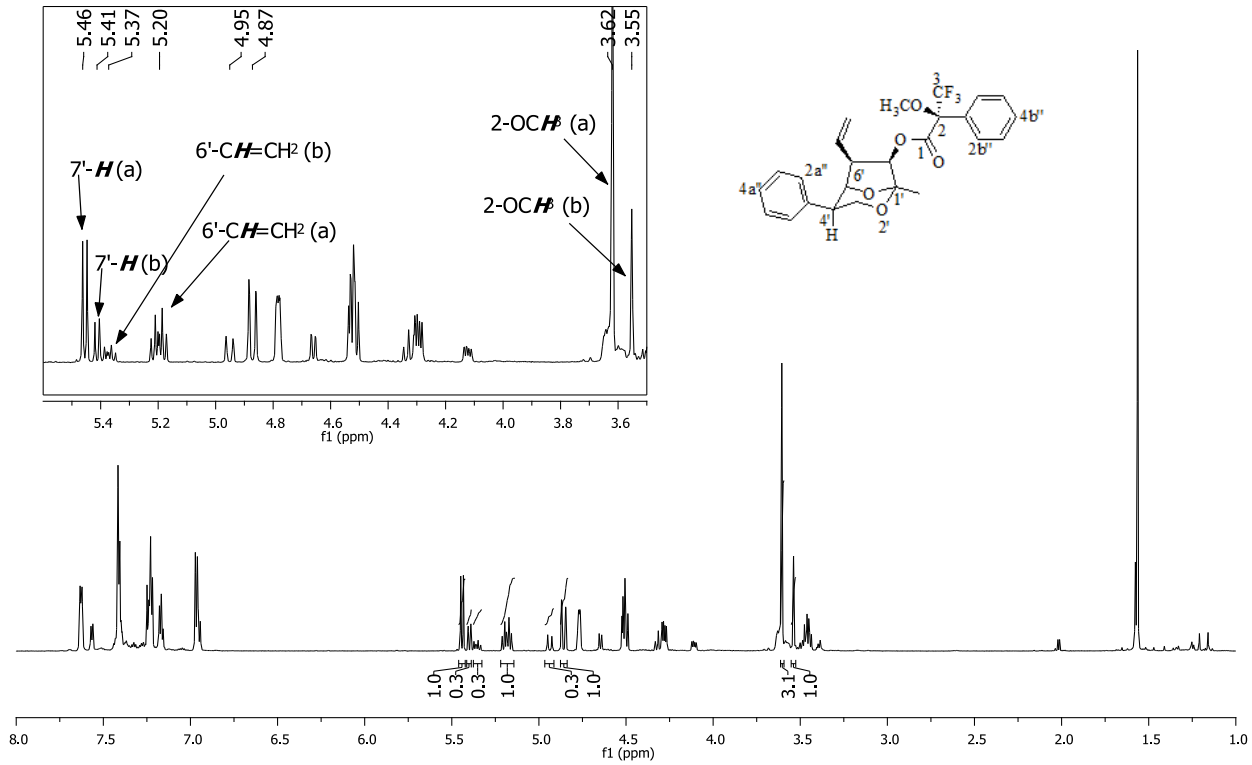


Figure 5.6

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.

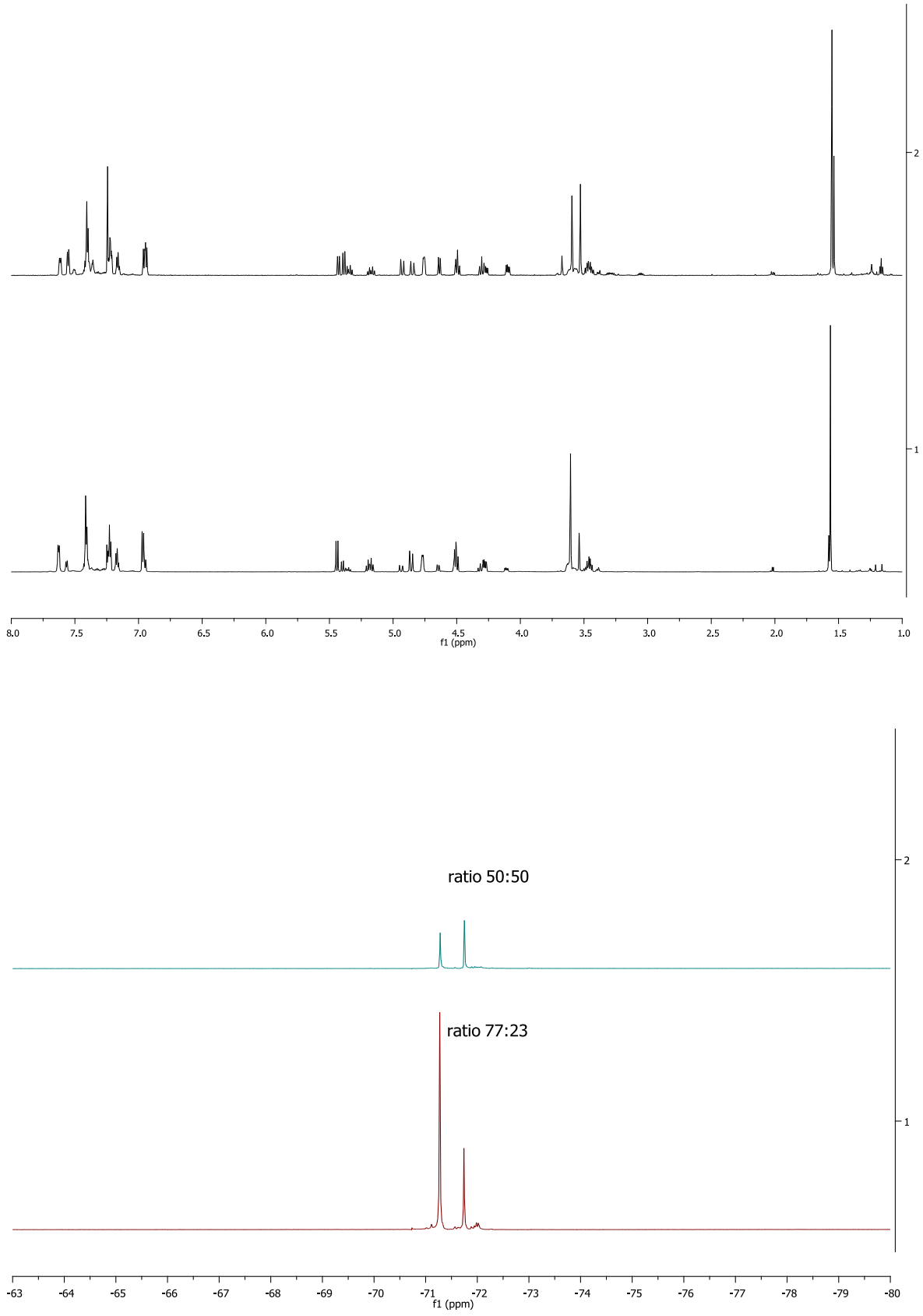
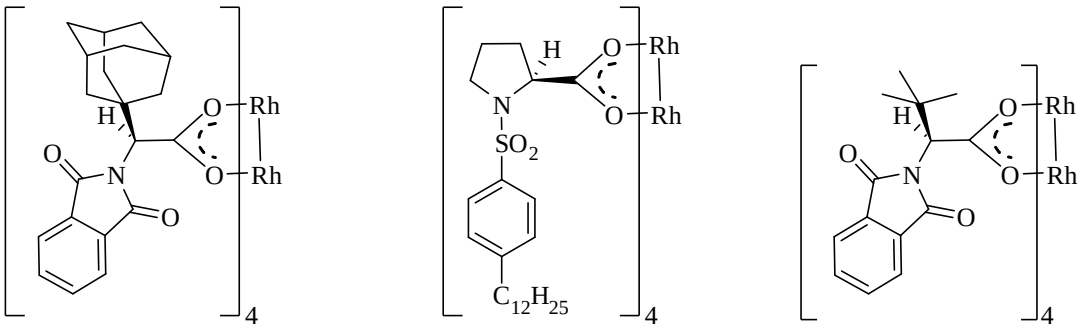

2
1
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
ratio 50:50
ratio 77:23
2
1
-63
-64
-65
-66
-67
-68
-69
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
f1 (ppm)

Figure 5.7

Pleased with the degree of asymmetry induction using the chiral Rh_2(*S*-TBSP)$_4$ catalyst, the enantiomeric excess (ee) of the scalemic mixture was calculated from the ^{19}F NMR spectrum to be a modest value of 54%. More importantly, this is the first report of asymmetry induction using the vinyldiazoketone **279** *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.

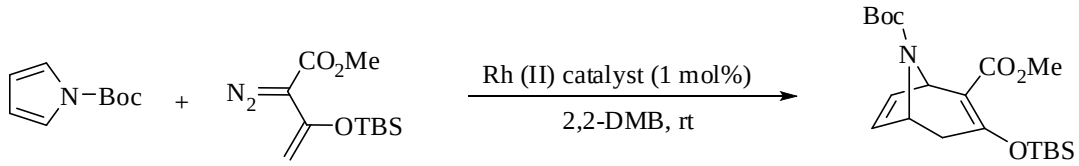
In 2006, Davies developed and demonstrated that higher enantioselectivities (ee) are obtained when the intermolecular reactions of, in particular, donor-acceptor carbenoids are catalysed by the bulky tetrakis[(*S*)-(1-adamantyl)-(N-phthalimido)acetate]dirhodium (II), Rh_2(*S*-PTAD)$_4$ **325** in comparison to other well recognised chiral catalysts for example tetrakis[1-[[(4-alkyl(C_{11}-C_{13})phenyl]sulfonyl]-(2*S*)-pyrrolidinecarboxylate]dirhodium (II), Rh_2(*S*-DOSP)$_4$ **326** and the Hashimoto's tetrakis[N-phthaloyl)-(*S*)-*tert*-leucinate]dirhodium (II), Rh_2(*S*-PTTL)$_4$ **327** (Figure 5.8).[15]



325 = Rh_2(*S*-PTAD)$_4$ **326** = Rh_2(*S*-DOSP)$_4$ **327** = Rh_2(*S*-PTTL)$_4$

Figure 5.8

In one such study, Davies showed that ee's of up to 91% can be achieved with Rh_2(*S*-PTAD)$_4$ **325** when *N*-Boc-pyrrole **328** reacts with the vinyldiazoacetate **329** to give the tropane derivative **330** as the only product (Scheme 5.36, Table 5.9). In contrast, Rh_2(*S*-DOSP)$_4$ **326** and Rh_2(*S*-PTTL)$_4$ **327** gave ee's of 29% and 88% respectively (entry 1 & 2).[16]



328 **329** 2 equiv. **330**, 38% yield 91% ee

Scheme 5.36

Entry	Catalyst	Yield of **330** (%)	ee of **330** (%)
1	Rh_2(*S*-DOSP)$_4$ **326**	31	29
2	Rh_2(*S*-PTTL)$_4$ **327**	34	88
3	Rh_2(*S*-PTAD)$_4$ **325**	38	91

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).

Entry	Catalyst	Overall yield of bicyclic alcohol **320** (%)	Specific rotation of bicyclic alcohol **320**	Yield of Mosher's ester derivatives (%)	Enantiomeric excess (%)
1	Rh_2(*S*-TBSP)$_4$	45	$[\alpha]^{20.1}_D$ = - 31.2° c = 0.4, $CDCl_3$	86	54
2	Rh_2(*S*-DOSP)$_4$	44	$[\alpha]^{19.4}_D$ = + 44.9° c = 0.3, $CHCl_3$	57	50
3	Rh_2(*S*-PTAD)$_4$	20	$[\alpha]^{19.7}_D$ = - 70.3° c = 0.4, $CHCl_3$	75	86

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 vinyldiazoketone 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.[17] 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**.[16,17] 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.

5.3 Conclusions

The synthesised aldehyde acetals were sequentially transformed into the allyalcohol 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. Gratifingly, 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 $Rh_2(pfb)_4$ gave separable mixtures of both C-H and O-H insertion bicyclic acetals. However, the use of the less reactive although more selective $Rh_2(hfb)_4$ 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 Rh_2(*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

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Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, 17, 1709.

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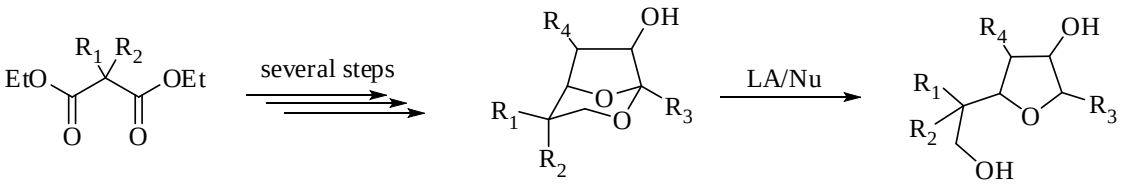
17 . Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, 9, 2625.

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).



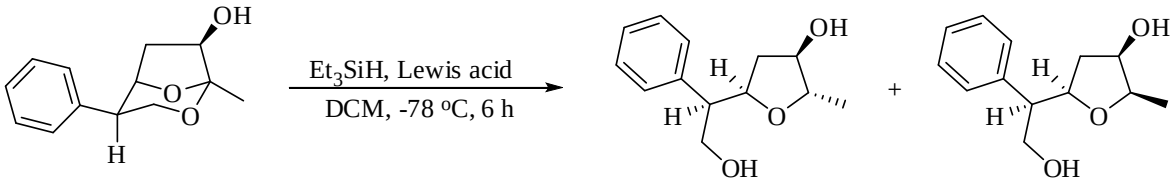
331 **332** **333**

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

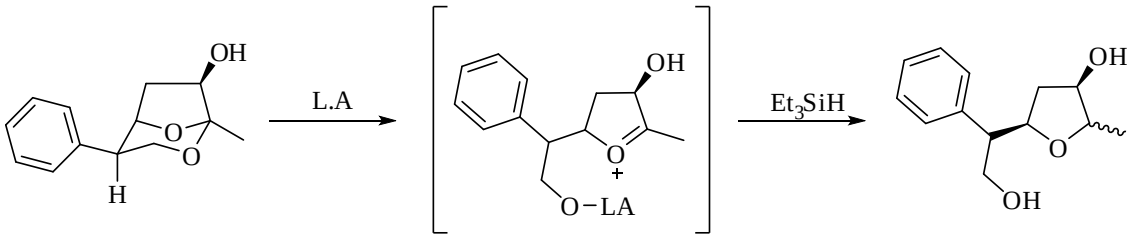
Previous reports by Garbi *et al* revealed that the bicyclic alcohol acetal **334** can undergo reductive cleavage of the acetal in a regioselective manner to give an inseparable mixture of trisubstituted tetrahydrofuran diastereoisomers **335** and **336** (Scheme 6.2).[1] This reaction outcome proved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



334 **335** **336**

Scheme 6.2

The reaction is believed to proceed via nucleophilic (in this case triethylsilane, Et_3SiH) 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).



334 **337** **335/336**

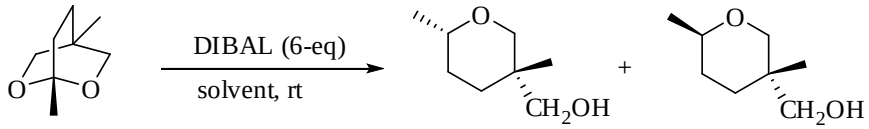
Scheme 6.3

Two Lewis acids, titanium tetrachloride ($TiCl_4$) and boron trifluoride etherate ($BF_3.Et_2O$) were explored, with both giving similar yields and diastereoselectivities (Table 6.1).

Entry	Lewis acid	Yield (%)	Ratio **335**:**336**	Ref.
1	$TiCl_4$	65	6:4	1
2	$BF_3.Et_2O$	60	7:3	1

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.



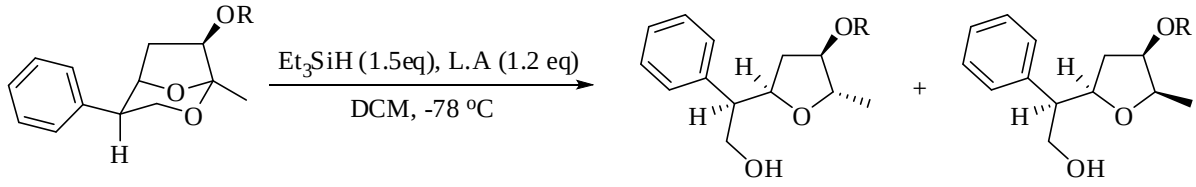
338 *cis* **339** *trans* **340**

Scheme 6.4

Entry	Solvent	Time (h)	Yield (%)	Ratio (*cis*:*trans*)
1	DCM	12	56	17:83
2	THF	15	51	82:18

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).



341 R=acetate **343** **344**

342 R=TBDMS ether **345** **346**

Scheme 6.5

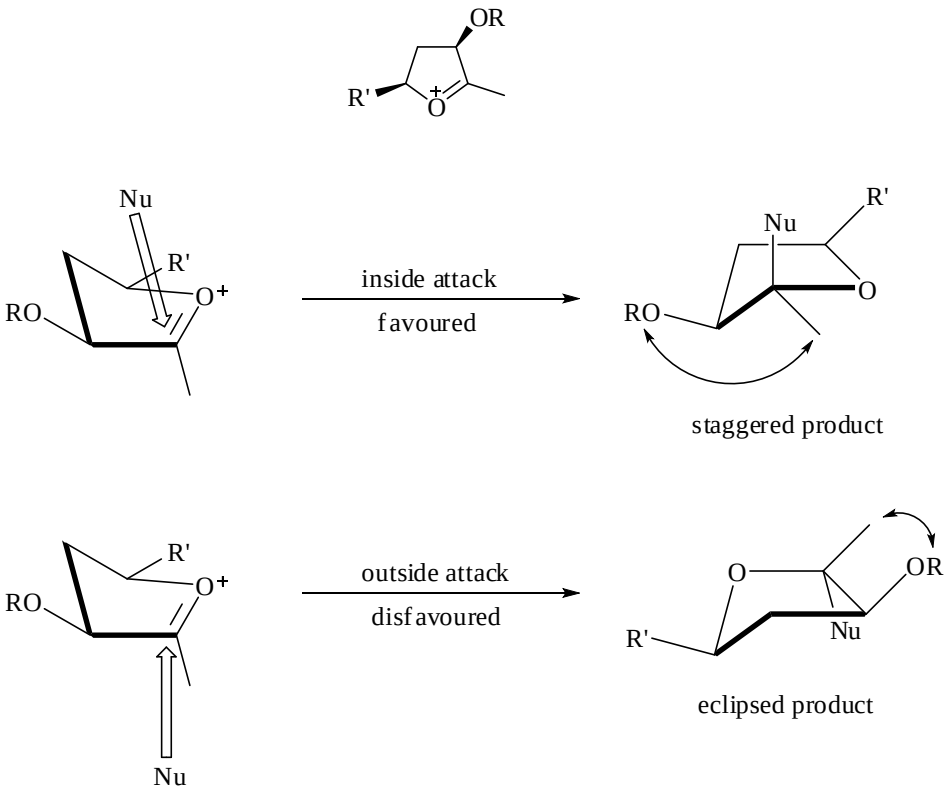
Entry	Substrate	Lewis acid	Time (h)	Yield (%)	Ratio[a]
1	**341**, R=Ac	$TiCl_4$	6	85	**343**:**344** (6:4)
		$BF_3.Et_2O$	8	70	**343**:**344** (7:3)
2	**342**, R=TBDMS	$TiCl_4$	8	80	**345**:**346** (95:5)
		$BF_3.Et_2O$	9	70	**345**:**346** (95:5)

[a]Results taken from Ref[1].

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).[3]

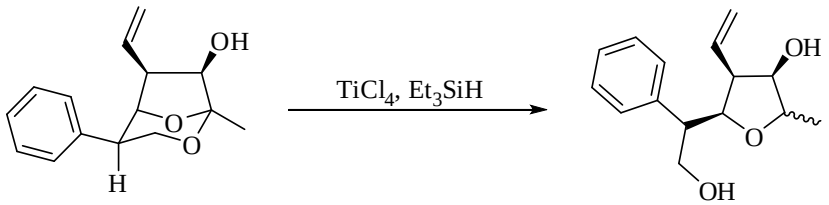


Scheme 6.6

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

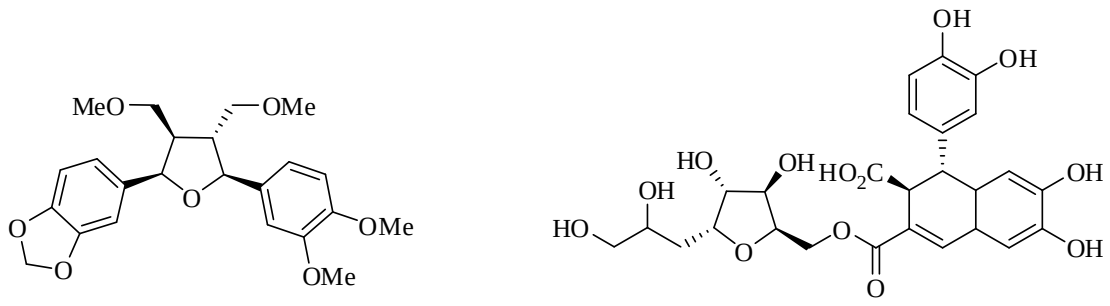
The Lewis acid catalysed nucleophilic cleavage of bicyclic acetals is therefore a well established method within the group for the stereoselective synthesis of tetrahydrofurans (THF). Consequently, the reductive cleavage of the acetals, for example **320** was examined *en route* to the construction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



320 **347**

Scheme 6.7

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).



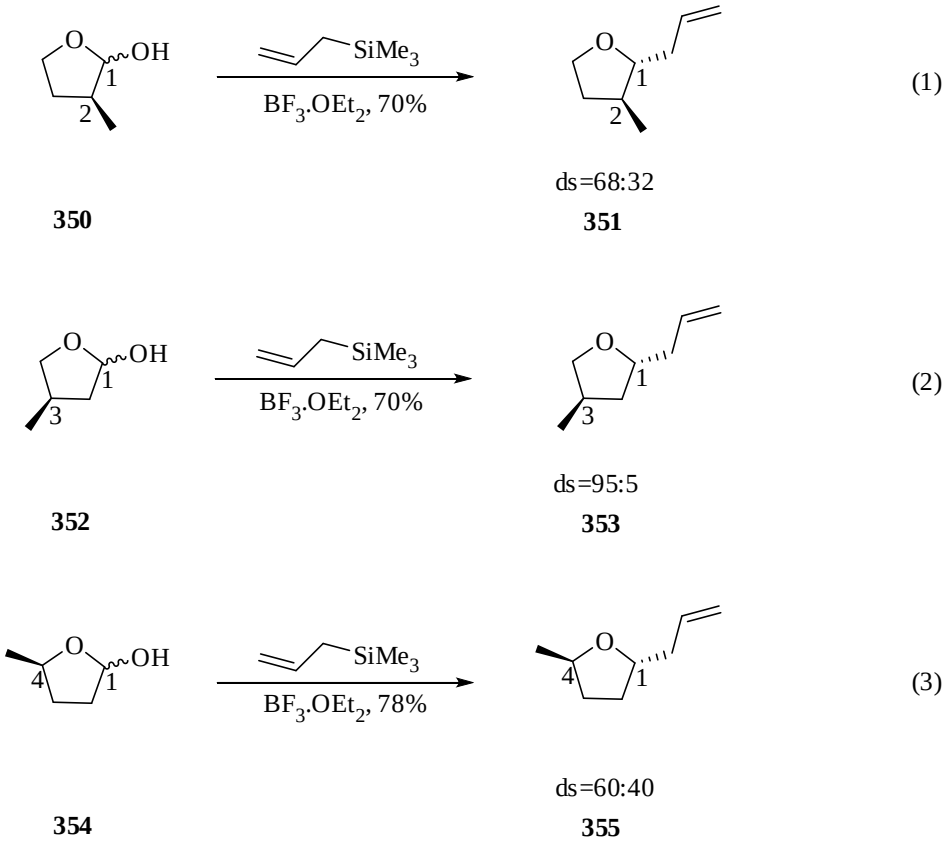
348 **349**

Figure 6.1

The study and results of the current efforts are presented below.

6.3.1 Reductive cleavage of bicyclic acetals

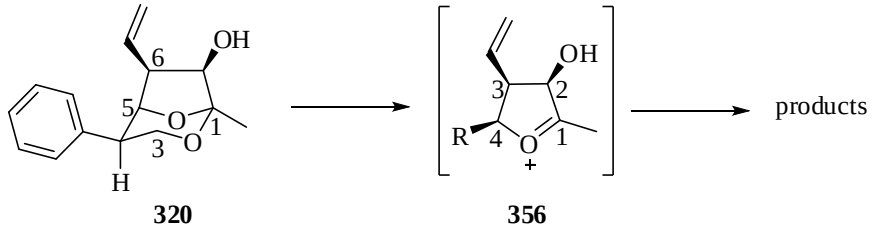
According to the basis of the ‘’inside attack’’ model, the C-3 substituent of the oxocarbenium ion greatly influences the stereoselectivity of the nucleophilic substitution reactions as can be seen from the results of the nucleophilic substitution reactions involving **350**, **352**, **354** and allyltrimethylsilane 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).

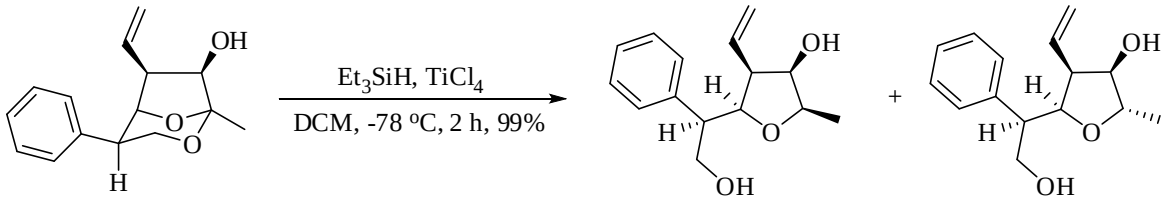
In an effort to take advantage of this influence, considering that the alkyl substituent at C-6 of the acetal **320** translates into the C-3 substituent in the oxocarbenium ion intermediate **356** (Scheme 6.9),[7] it was decided to explore the substituent effect in the reductive cleavage reaction.



320 **356**

Scheme 6.9

Following the method established by Garbi *et al*, the acetal **320** in DCM was treated with $TiCl_4$ at -78 ^oC followed by the addition of Et_3SiH (Scheme 6.10).



320 **357** **358**

6:4

Scheme 6.10

Analysis of the ^1H NMR spectrum of the crude reaction mixture obtained showed the presence of two diastereoisomeric products **357** and **358** in a 3:2 ratio (Figure 6.2), which could be separated by careful column chromatography.

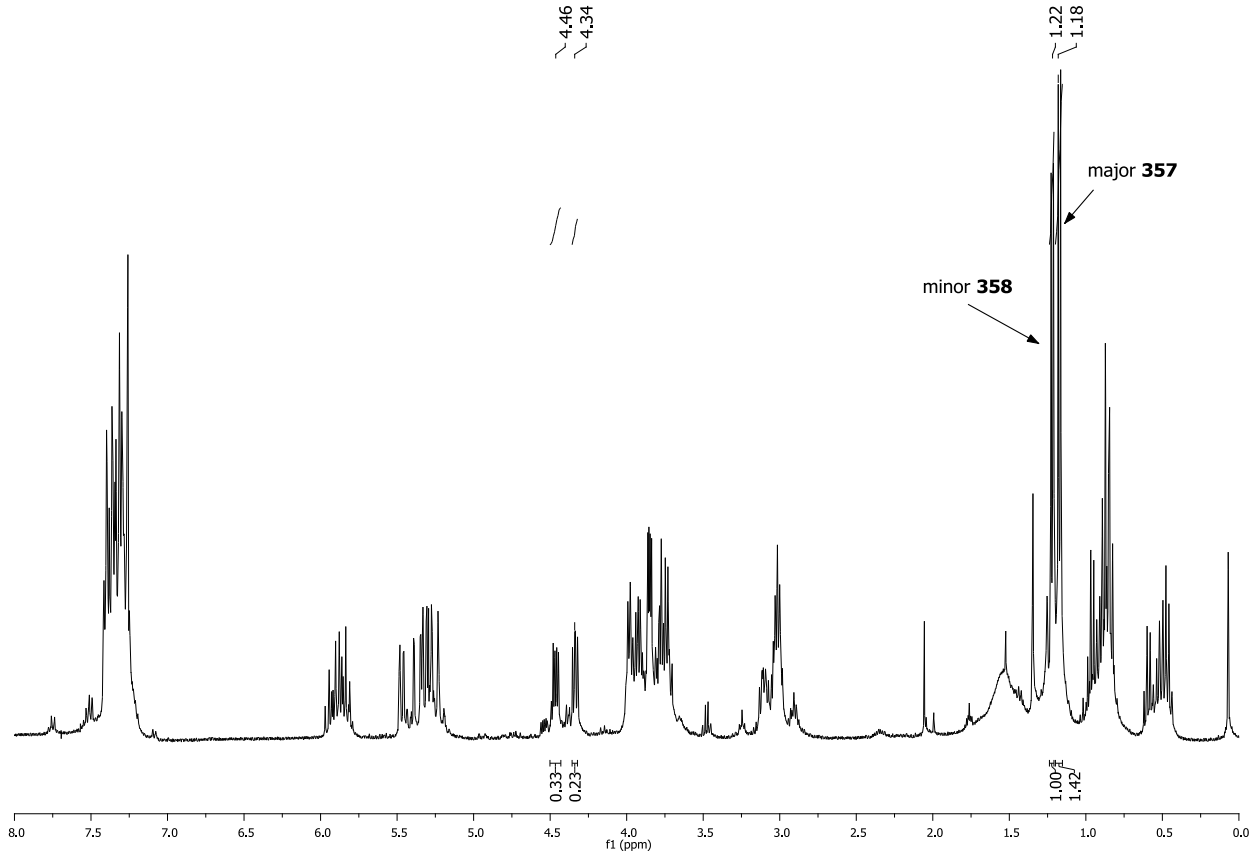


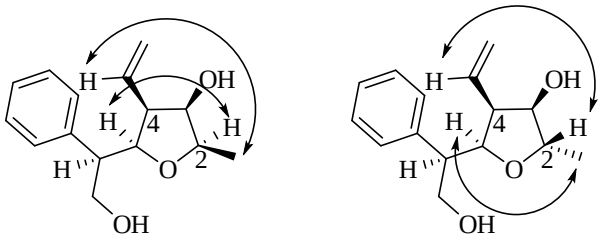
Figure 6.2

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-

C*H*$_3$ signal showed a significant correlation to the 4-C*H*=CH$_2$ proton which implied that the 2-C*H*$_3$ and 4-C*H*=CH$_2$ groups were on the same side of the molecule (Figure 6.3).

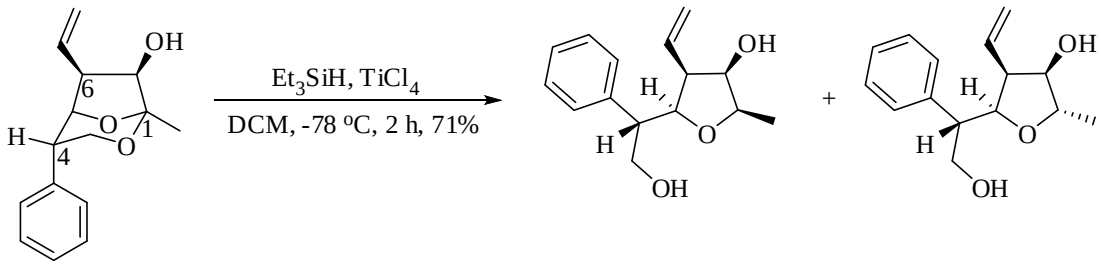


357 **358**

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-C*H*=CH$_2$ protons and also between the 2-C*H*$_3$ 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 **340** in a ratio of 6:4 (Scheme 6.11).



322 **359** **360**

6:4

Scheme 6.11

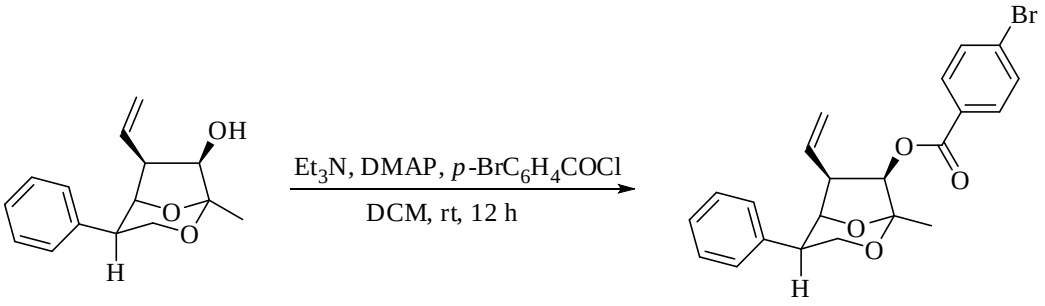
Evidence for the formation of the THF derivatives **359** and **360** obtained from analytical and spectroscopic data was satisfactory and consistent with that described above. It is noteworthy that the alternate stereochemistry at C-4 of the bicyclic alcohol acetal **322** had no effect on the stereochemical 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_3N) and 4-bromobenzoyl chloride in the presence of catalytic amount of 4-dimethylamino pyridine (DMAP) (Scheme 6.12).[8]



320 **361**, 96%

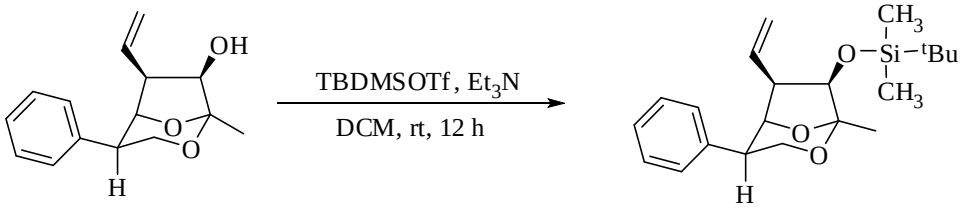
Scheme 6.12

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**.

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[9] and Igarashi[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_3N proved successful giving the desired product in good yield (Scheme 6.13).



320 **362**, 80%

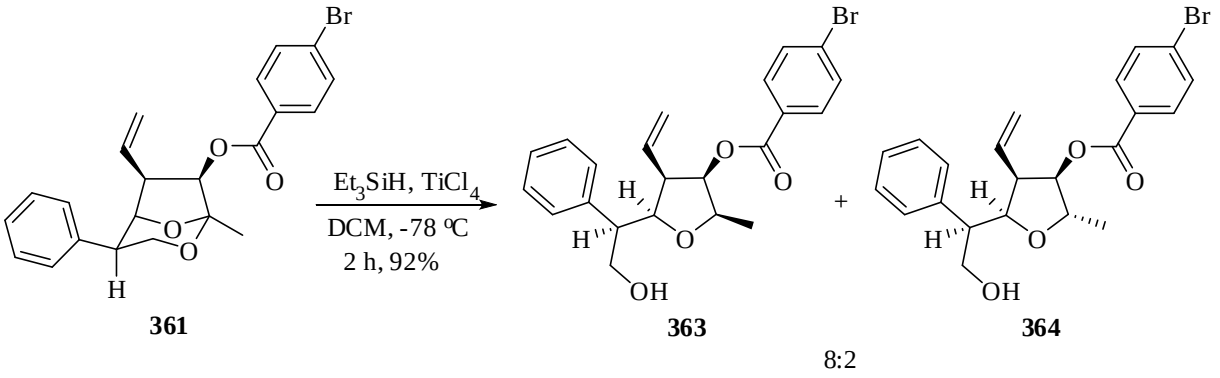
Scheme 6.13

Evidence for the formation of the silylated product **362** was obtained from the IR spectrum with the disappearance of the signal at 3410cm^{-1} corresponding to the hydroxyl stretch. Formation of the silylated product **362** was confirmed by the ^{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 *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 $TiCl_4$ and Et_3SiH 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).



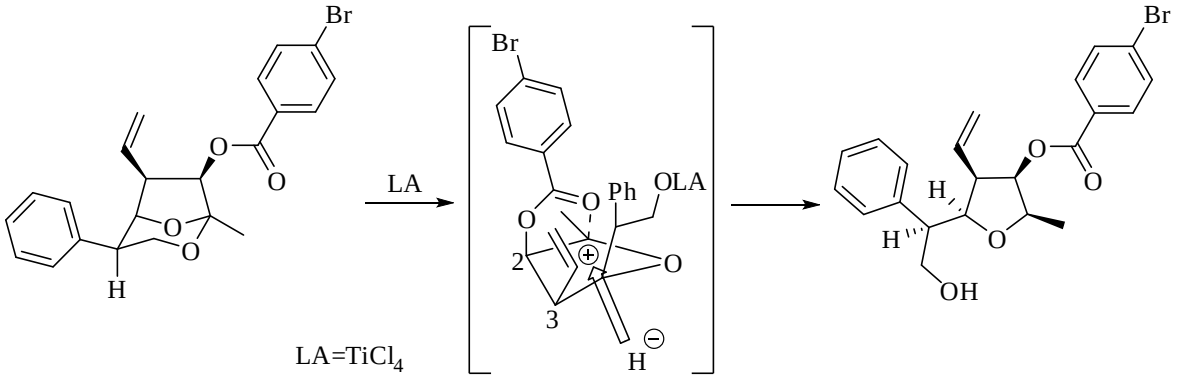
361 **363** **364**

8:2

Scheme 6.14

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).



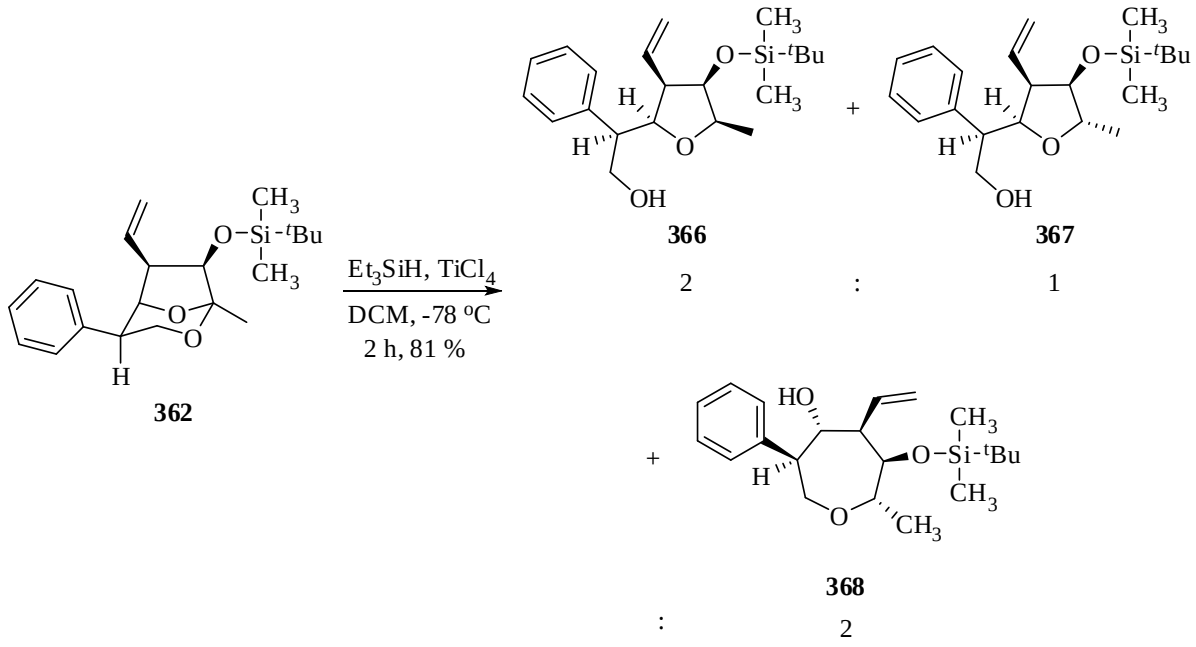
361 **365** **363**

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.

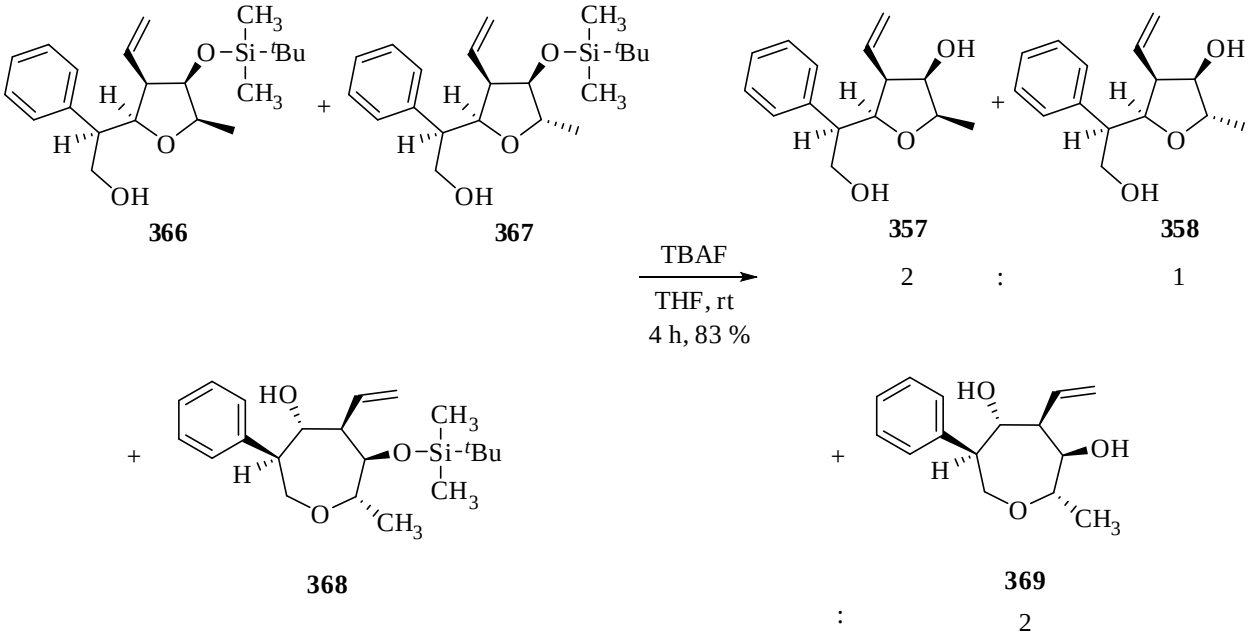
Thus, the TBDMS ether derivative **362** in solution was subjected to the same reductive cleavage reaction as earlier described (Scheme 6.16).



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.

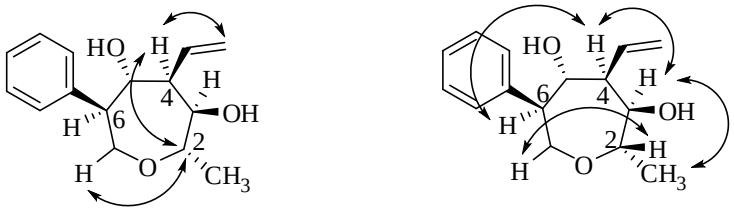
Further evidence for the formation of the silylated THF isomers **366**, **367** and in particular the oxepane isomer **368** was obtained after a subsequent silicon group deprotection protocol. Thus, following the reductive cleavage reaction of TBDMS ether derivative **362** to give the silylated mixtures **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).



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).



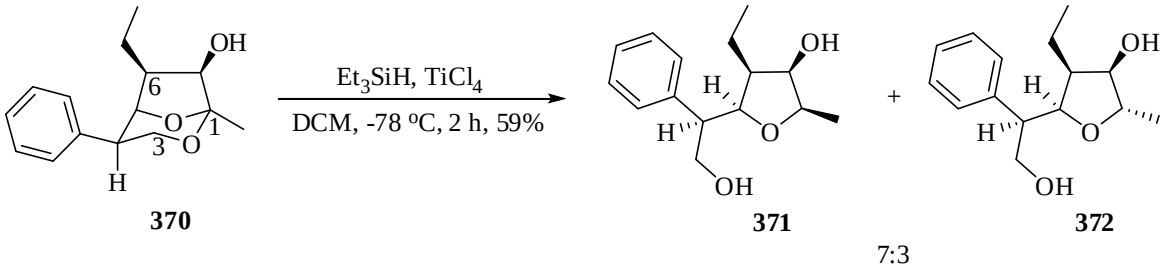
369 (A) **369** (B)

Figure 6.4

For example, in the HMBC spectrum, strong three (3) bond couplings were observed between 4-*H* and 4-CH=*C*H_2, 4-*H* and *C*-2 and the correlation across the oxygen heteroatom of the oxepane derivative between *C*-2 and 7-H_2 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-CH_3 and 3-*H* protons, 3-*H* and 4-*H*, 4-*H* and 6-*H* and across 2-*H* to 7-H_2 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 infact 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]



370 **371** **372**

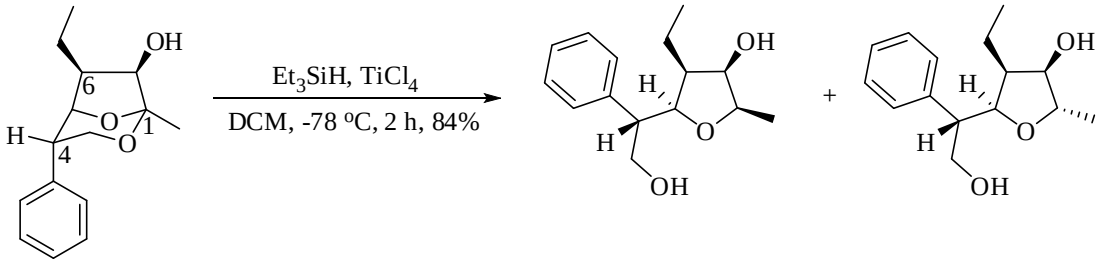
7:3

Scheme 6.18

Treatment of **370** with triethylsilane and titanium tetrachloride in DCM at -78 ^{o}C gave two diastereomeric THF derivatives **371** and **372** in a ratio of 7:3 as observed in the ^{1}H 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).



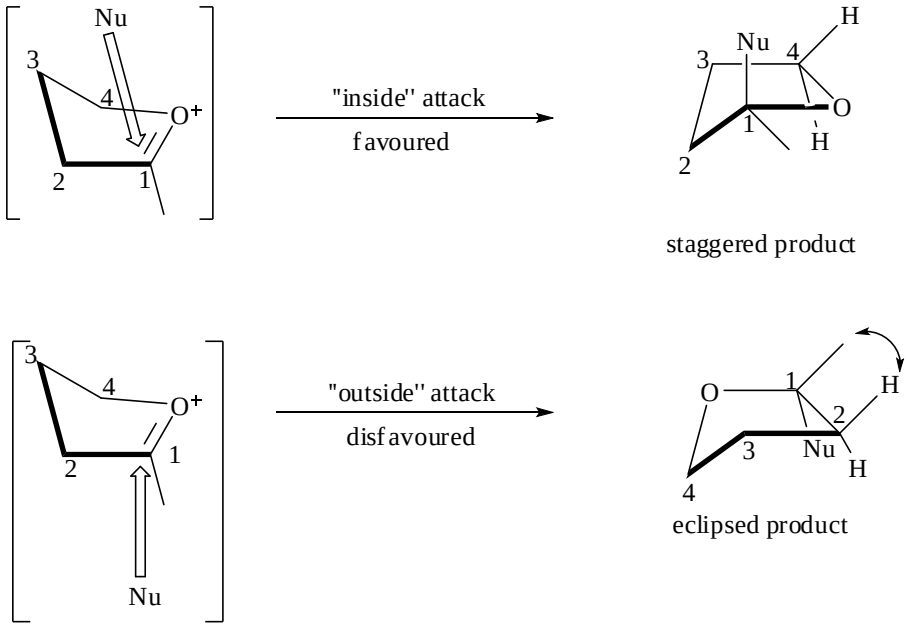
373 **374** **375**

7:3

Scheme 6.19

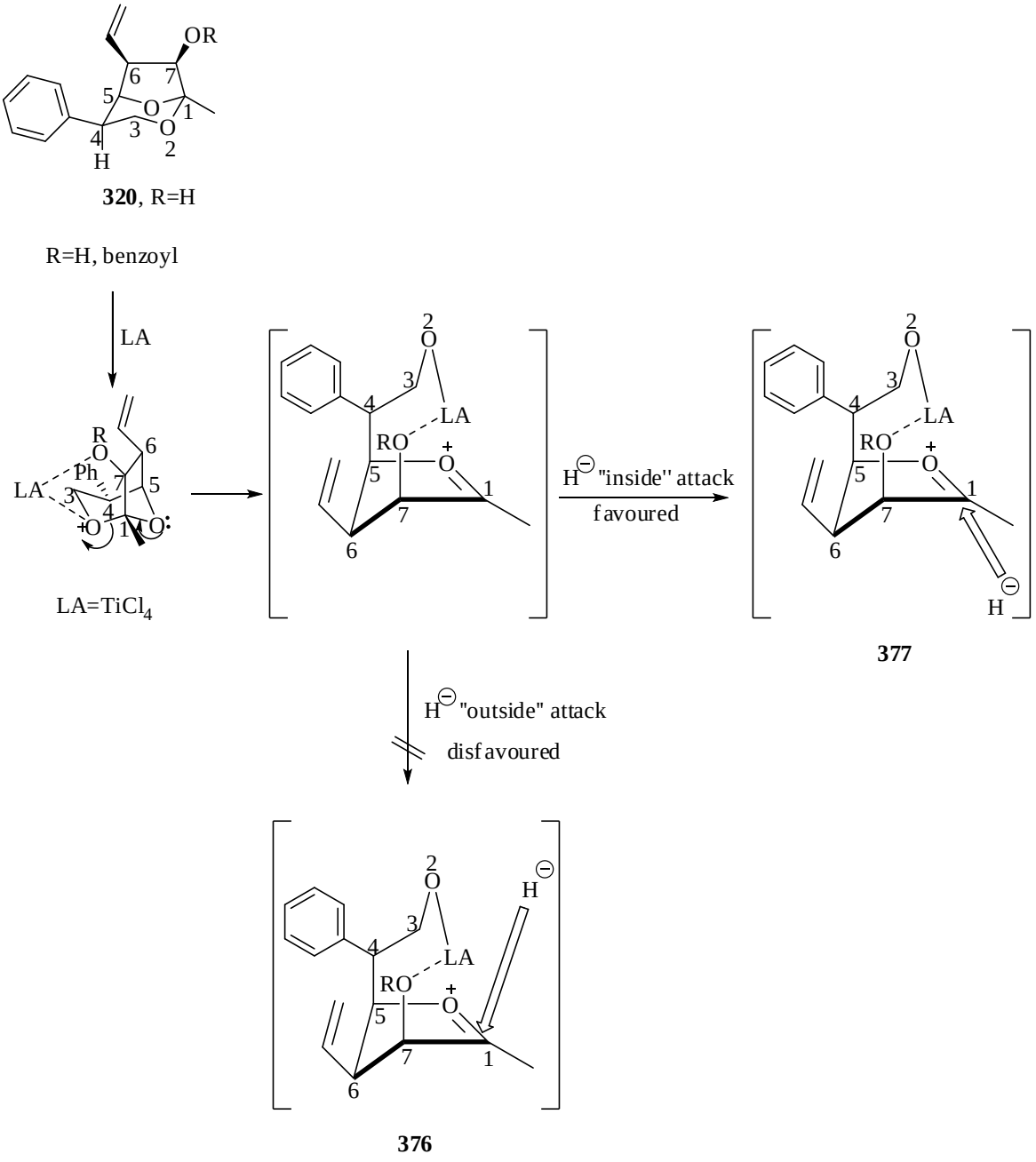
As before, satisfactory evidence for the formation of the THF derivatives **374** and **375** was obtained from analytical and spectroscopic data.

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 sterics 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).



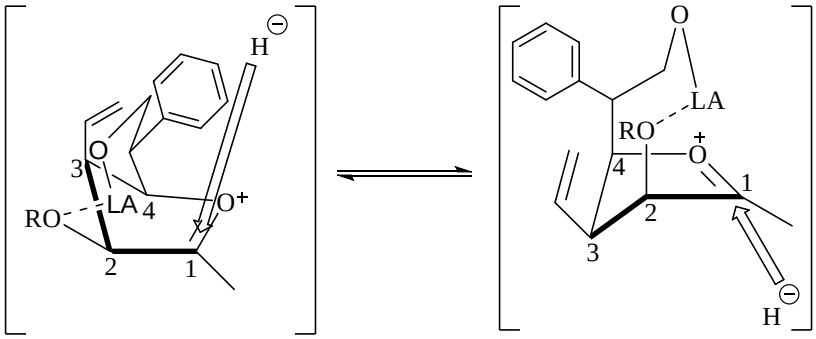
Scheme 6.20

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).



Scheme 6.21

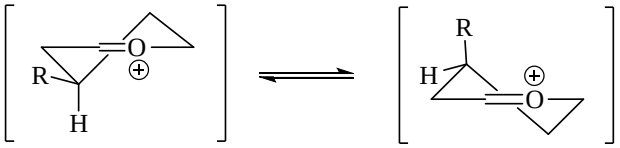
By this model, transition state **376** is disfavoured as attack by the nucleophile from the ‘’outside’’of the oxocarbeniun ion gives rise to the eclipsed product. In contrast, transition state **377** gives the more stable staggered product following an ‘’inside’’ attack by the nucleophile. However, the oxocarbenium ion of transition state **377** can exist as an additional conformer **378** (Scheme 6.22).



378 **377**

Scheme 6.22

Both of these ‘’envelope’’ conformers **378** and **377** would favour ‘’inside’’ attack by an approaching nucleophilic. Furthermore, certain alkoxyl-substituted six-membered-ring oxocarbenium ions have being noted to assume conformations in which the alkoxyl group resides preferentially in the pseudoaxial position (Scheme 6.23).[11]



379 **380**

Scheme 6.23

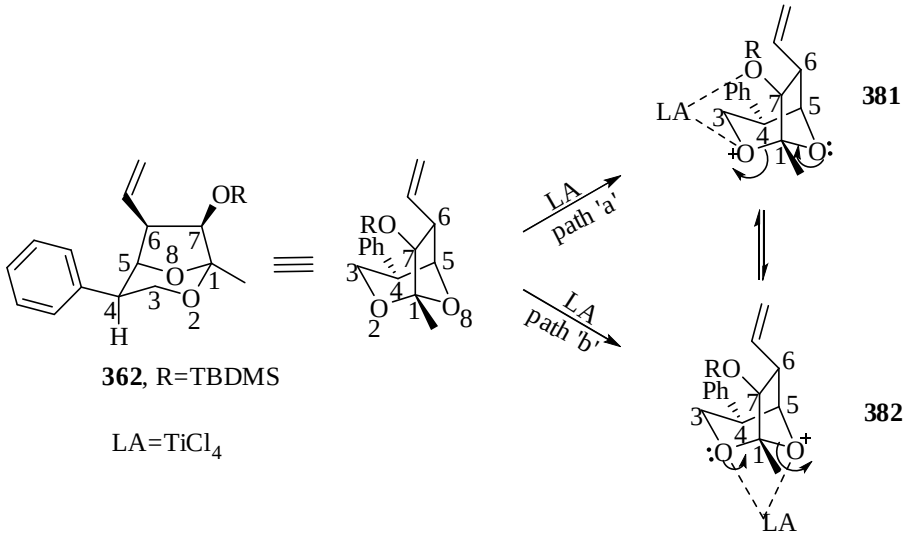
Whilst **379** is the favoured conformation when R is an alkyl substituent, **380** becomes the preferred conformation when R is an alkoxyl group. Logically, this has being successfully extended to five-membered-ring oxocarbenium ions.[3] In addition, this conformational preference has being shown to be consistent with computational investigations.[12] Based on these, the conformation **377** bearing the 2-alkoxyl 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 arises in the transition structures with nucleophilic attacks influences the stereochemical outcomes of such

reactions. Inside attack of the nucleophile on the conformers **377** and **378** each involve destabilized transition structures. The transition structure for ‘’inside’’ attack on conformer **378** develops a destabilizing 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).



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.

6.7 References

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10 . The bicyclic alcohols **370** and **373** were prepared from the bicyclicketones **436** and **437** (section 7.5.1) respectively by sodium borohydride ($NaBH_4$) reduction. Satisfactory analytical and spectroscopic data were obtained and are reported.

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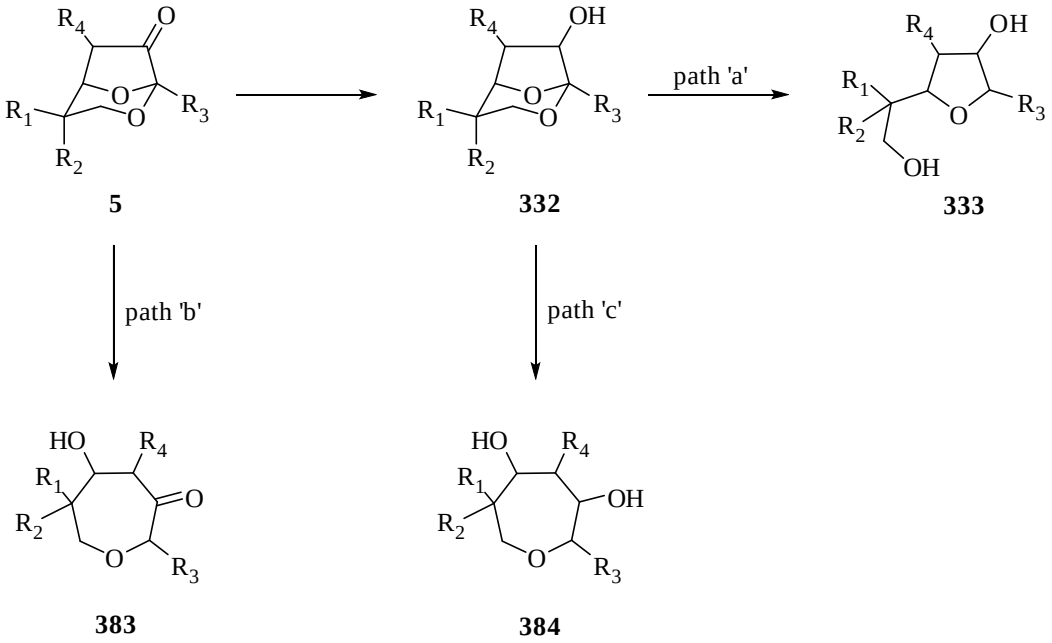
7.1 Introduction

The preceeding chapter described the use of the combination of titanium tetrachloride and triethylsilane that resulted in the successful synthesis of tetrasubstituted tetrahydrofurans (THF) **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 **383** and **384** (Scheme 7.1, paths 'b' and 'c' respectively).



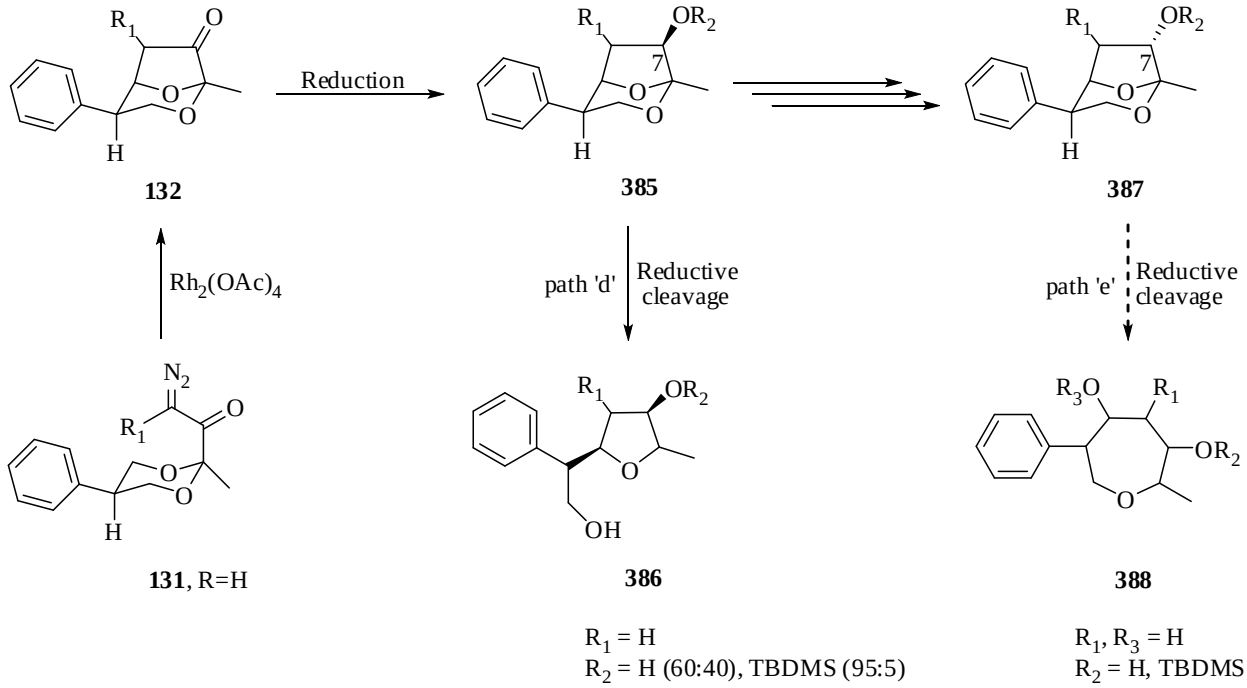
Scheme 7.1

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 **131** (representative of the acceptor substituted class of carbenoids) with rhodium (II) acetate gives the bicyclic ketone **132**. Subsequent reduction of **132** affords **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

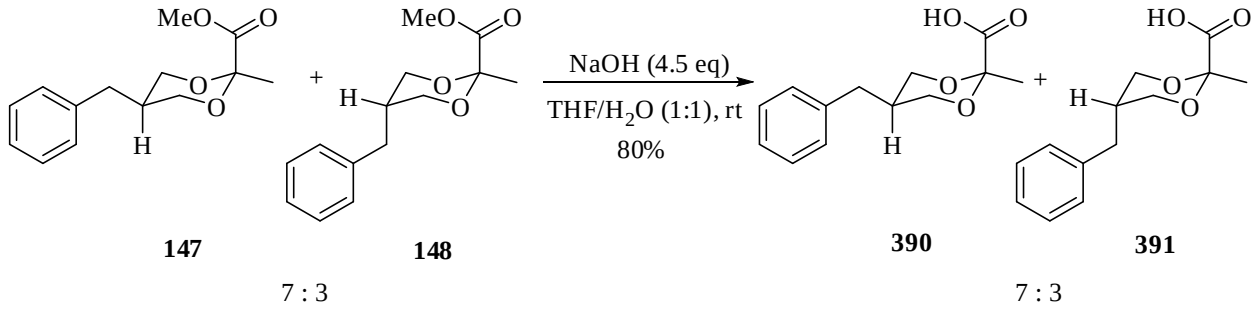
Based on this observation, it was decided to examine both the reaction and the robustness of the reductive cleavage step (path 'e'), by exploring a bicyclic alcohol analogous to **387** but with a different substitution pattern. It was hoped that this would provide access to pentasubstituted oxepane 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.

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.[2] 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/H_2O mixture (1:1) to afford the corresponding acids **390**, **391** in an 80% yield (Scheme 7.3).



Scheme 7.3

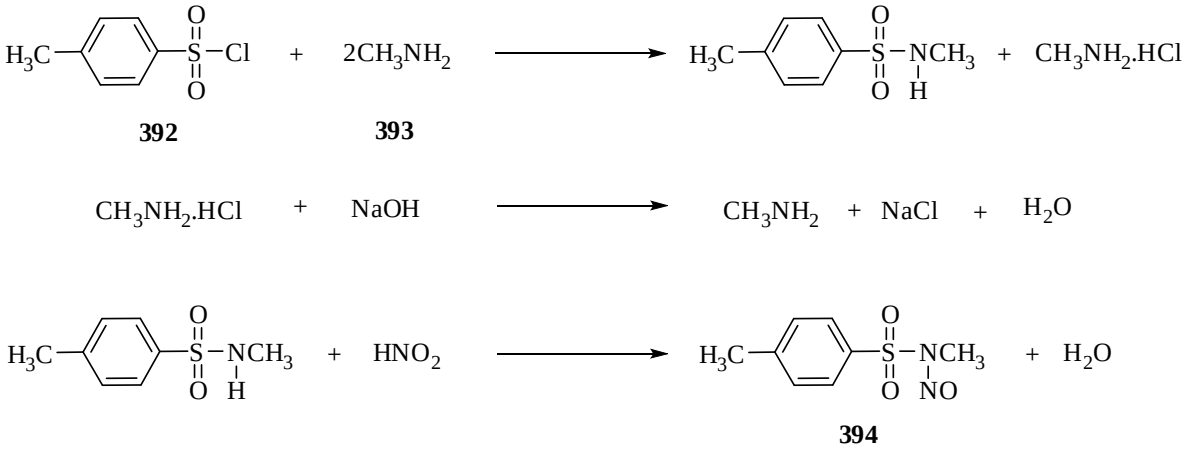
The acid acetals **390**, **391** were inseparable by column chromatography. However, recrystallisation from petroleum ether afforded the major acid acetal **390** as a pure sample while the mother liquor was enriched with the minor acid acetal **391**. Analytical and spectroscopic data was obtained 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 ^{1}H 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.

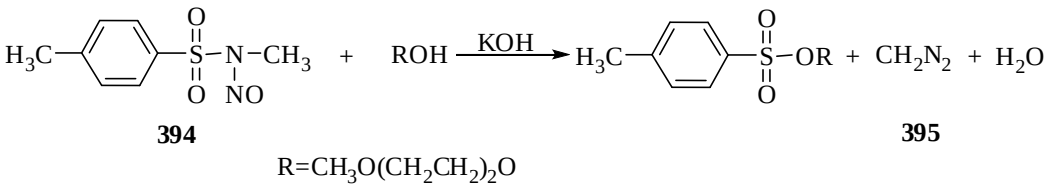
7.3.2 Preparation of the diazoketone 397

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]



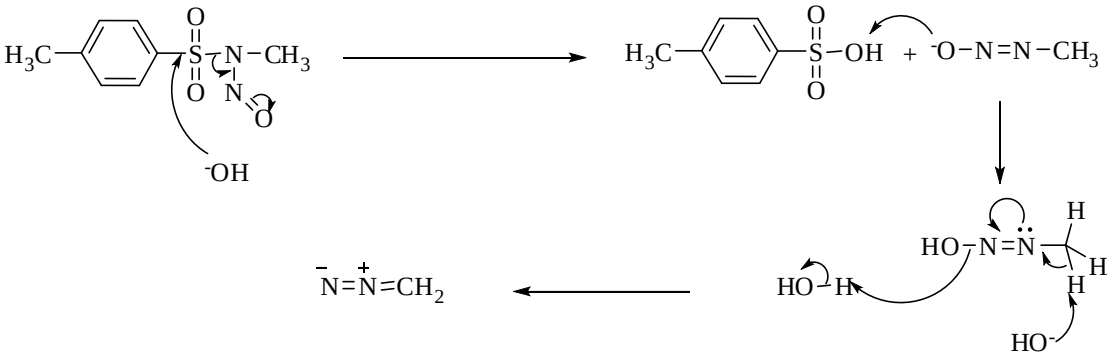
Scheme 7.4

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 H_2O/ether at 60 ^oC.[4] The resultant diazomethane **395** was distilled as an ethereal solution (Scheme 7.5).



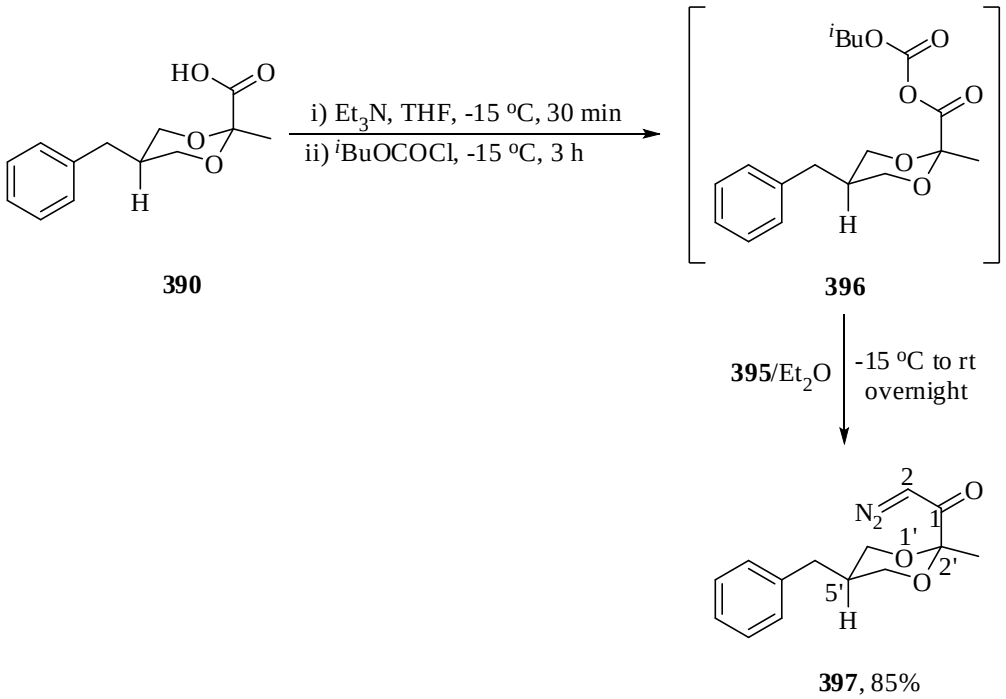
Scheme 7.5

The mechanistic rationale for the above process that leads to the formation of diazomethane is depicted below (Scheme 7.6).[4]



Scheme 7.6

Concurrently with the preparation of diazomethane, the acid **390** was activated by treating with isobutyl chloroformate in the presence of triethylamine (Et_3N) 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).



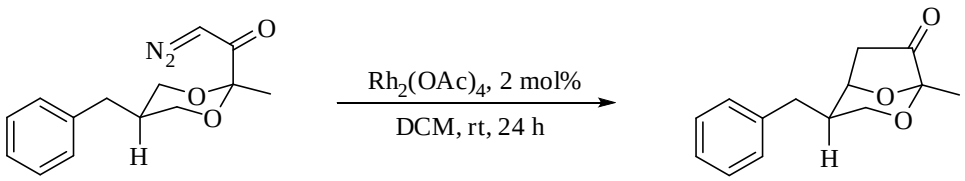
Scheme 7.7

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).



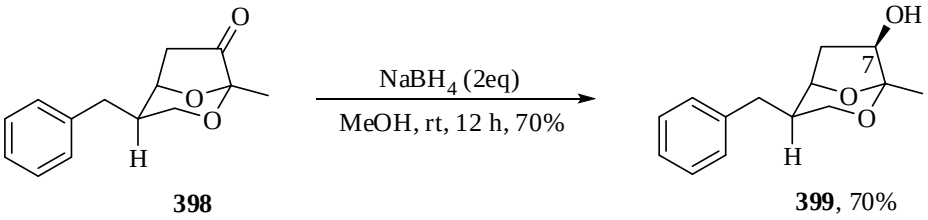
397 **398**, 50%

Scheme 7.8

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).

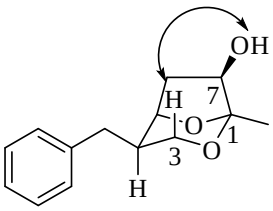


398 **399**, 70%

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]



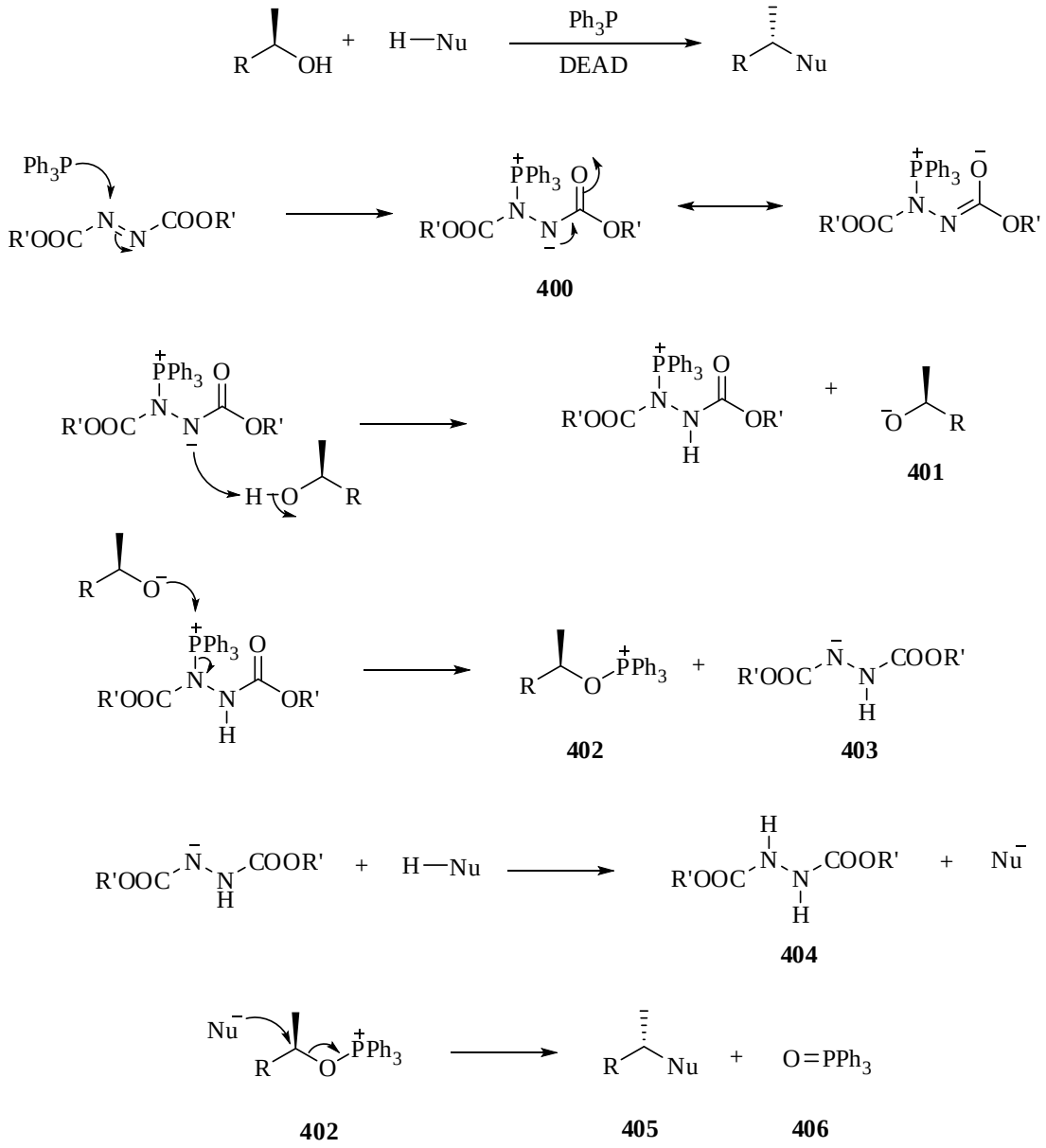
399

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).

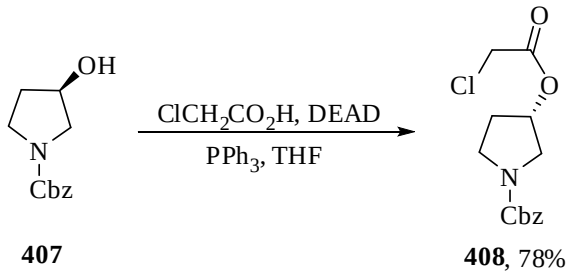
The reaction proceeds by attack of triphenyl phosphine (PPh_3) on the weak N=N *pi* bond of the azo ester e.g. diethyl azodicarboxylate (DEAD) to give the anion **400** stabilised by resonance to the adjacent ester groups. The anion **400** subsequently abstracts a proton from the alcohol to form the 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 PPh_3, acetic acid, diisopropyl azodicarboxylate (DIAD); PPh_3, *p*-nitrobenzoic acid, DIAD were unsuccessful. Further efforts to vary the order of addition of reagents with a view to generating the betaine (PPh_3-DIAD adduct) were equally unsuccessful. Ultimately, it was thought that the alcohol group in **399** was too hindered for reaction with the betaine.

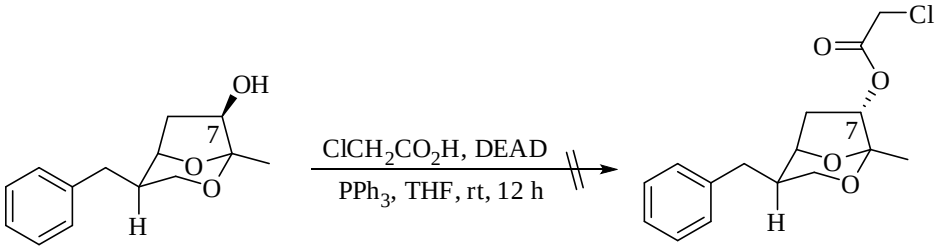
In 2001, Wee reported an application of the combination of DEAD, PPh_3 and chloroacetic acid (pK_a of 2.86 compared to acetic acid pK_a 4.76) for the successful inversion of the configuration of the secondary alcohol **407** to give the chloroacetate derivative **408** in good yield (Scheme 7.11).[5]



407 **408**, 78%

Scheme 7.11

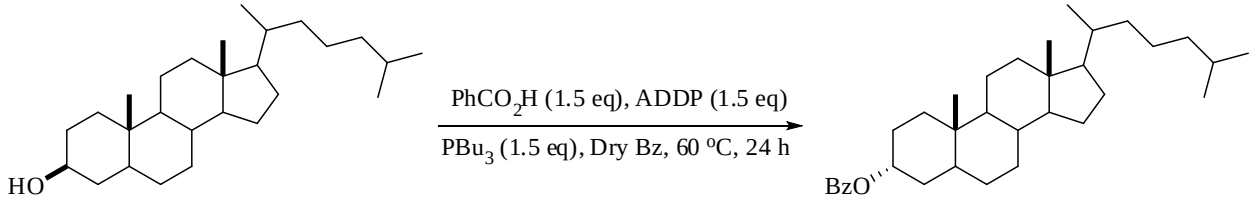
In view of this precedent, it was decided to investigate the conditions of Wee *et al* using the bicyclic alcohol **399**. Thus the alcohol **399** was dissolved in THF followed by the successive addition of chloroacetic acid, PPh_3 and DEAD according to the literature procedure (Scheme 7.12).



399 **409**

Scheme 7.12

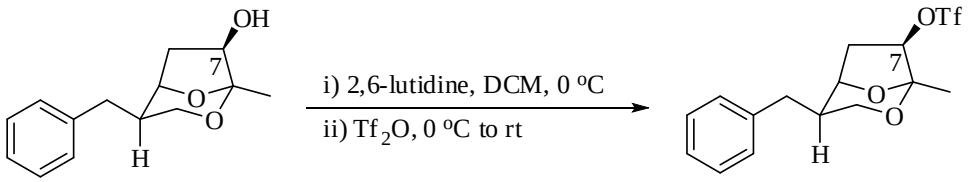
However, the reaction led to recovery of the starting material **399** with no trace of the chloroacetate derivative product **409** in the ^{1}H NMR spectrum of the crude reaction mixture. Further efforts to change the bulky PPh_3 and azo ester DEAD led to the use of the less hindered tributyl phosphine (TBP) in combination with azodicarbonyldipiperidine (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]



410 **411**, 81%

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* 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]



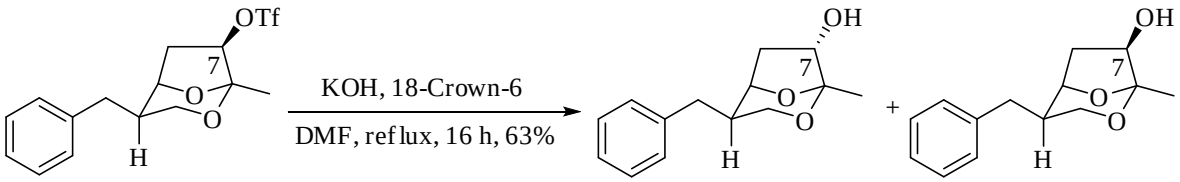
399 **412**, 78%

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 (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 (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 ^{o}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).



412 **413** **414**

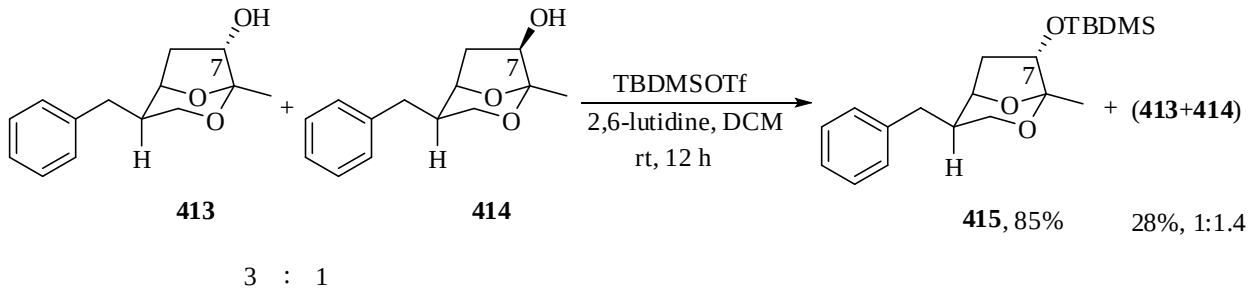
3 : 1

Scheme 7.15

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_3N). 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).



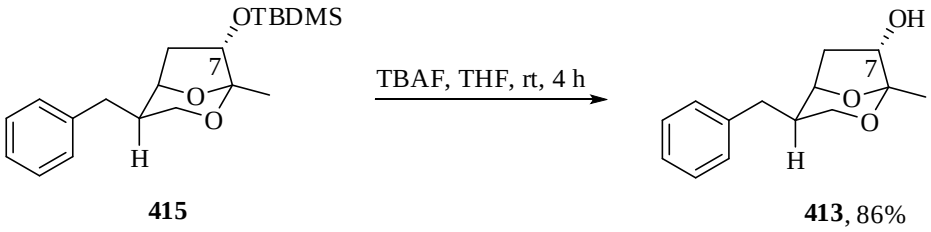
413 **414** **415**, 85% 28%, 1:1.4

3 : 1

Scheme 7.16

Evidence obtained for the formation of the silylated alcohol **415** was obtained from the IR and ^{1}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}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).

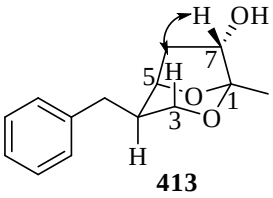


415 **413**, 86%

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

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).



413

Figure 7.2

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).

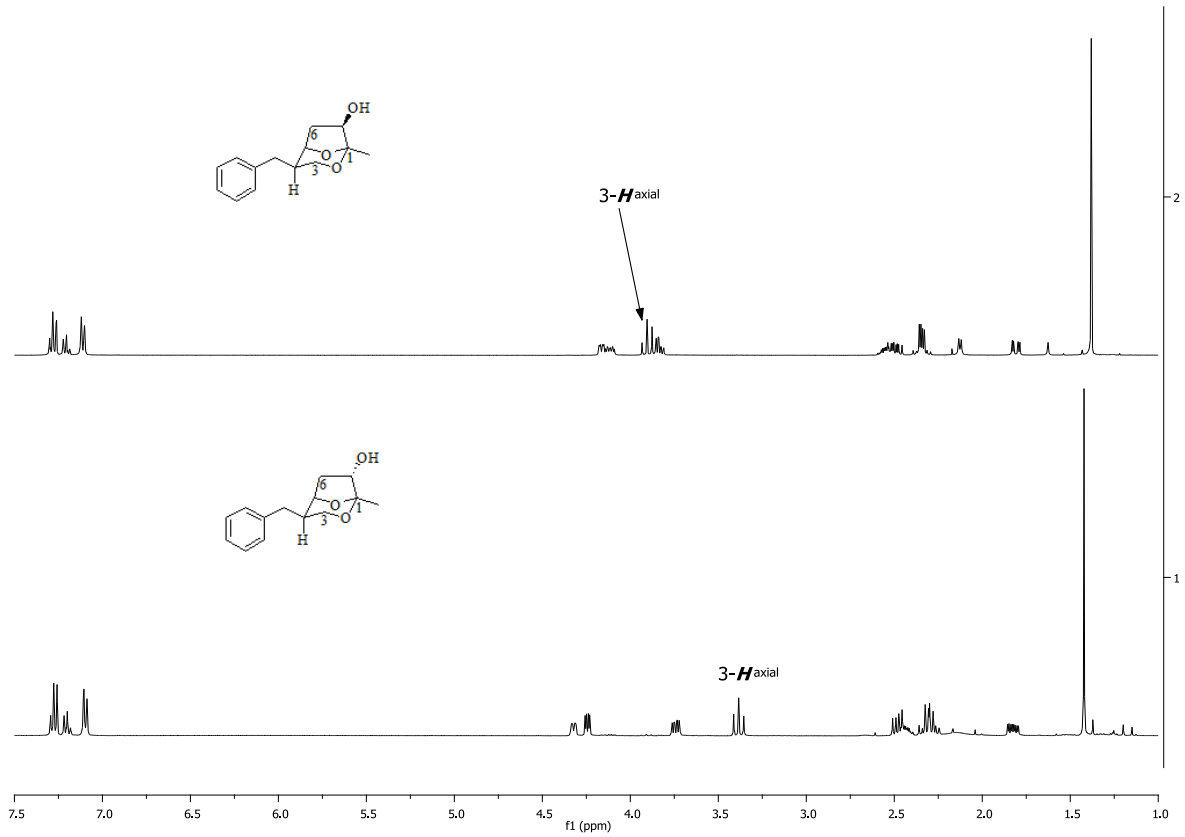
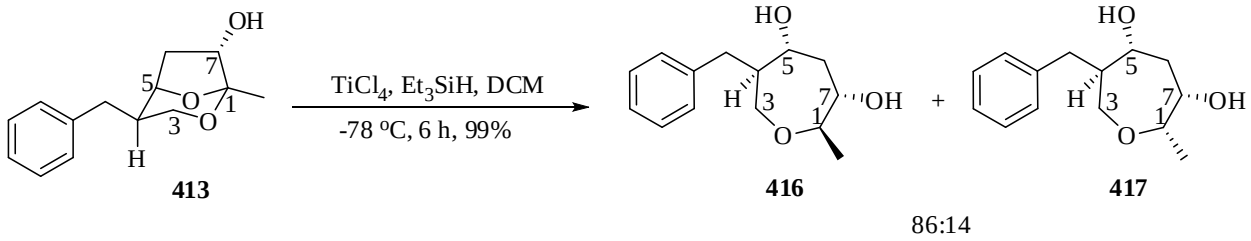


Figure 7.3

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 (Et_3SiH) and a 1M solution of titanium tetrachloride ($TiCl_4$) (Scheme 7.18).



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).

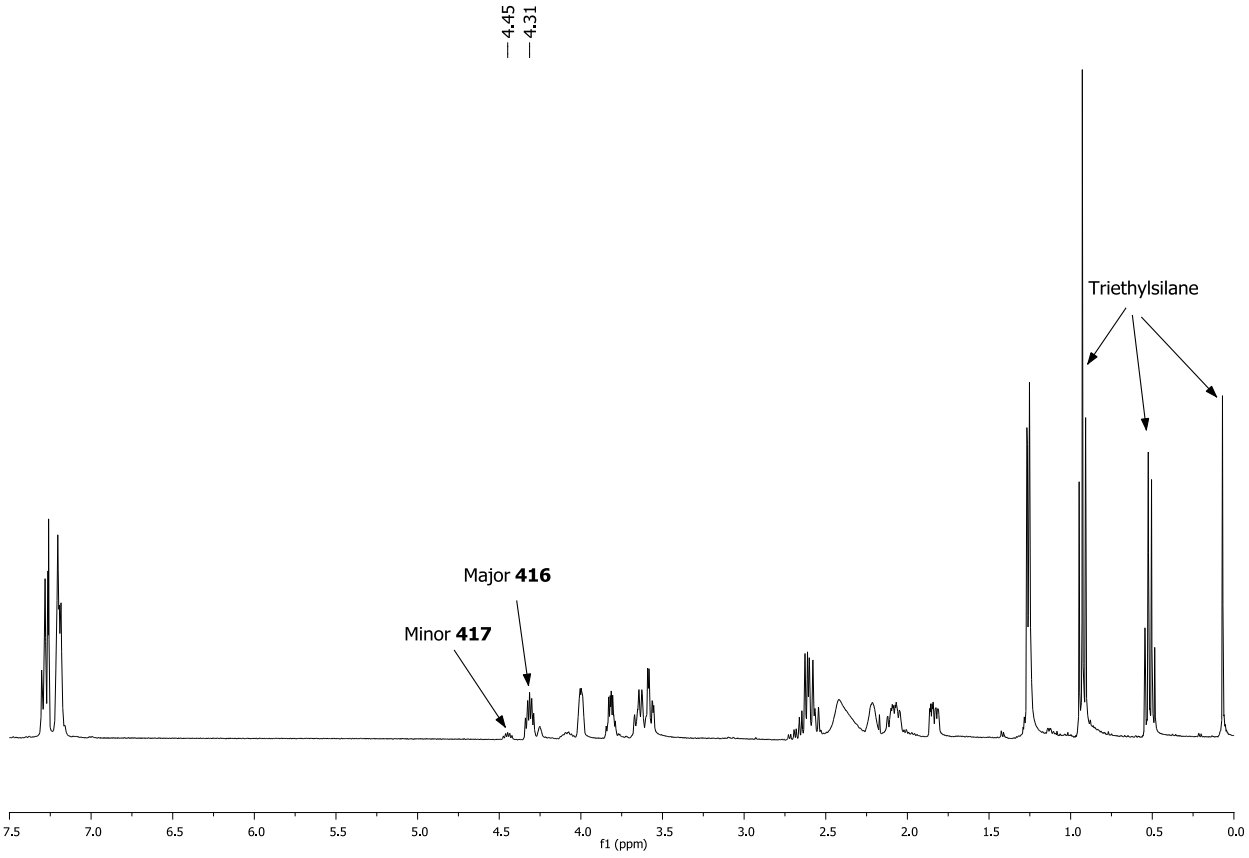
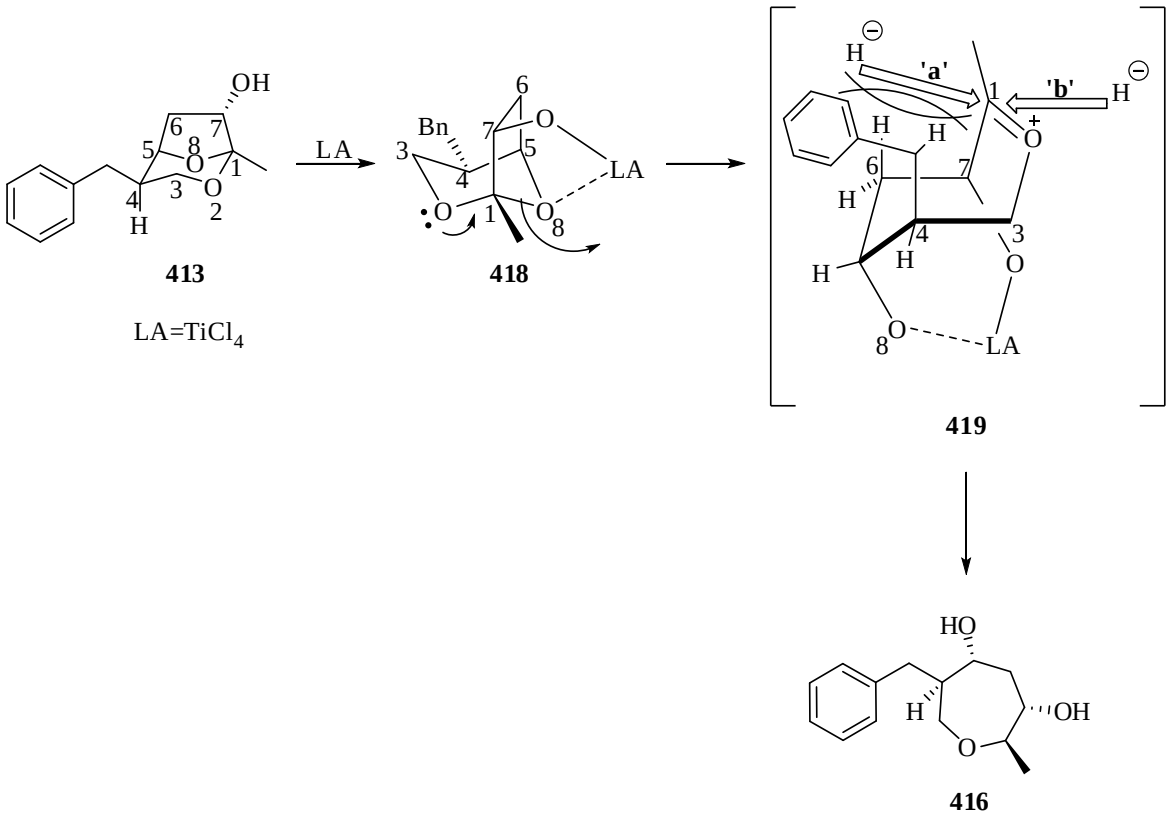


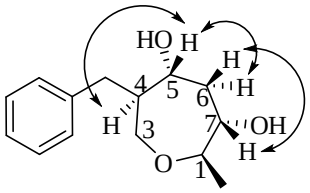
Figure 7.4

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

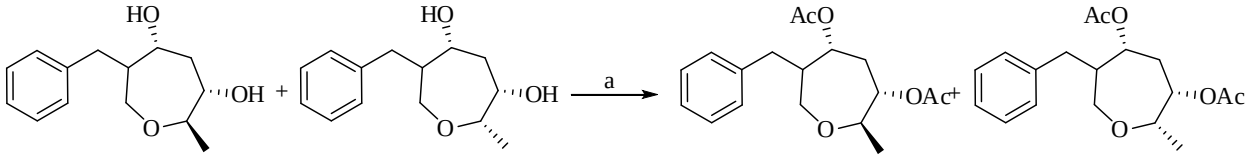


416

Figure 7.5

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).



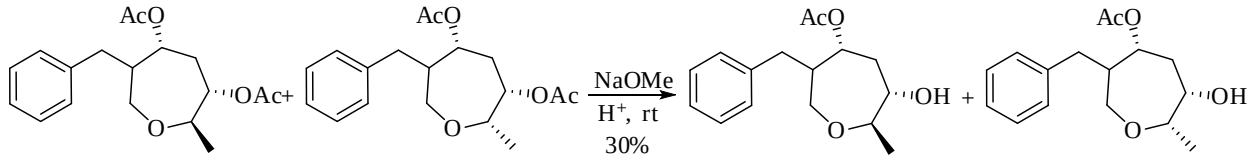
416 **417** **420** **421**

(a) Ac_2O, Et_3N, DMAP, DCM, rt, 4 h, 55% (86:14)

Scheme 7.20

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).

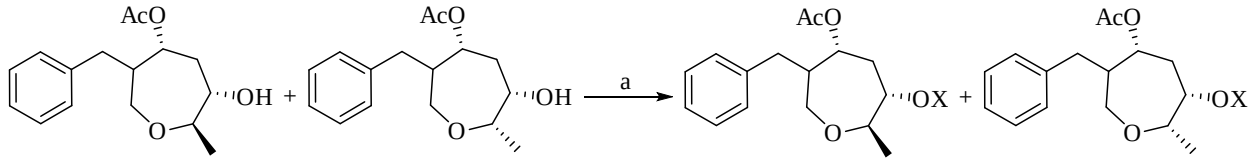


420 **421** **422** **423**

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 (Et_3N) 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).



422 **423** **424** **425**

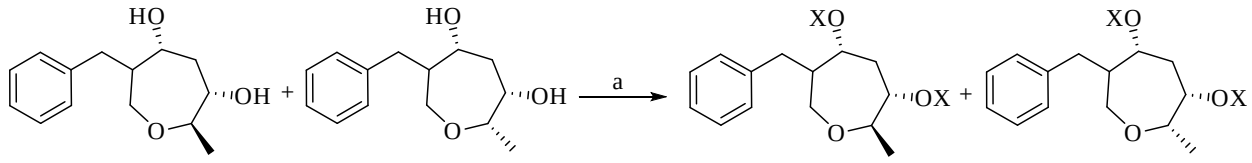
X= 4-bromobenzoyl

(a) 4-bromobenzoylchloride, Et_3N, DMAP, DCM, rt, 4 h, 60%

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_3N), dimethylaminopyridine (DMAP) and 4-bromobenzoylchloride successively to the alcohols **416** and **417** in DCM gave the bisbenzoate derivative mixtures **426** and **427** in 68% yield (Scheme 7.23).



416 **417** **426** **427**

(a) 4-bromobenzoylchloride, Et_3N, DMAP, DCM, rt, 4 h, 68%

X = 4-bromobenzoyl

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.

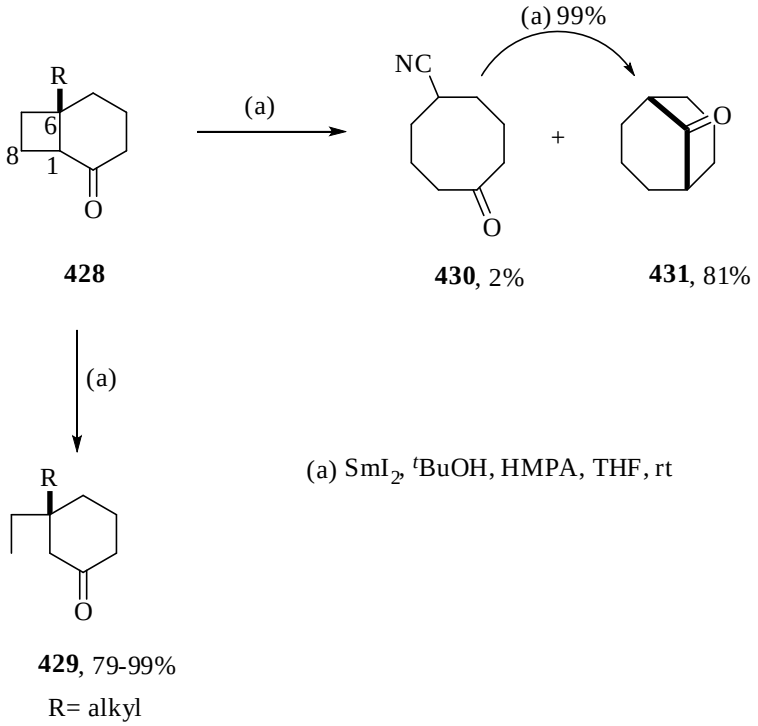
More importantly, the bisbenzoate mixtures **426** and **427** were obtained as solids. However, efforts to grow crystals suitable for X-ray analysis have proven to be unsuccessful and

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

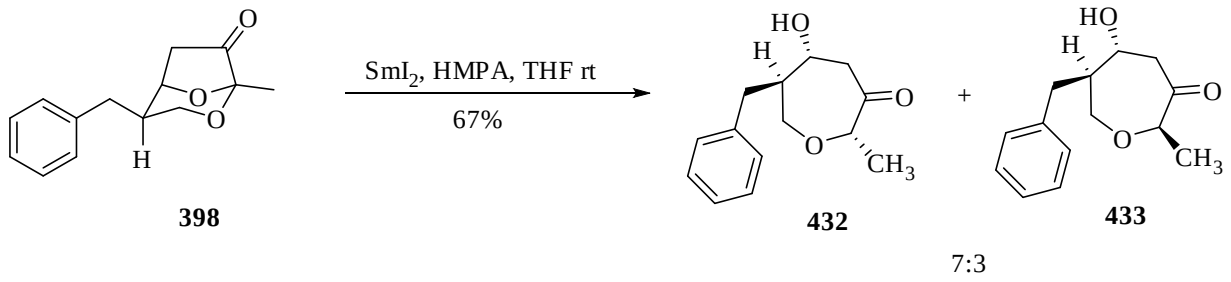
Samarium (II) iodide (SmI_2) is a powerful one-electron reducing agent, which has found widespread applications. For example, this reagent has been utilised for the reduction of carbonyl compounds and the ring opening of cyclic ethers.[8] In 2003, Kakiuchi *et al* highlighted the usefulness of samarium (II) iodide in regioselective radical ring-opening of bicyclo[4.2.0]octan-2-ones (Scheme 7.24).[9]



Scheme 7.24

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 SmI_2 reagent led to a near quantitative conversion of **430** into **431**.

Considering this, it was decided to explore the use of the SmI_2 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 SmI_2 reagent as the commercially available material decomposed readily during an attempt to syringe an aliquot. Therefore, a solution of freshly prepared SmI_2 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).



398 **432** **433**

7:3

Scheme 7.25

Following work-up and analysis of the ^{1}H 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 ^{1}H NMR spectrum and GCMS data obtained on the purified mixtures are shown in Figure 7.6 and 7.7 (A,B and C) respectively.

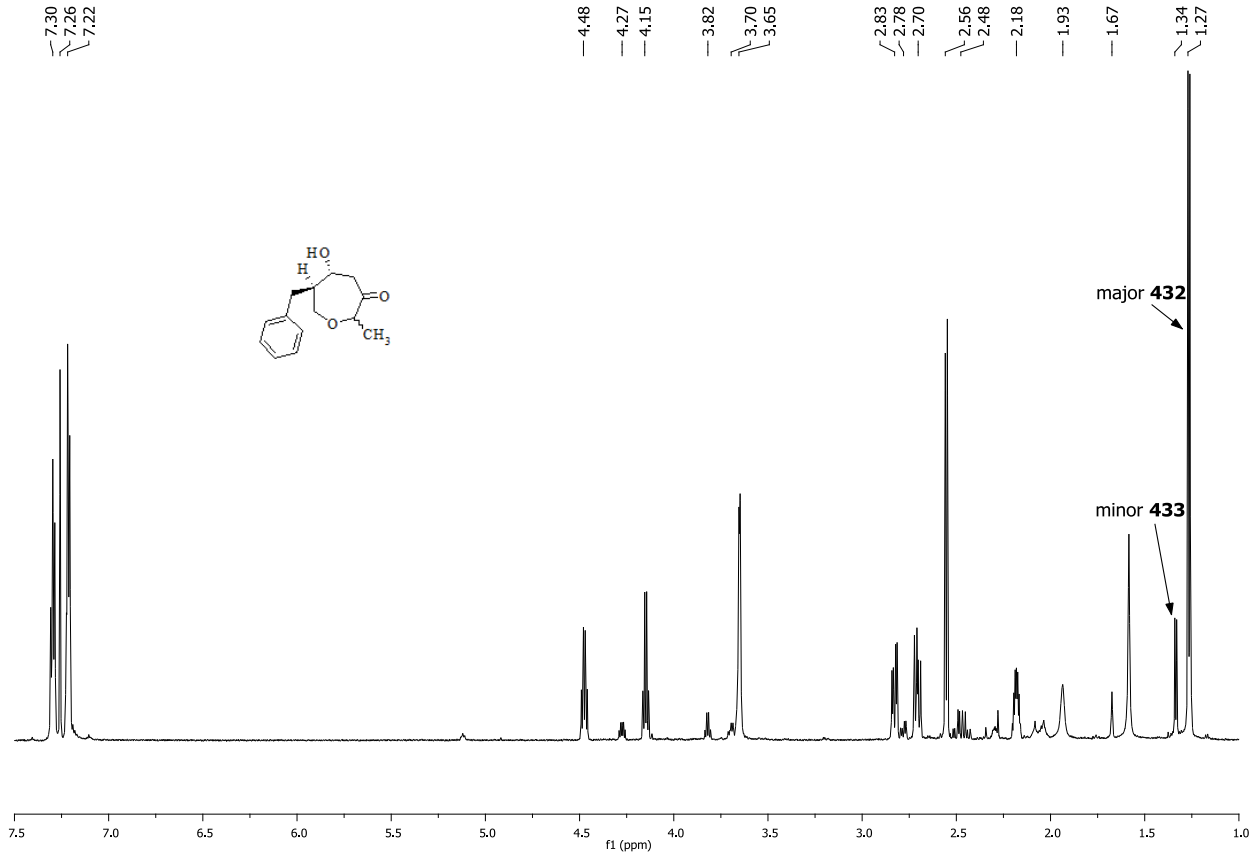


Figure 7.6

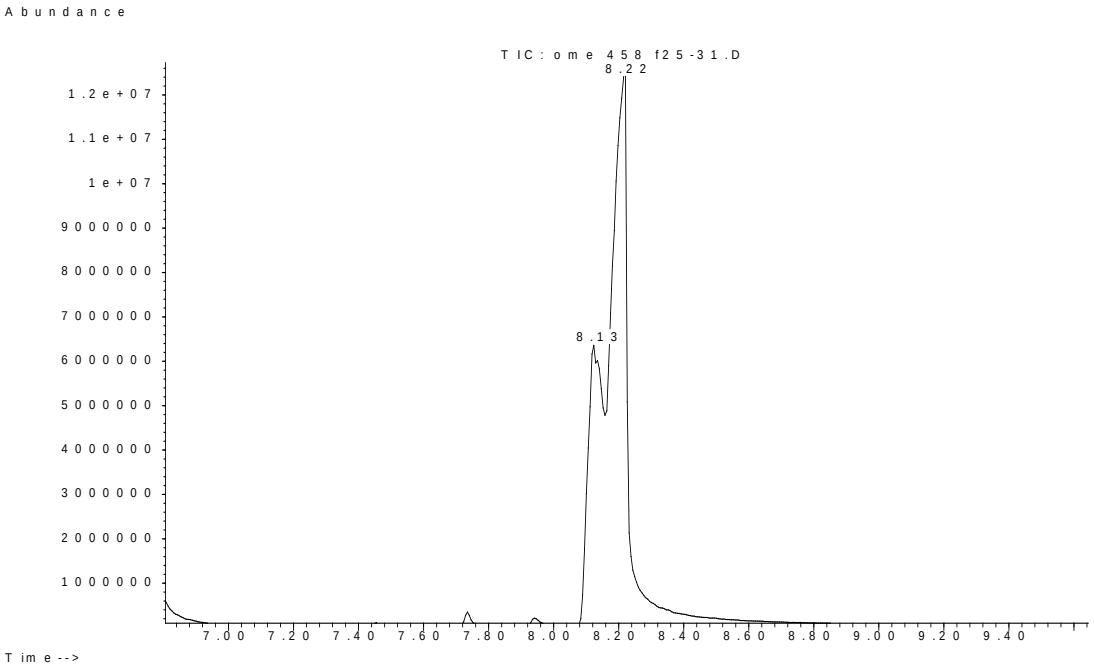


Figure 7.7A

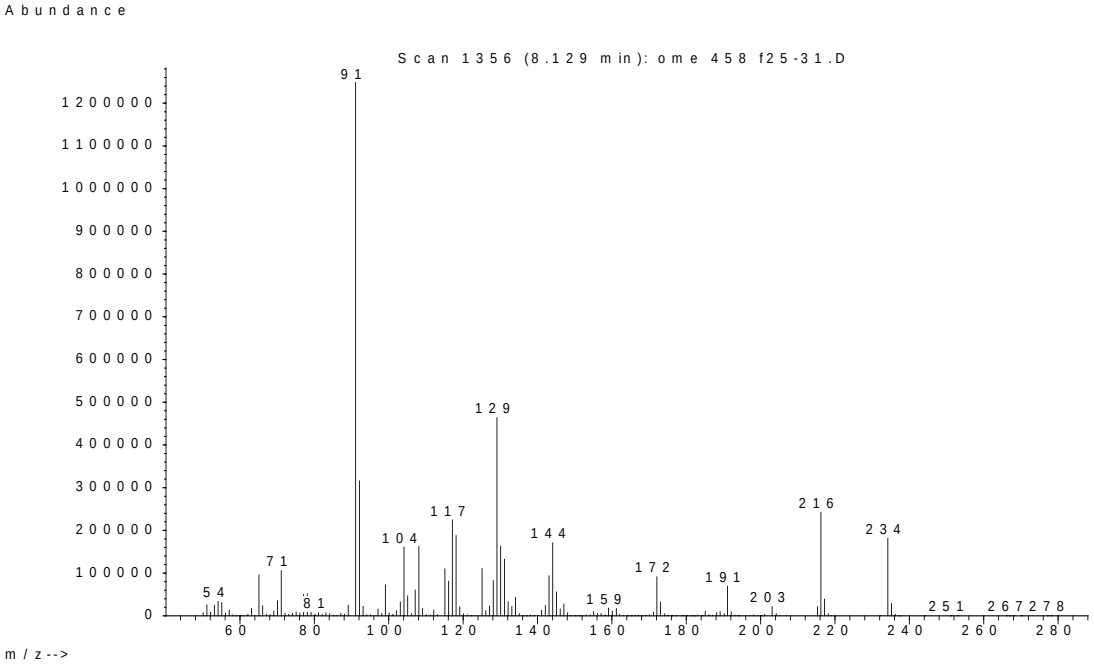
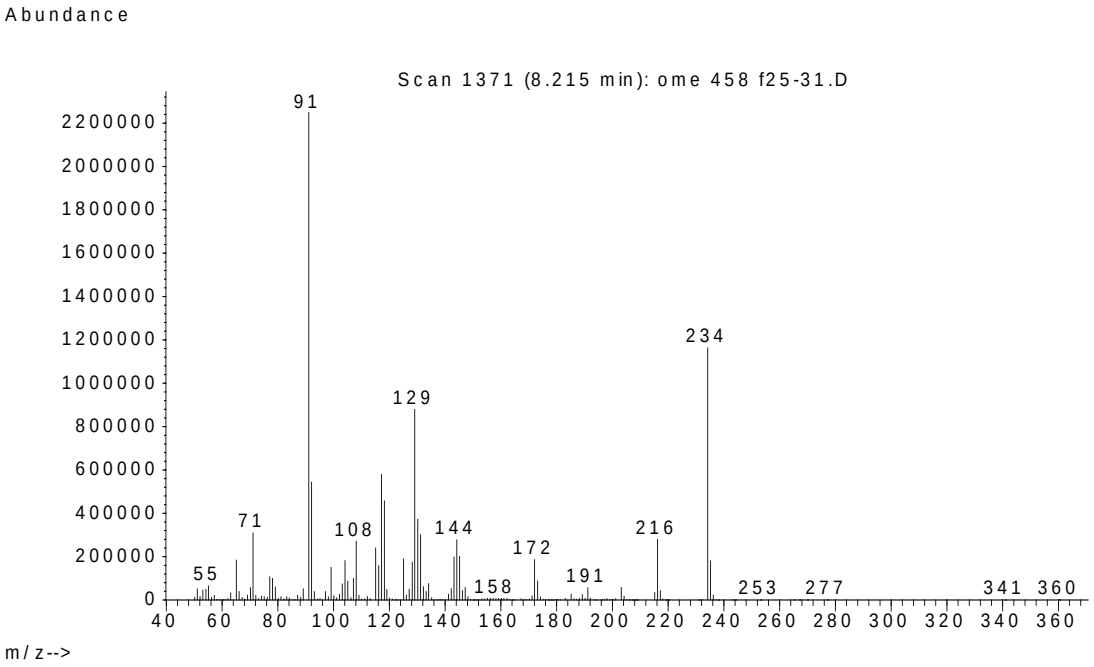


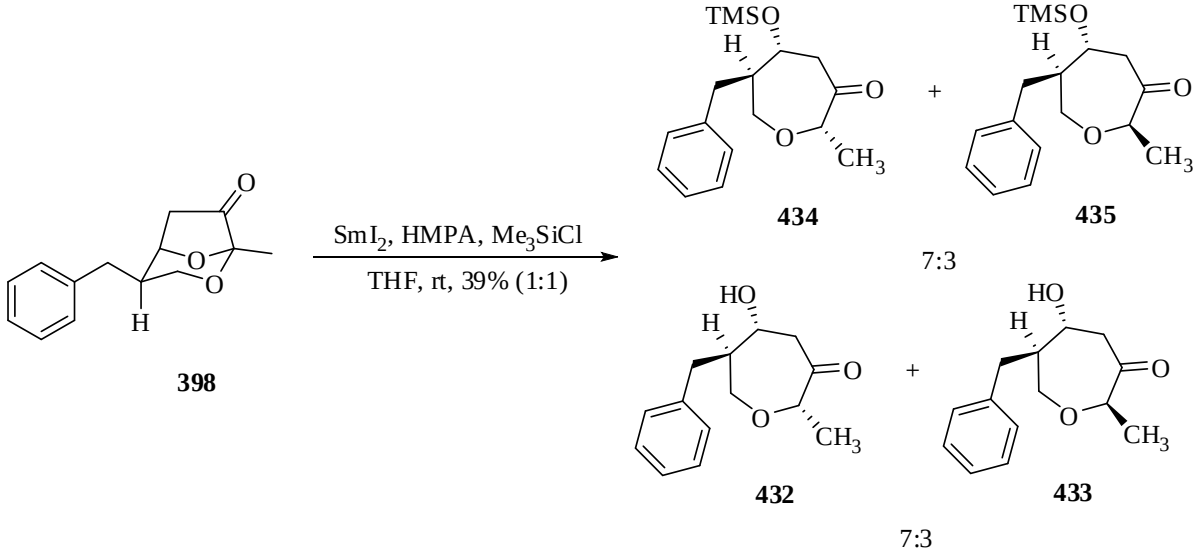
Figure 7.7B



peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	8.129	1340	1356	1361	BV	6219031	194002648	42.61%	29.880%
2	8.215	1361	1371	1452	VB	12319729	455277137	100.00%	70.120%

Figure 7.7C

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-C*H*$_3$ 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 $C_{14}H_{17}O_3$ (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 SmI_2 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 SmI_2 was unsuccessful due to the limiting solubility of samarium. While the use of a freshly prepared 0.1 M solution of SmI_2 without the addition of HMPA led to a complex mixture of products which proved difficult to identify. Furthermore, attempts to accelerate[10] the reaction by the addition of trimethylsilylchloride (Me_3SiCl) 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

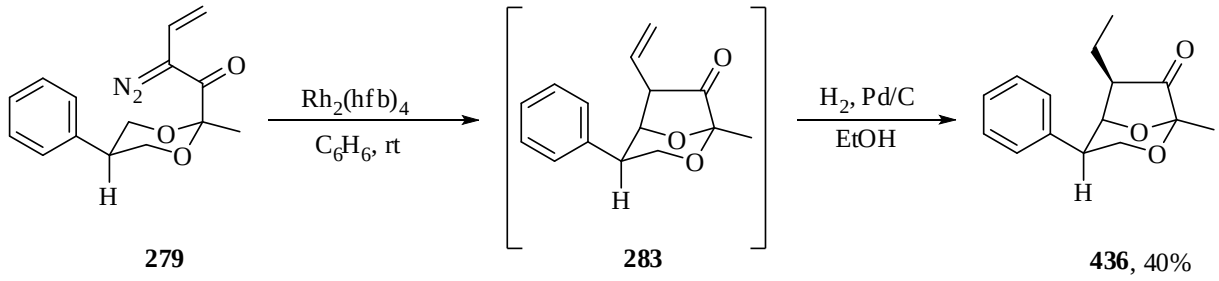
The silylated **434**, **435** / unsilylated **432**, **433** derivatives were obtained in a combined yield of 39% as a 1:1 ratio. Evidence for the formation of the major silylated derivative **434** obtained from analytical and spectroscopic data was satisfactory. As before, data for the minor silylated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

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).

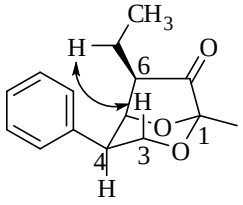


279 **283** **436**, 40%

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 ^1H NMR spectra. The IR showed the disappearance of the signal at 2082 cm^{-1} attributed to the diazo functionality and the ^1H 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

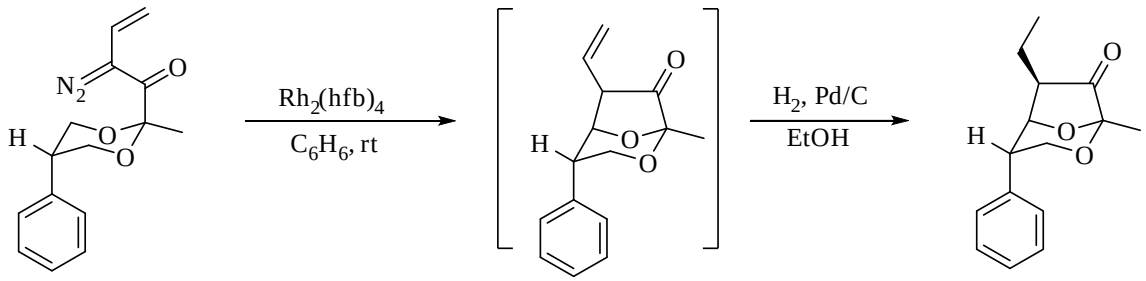
in particular the NOESY experiment which showed correlation between the 6-C*H*$_2$CH$_3$ proton and the axial 3-*H* proton, suggesting that these protons are on the same side of the molecule (Figure 7.8).



436

Figure 7.8

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

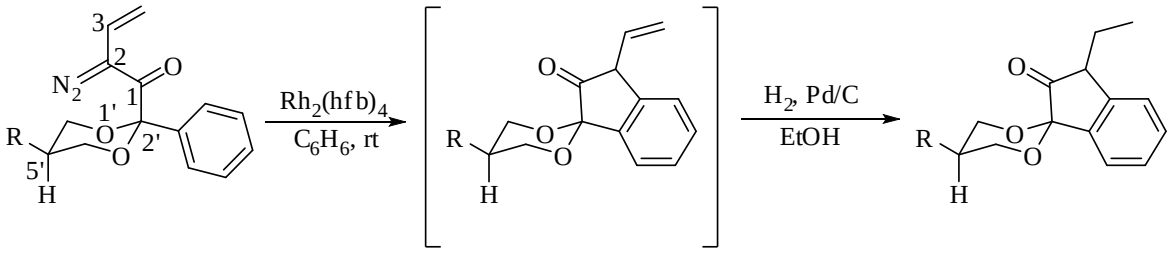


280 **321** **437**, 37%

Scheme 7.28

Satisfactory analytical and spectroscopic evidence was obtained for the bicyclicketone **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).



281, R=Ph
282, R=Bn

438, R=Ph
439 R=Bn

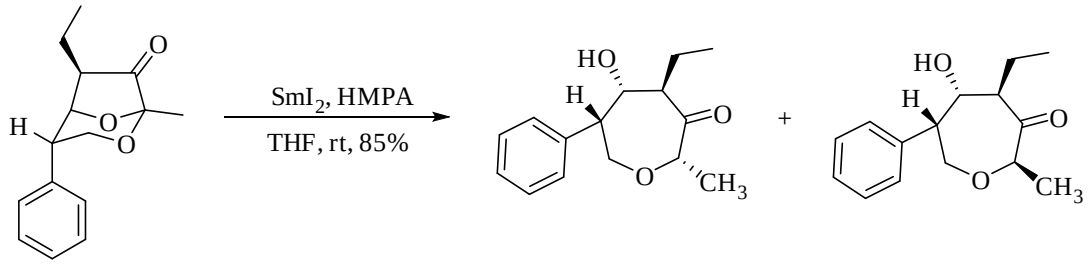
440, R=Ph, 41%
441, R=Bn, 25%

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 bicyclicketones, 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).



437

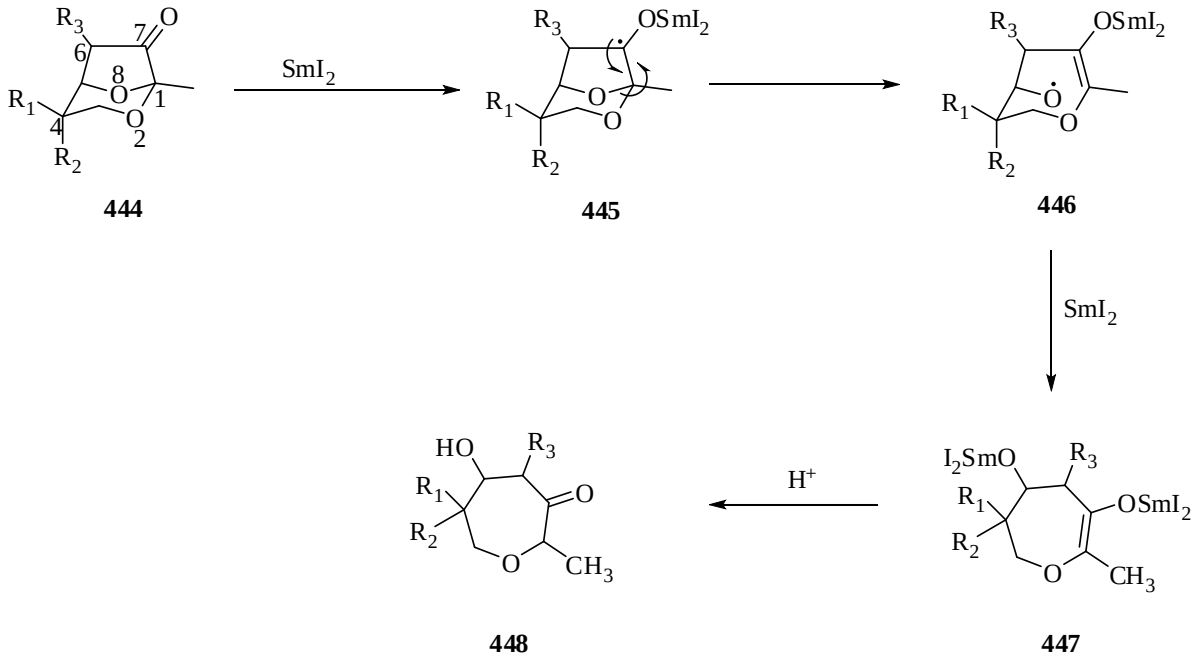
442

443

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).



444 **445** **446** **447** **448**

Scheme 7.31

A one electron transfer from SmI_2 to bicyclicketone **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.

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.

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.

7.7 References

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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 hinderance 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.

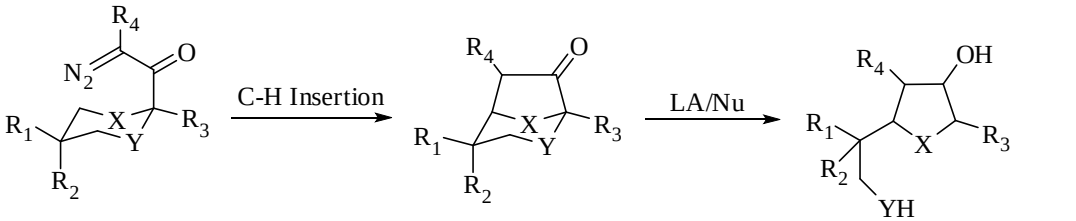
Initial efforts aimed at forcing the diazo ketones to undergo C-H insertion at elevated temperatures resulted in an unprecedented rearrangement of the acetal skeletal framework providing a novel synthesis of Barceloneic lactones previously isolated from a fungus of the genus *Phoma* during a screen for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

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).



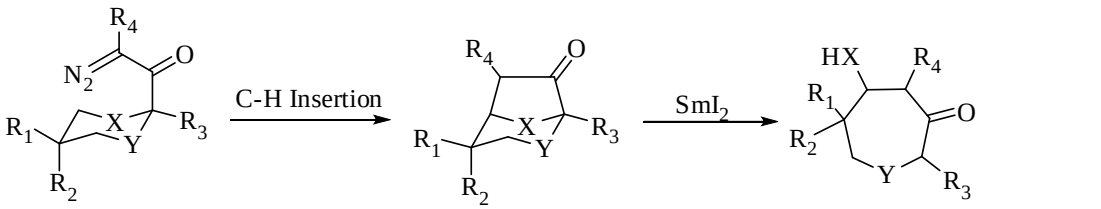
X=Y: O, N, S
X=Y: O, N, S
R_1,R_2,R_3,R_4= alkyl, aryl

2,3,4,5-tetrasubstituted heterocycle

Scheme 8.1

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).



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 ^{o}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^{TM} 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 δ (ppm) (number of protons, multiplicity, coupling constant *J* (Hz), assignment). The residual protic solvent was used as the internal reference: $CHCl_3$ δ_H = 7.26 ppm; δ_C = 77.0 ppm: CH_3OH δ_H = 3.41 ppm, 1.09 ppm; δ_C = 49.9 ppm. Assignment and determination of stereochemistry were realised using DEPT, COSY, HSQC, HMBC and NOESY experiments.

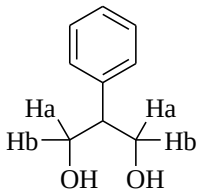
Mass spectrometry

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.

9.2 Experimental details

2-Phenylpropane-1,3 -diol (141) :

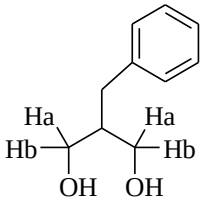
A cooled suspension of lithium aluminium hydride (8.03 g, 211 mmol) in Et_2O (240 ml) at 0 ^oC was treated dropwise with a solution of phenyl diethyl malonate (9.10 ml, 42.3 mmol) in Et_2O (50.0 ml). After stirring for 3 h at room temperature, the reaction mixture was cooled in an external ice bath and treated successively by the dropwise addition of 8.00 ml of H_2O, 8.00 ml of aqueous NaOH 15% and 24.0 ml of H_2O. 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 ^oC (lit.[1] 53 ^oC). ν_{max} (ATR) : 3440-2990 (***OH*** br),1260, 1037, 744, 699 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 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-$\boldsymbol{H}_a$, 3-$\boldsymbol{H}_a$), 3.91 (2H, dd, *J* 7.6, 5.4, 1-$\boldsymbol{H}_b$, 3-$\boldsymbol{H}_b$), 3.30-3.25 (1H, m, 2-***H***), 2.64 (2H, bs, 2 × O***H***). δ_C (125 MHz; $CDCl_3$) : 139.2 (***C***-1'), 128.8 (Ar-***C***), 128.0 (Ar-***C***), 121.2 (Ar-***C***), 66.0 (***C***-1, ***C***-3), 49.7 (***C***-2). *m/z* (EI) : 121 (M^+-CH_2OH, 50%), 103 (M^+-CH_2OH-OH, 100), 91 (M^+-2 × CH_2OH, 50), 77 ($C_6H_5^+$, 80).

2-Benzylpropane-1,3 -diol (143) :

A cooled suspension of lithium aluminium hydride (10.0 g, 264 mmol) in Et_2O (250 ml) at 0 ^oC was treated dropwise with a solution of benzyl diethyl malonate (15.5 ml, 66.0 mmol) in Et_2O (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 H_2O, 10.0 ml of aqueous NaOH 15% and 30.0 ml of H_2O. 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). ν_{max} (ATR) : 3440-2980 (***OH*** br),1260, 1037, 744, 699 cm^{-1}. δ_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-$\boldsymbol{H}_a$, 3-$\boldsymbol{H}_a$), 3.75 (2H, dd, *J* 10.5, 6.8, 1-$\boldsymbol{H}_b$, 3-$\boldsymbol{H}_b$), 2.70 (2H, d, *J* 7.8, 2-C$\boldsymbol{H}_2$Ph**)**, 2.31 (2H, bs, 2 × O***H***), 2.15 (1H, m, 2-***H***). δ_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-***C***H_2Ph). *m/z* (ES^+) : 189.1 ($[M+Na]^+$, 100%). ^{1}H NMR spectra data for **2** was consistent with that previously reported[2].

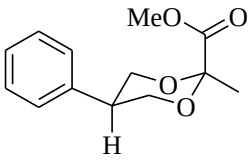
Typical procedure for ester acetal synthesis from methyl pyruvate (A1) :

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_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. 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) :

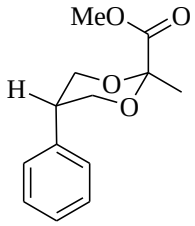
Similar to procedure **A1**, methyl pyruvate (6.00 ml, 66.0 mmol) and boron trifluoride diethyletherate ($BF_3.OEt_2$, 8.10 ml, 66.0 mmol) were combined with 2-phenylpropane-1,3-diol **141** (5.00 g, 33.0 mmol) to afford a 8:2 mixture of isomeric ester acetals. Separation by flash column chromatography (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.

Major isomer **145** :



mp.: 65-67 °C. ν_{max} (ATR) : 2923-2845, 1742 (***C*=*O***), 1103, 1078, 724, 659 cm^{-1}. δ_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-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 3.95 (3H, s, OC$\boldsymbol{H}_3$), 3.95 (2H, t, *J* 11.7, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 3.30-3.20 (1H, m, 5-***H***), 1.60 (3H, s, 2-C$\boldsymbol{H}_3$). δ_C (100.5 MHz; $CDCl_3$) : 171.0 (***C***=O), 137.1 (***C***-1'), 128.7 (Ar-***C***), 127.55 (Ar-***C***), 127.5 (Ar-***C***), 98.1 (***C***-2), 68.1 (***C***-4, ***C***-6), 52.6 (***C***H_3O), 39.9 (***C***-5), 26.0 (2-***C***H_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** :



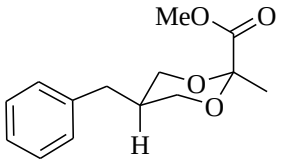
mp.: 55-57 °C. δ_H (400 MHz; $CDCl_3$) : 7.45-7.40 (2H, m, Ar-***H***), 7.35-7.20 (3H, m, Ar-***H***), 4.25 (2H, dd, *J* 12.1, 3.3, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 4.10 (2H, dd, *J* 12.1, 2.0, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 3.80 (3H, s, OC$\boldsymbol{H}_3$), 2.80-2.70 (1H, m, 5-***H***), 1.60 (3H, s, 2-C$\boldsymbol{H}_3$). δ_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 (***C***H_3O), 37.9 (***C***-5), 24.1 (2-***C***H_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

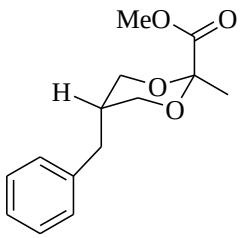
chromatography (cyclohexane/EtOAc : 95/5 then 9/1) afforded the title ester acetals **147** and **148** as an inseparable mixture (7:3 ratio, 7.90 g, 85%).
However, a very small pure sample of each isomer was obtained and used for analysis.

Major isomer **147** :



ν_{max} (ATR) : 3030-2853, 1741 (***C*=*O***), 1261, 1216, 1187, 1139, 1113, 1033, 760, 735, 699, 675 cm^{-1}. δ_H (400 MHz; $CDCl_3$) : 7.35-7.20 (3H, m, Ar-***H***), 7.10 (2H, d, *J* 7.4, Ar-***H***), 3.83 (3H, s, OC***H***$_3$), 3.80 (2H, dd, *J* 11.5, 4.4, 4-***H***$_{eq}$, 6-***H***$_{eq}$), 3.50 (2H, t, *J* 11.5, 4-***H***$_{ax}$, 6-***H***$_{ax}$), 2.40-2.30 (3H, m, 5-***H***, 5-C***H***$_2$Ph), 1.50 (3H, s, 2-C***H***$_3$). δ_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 (***C***H_3O), 35.1 (***C***-5), 34.8 (5-***C***H_2Ph), 26.1 (2-***C***H_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 ($C_{14}H_{18}O_4Na$ requires $[M+Na]^+$ 273.1097).

Minor isomer **148** :



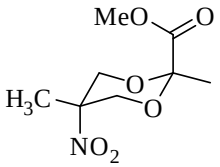
δ_H (400 MHz; $CDCl_3$) : 7.35-7.20 (5H, m, Ar-***H***), 3.95-3.90 (2H, m, 4-***H***$_{eq}$, 6-***H***$_{eq}$), 3.81 (3H, s, OC***H***$_3$), 3.78 (2H, d, *J* 11.0, 4-***H***$_{ax}$, 6-***H***$_{ax}$), 3.00 (2H, d, *J* 8.0, 5-C***H***$_2$Ph), 1.70-1.60 (1H, m, 5-***H***), 1.57 (3H, s, 2-C***H***$_3$). δ_C (100.5 MHz; $CDCl_3$) : 171.3 (***C***O), 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 (***C***H_3O), 35.4 (***C***-5), 35.3 (5-***C***H_2Ph), 26.0 (2-***C***H_3). *m/z* (EI) : 235 (M^+-Me, 6%), 191 (M^+-COOMe, 88), 131 (100), 117

(30), 91 ($PhCH_2^+$, 90), 65 (28). HRMS (ES^+) found: 273.1095 ($C_{14}H_{18}O_4Na$ requires $[M+Na]^+$ 273.1097).

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

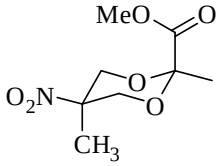
Similar to procedure **A1**, methyl pyruvate (6.70 ml, 74.1 mmol) and boron trifluoride diethyletherate ($BF_3.OEt_2$, 9.40 ml, 74.1 mmol) were combined with 2-methyl-2-nitropropane-1,3-diol (5.00 g, 37.1 mmol) to afford an 8.6:1 mixture of C-5 diastereoisomeric ester acetals. Separation by flash column 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** :



mp.: 80-81 ^oC. ν_{max} (ATR) : 2882, 1738 (***C*=*O***), 1550+1349 (**NO_2**), 1270, 1213, 1184, 1122, 1077, 1048, 880, 803, 665, 572 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 4.70 (2H, d, *J* 13.3, 4-***H***$_{eq}$, 6-***H***$_{eq}$), 3.85 (2H, d, *J* 13.3, 4-***H***$_{ax}$, 6-***H***$_{ax}$), 3.84 (3H, s, OC***H***$_3$), 1.50 (3H, s, 2-C***H***$_3$), 1.35 (3H, s, 5-C***H***$_3$). δ_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 (***C***H_3O), 25.2 (2-***C***H_3), 19.5 (5-***C***H_3). *m/z* (ES^+) : 242 ($[M+Na]^+$, 100%), 220 ($[M+H]^+$, 50). Anal. [Found: C, 43.9; H, 6.0; N, 6.1. $C_8H_{13}O_6N$ requires C, 43.8; H, 6.0; N, 6.4%].

Minor isomer **150** :



mp.: 80-81 ^oC. ν_{max} (ATR) : 2955, 1738 (***C*=*O***), 1534+1353 (**NO_2**), 1281, 1227, 1189, 1127, 1081, 1051, 967, 889, 807, 750 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 4.15 (2H, d, *J* 11.7, 4-***H***$_{eq}$, 6-***H***$_{eq}$), 4.05 (2H, d, *J* 11.7, 4-***H***$_{ax}$, 6-***H***$_{ax}$), 3.84 (3H, s, OC***H***$_3$), 1.84 (3H, s, 5-C***H***$_3$), 1.57 (3H, s, 2-

C***H***$_3$). δ_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 (***C***H_3O), 24.5 (2-***C***H_3), 21.5 (5-***C***H_3). *m/z* (ES^+) : 283 ($[M+Na+CH_3CN]^+$, 90%), 242 ($[M+Na]^+$, 30). Anal. [Found: C, 43.9; H, 6.0; N, 6.3. $C_8H_{13}O_6N$ requires C, 43.8; H, 6.0; N, 6.4%].

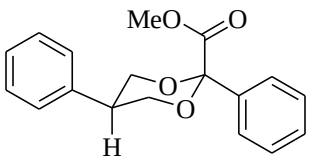
Typical procedure for ester acetal synthesis from methyl benzoylformate (A2) :

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%).

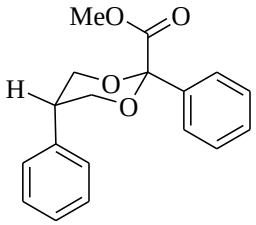
Major isomer **151** :



mp.: 115-116 ^oC. ν_{max} (ATR) : 2995-2865, 1737 (***C=O***), 1452, 1237, 1092, 810, 724, 610 cm^{-1}. δ_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***$_{eq}$, 6-

H$_{eq}$), 4.10 (2H, t, *J* 11.6, 4-***H***$_{ax}$, 6-***H***$_{ax}$), 3.82 (3H, s, OC***H***$_3$), 3.37-3.31 (1H, m, 5-***H***). δ_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 (***C***H_3O), 40.1 (***C***-5). *m/z* (ES^+) : 362 ($[M+Na+CH_3CN]^+$, 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** :

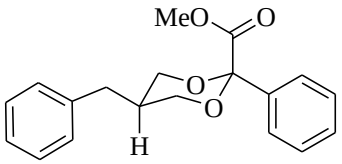


mp.: 106-107 ^oC. ν_{max} (ATR) : 2864, 1737 (***C=O***), 1495, 1227, 1054, 942, 810, 745, 722, 696, 664 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.69 (2H, d, *J* 6.9, Ar-***H***), 7.49-7.42 (3H, m, Ar-***H***), 7.28-7.21 (3H, m, Ar-***H***), 7.11 (2H, d, *J* 7.0, Ar-***H***), 4.25 (2H, dd, *J* 11.8, 4.5, 4-***H***$_{ax}$, 6-***H***$_{ax}$), 4.05 (2H, t, *J* 11.8, 4-***H***$_{eq}$, 6-***H***$_{eq}$), 3.78 (3H, s, OC***H***$_3$), 3.27-3.22 (1H, m, 5-***H***). δ_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 (***C***H_3O), 40.1 (***C***-5). *m/z* (ES^+) : 619 ($[2M+Na]^+$, 100%), 362 ($[M+Na+CH_3CN]^+$, 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) :

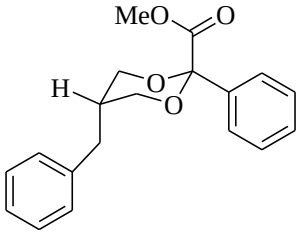
Similar to procedure **A2**, methyl benzoylformate (3.70 ml, 26.3 mmol) and boron trifluoride diethyletherate ($BF_3.OEt_2$, 3.30 ml, 26.3 mmol) were combined with 2-benzylpropane-1,3-diol **143** (2.18 g, 13.1 mmol) to afford a 1.5:1 mixture of isomeric ester acetals. Separation by flash column chromatography (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%).

Major isomer **153** :



mp.: 105-106 °C. ν_{max} (ATR) : 2879, 1734 (***C*=*O***), 1496, 1452, 1243, 1188, 1135, 1020, 980, 808, 725, 678 cm^{-1}. δ_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-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 3.75 (3H, s, OC$\boldsymbol{H}_3$), 3.69 (2H, t, *J* 11.5, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 2.50 (2H, d, *J* 7.7, 5-C$\boldsymbol{H}_2$Ph), 2.25-2.34 (1H, m, 5-***H***). δ_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 (***C***H_3O), 35.2 (***C***-5), 34.8 (5-***C***H_2Ph). *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** :



ν_{max} (ATR) : 2865, 1741 (***C*=*O***), 1493, 1451, 1247, 1182, 1128, 1021, 916, 807, 747, 697 cm^{-1}. δ_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, 3.6, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 3.78 (2H, dd, *J* 11.9, 5.8, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 3.73 (3H, s, OC$\boldsymbol{H}_3$), 2.67 (2H, d, *J* 7.8, 5-C$\boldsymbol{H}_2$Ph), 2.08 (1H, m, 5-***H***). δ_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 (***C***H_3O), 35.5 (***C***-5), 35.0 (5-***C***H_2Ph). *m/z* (ES^+) : 647 ($[2M+Na]^+$, 10%), 376 ($[M+Na+CH_3CN]^+$, 60), 313 ($[M+H]^+$, 90), 105 (100). HRMS (ES^+) found: 313.1434 ($C_{19}H_{21}O_4$ requires $[M+H]^+$ 313.1434).

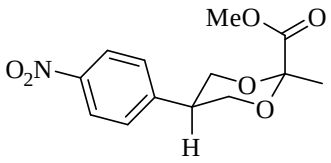
Typical procedure for nitration of ester acetal (A3) :

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 ^{o}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 $MgSO_4$ 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) :**

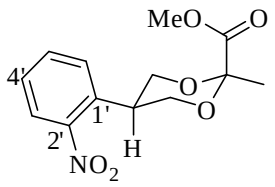
Similar to procedure **A3**, trifluoroacetic anhydride (11.9 ml, 84.4 mmol) was added to a solution of ester acetal **145** (4.98 g, 21.1 mmol) and ammonium nitrate (1.86 g, 23.2 mmol) in $CHCl_3$ (60.0 ml). The NMR of the crude reaction mixture showed the presence of two isomeric products **159** and **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** :



mp.: 119-121 ^{o}C. ν_{max} (ATR) : 2930, 2928, 2853, 1743 (***C*=*O***), 1514+1350 (***NO*$_2$**), 1142, 1053, 906, 726 cm^{-1}. δ_H (400 MHz; $CDCl_3$) : 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-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 3.90 (2H, t, *J* 11.2, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 3.85 (3H, s, OC$\boldsymbol{H}_3$), 3.40 (1H, dd, *J* 11.2, 4.6, 5-***H***), 1.60 (3H, s, 2-C$\boldsymbol{H}_3$). δ_C (100.5 MHz; $CDCl_3$) : 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 (***C***H_3O), 40.1 (***C***-5), 26.0 (2-***C***H_3). *m/z* (ES$^+$) : 304 ([M+Na]$^+$, 100%). Anal. [Found: C, 55.5; H, 5.4; N, 4.9. $C_{13}H_{15}NO_6$ requires C, 55.5; H, 5.4; N, 5.0%].

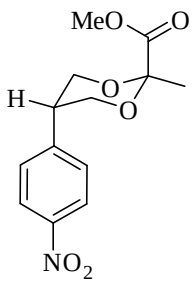
Isomer **160** :



mp.: 161-162 °C. ν_{max} (ATR) : 2872, 2377, 1978, 1734 (***C*=*O***), 1524+1350 (***NO₂***), 1269, 1216, 1131, 1043, 975, 886, 795, 726 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.79 (1H, d, *J* 8.0, 3'-***H***), 7.54 (1H, t, *J* 8.0, 5'-***H***), 7.40 (1H, t, *J* 8.0, 4'-***H***), 7.29 (1H, d, *J* 8.0, 6'-***H***), 4.14 (2H, dd, *J* 11.7, 4.6, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 3.96 (2H, t, *J* 11.7, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 3.89 (3H, s, OC$\boldsymbol{H}_3$), 3.75-3.70 (1H, m, 5-***H***), 1.59 (3H, s, 2-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 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 (***C***H_3O), 35.0 (***C***-5), 25.6 (2-***C***H_3). *m/z* (ES^+) : 345 ($[M+Na+CH_3CN]^+$, 20%), 287 (30), 246 (70), 180 (100). Anal. [Found: C, 55.6; H, 5.5; N, 4.9. $C_{13}H_{15}NO_6$ requires C, 55.5; H, 5.4; N, 5.0%].

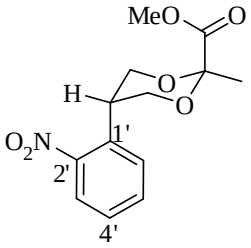
Minor isomer **161** :

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%).



mp.: 78-80 °C. ν_{max} (ATR) : 2940, 2932, 2860, 1742 (***C*=*O***), 1516+1346 (***NO*$_2$**), 1127, 1031, 909, 727 cm^{-1}. δ_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, OC***H***$_3$), 2.78 (1H, m, 5-***H***), 1.58 (3H, s, 2-C***H***$_3$). δ_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 (***C***H$_3$O), 38.2 (***C***-5), 26.0 (2-***C***H$_3$). *m/z* (ES$^+$) : 304 ([M+Na]$^+$, 100%). HRMS (ES$^+$) found: 304.0788 ($C_{13}H_{15}NO_6Na$ requires [M+Na]$^+$ 304.0792).

Isomer **162** :



mp.: 99-100 °C. ν_{max} (ATR) : 2999, 2949, 2878, 1740 (***C*=*O***), 1609, 1511+1339 (***NO*$_2$**), 1258, 1187, 1122, 1027, 970, 853, 743, 635 cm^{-1}. δ_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, OC***H***$_3$), 3.23-3.22 (1H, m, 5-***H***), 1.61 (3H, s, 2-C***H***$_3$). δ_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 (***C***H$_3$O), 32.9 (***C***-5), 25.8 (2-***C***H$_3$). *m/z* (ES$^+$) : 345 ([M+Na+CH_3CN]$^+$, 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) :

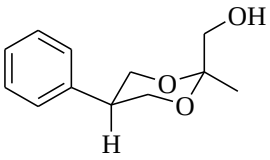
A solution of ester acetal (1 eq) in THF was cooled to -78 °C and DIBAL (3 eq, 1.0 M solution in toluene) was added. Upon complete addition, the reaction was maintained at this temperature for 2 h, then at room temperature for 1 h. It was then recooled to -78 °C, methanol was added and the resultant 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.

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

Major isomer **166** :

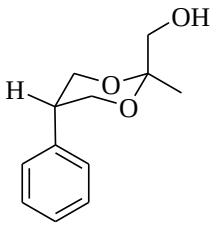
Similar to procedure **A4**, DIBAL (19.9 ml of a 1.0 M solution in toluene, 19.9 mmol) was added to a solution of **145** (1.56 g, 6.62 mmol) in THF (40.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal **166** (1.30 g, 95%) as a white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



mp.: 94-95 ^{o}C. ν_{max} (ATR) : 3390 (***OH***), 1175, 1130, 1050, 1021, 853, 670 cm^{-1}. δ_H (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'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.96 (2H, dd, *J* 12.0, 7.9, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.73 (2H, d, *J* 6.1, 1-$\boldsymbol{H}_2$), 3.01-2.96 (1H, m, 5'-***H***), 1.83 (1H, t, *J* 6.1, O***H***), 1.43 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (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'-***C***H_3). *m/z* (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.

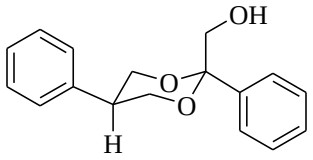


mp.: 74-76 °C. ν_{max} (ATR) : 3460 (***OH***), 1259, 1152, 1119, 1020, 948, 850, 764, 678 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.29-7.26 (3H, m, Ar-***H***), 7.16-7.14 (2H, m, Ar-***H***), 4.03 (2H, t, *J* 12.1, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.94 (2H, dd, *J* 12.1, 5.4, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.52 (2H, d, *J* 5.9, 1-$\boldsymbol{H}_2$), 3.17-3.11 (1H, m, 5'-***H***), 2.23 (1H, t, *J* 5.9, O***H***), 1.48 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 137.9 (***C***-1''), 128.8 (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'-***C***H_3). *m/z* (ES^+) : 272 ($[M+Na+CH_3CN]^+$, 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** :

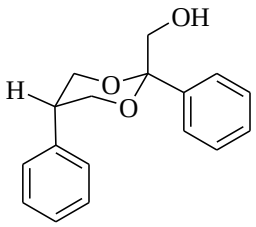
Similar to procedure **A4**, DIBAL (25.2 ml of a 1.0 M solution in toluene, 25.2 mmol) was added to a solution of **151** (2.50 g, 8.39 mmol) in THF (64.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal **168** (2.27 g, 100%) as a white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



mp.: 112-114 °C. ν_{max} (ATR) : 3567 (***OH***), 1407, 1439, 1345, 1243, 1162, 1006, 742, 695, 659 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 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'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 4.02 (2H, t, *J* 11.2, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.49 (2H, d, *J* 6.7, 1-$\boldsymbol{H}_2$), 2.47 (1H, m, 5'-***H***), 2.01 (1H, t, *J* 6.7, O***H***). δ_C (125 MHz; $CDCl_3$) : 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 ($[M+Na+CH_3CN]^+$, 70%), 293 ($[M+Na]^+$, 100), 288 ($[M+H_2O]^+$, 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.

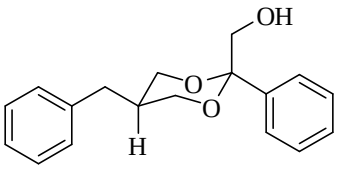


mp.: 98-100 °C. ν_{max} (ATR) : 3465 (***OH***), 1407, 1439, 1345, 1243, 1162, 1046, 742, 695, 659 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.56-7.54 (2H, m, Ar-***H***), 7.50 (2H, t, *J* 7.7, Ar-***H***), 7.45-7.42 (1H, m, Ar-***H***), 7.30-7.22 (3H, m, Ar-***H***), 7.03 (2H, d, *J* 7.2, Ar-***H***), 4.10 (2H, dd, *J* 11.6, 4.7, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.96 (2H, t, *J* 11.6, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.64 (2H, d, *J* 6.6, 1-$\boldsymbol{H}_2$), 3.43-3.36 (1H, m, 5'-***H***), 2.30 (1H, t, *J* 6.6, O***H***). δ_C (125 MHz; $CDCl_3$) : 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'), 41.0 (***C***-5'). *m/z* (ES^+) : 334 ($[M+Na+CH_3CN]^+$, 100%), 271 ($[M+H]^+$, 10). Anal. [Found: C, 75.5; H, 6.7. $C_{17}H_{18}O_3$ requires C, 75.5; H, 6.7%].

(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.

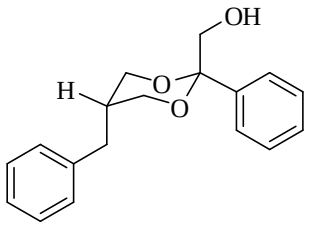


mp.: 85-87 °C. ν_{max} (ATR) : 3487 (***OH***), 1449, 1221, 1171, 1141, 1078, 1024, 857, 743, 698 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.46 (2H, t, *J* 7.7, Ar-***H***), 7.42 (2H, t, *J* 7.7, Ar-***H***), 7.36 (1H, t, *J* 7.7, Ar-***H***), 7.32 (2H, t, *J* 7.4, Ar-***H***), 7.25 (2H, d, *J* 7.4, Ar-***H***), 7.22 (1H, t, *J* 7.4, Ar-***H***), 3.95 (2H, d, *J* 11.7, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.75 (2H, d, *J* 11.7, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.59 (2H, bs, 1-$\boldsymbol{H}_2$), 3.14 (2H, d, *J* 7.9, 5'-C$\boldsymbol{H}_2$Ph), 2.10 (1H, bs, O***H***), 1.53 (1H, m, 5'-***H***). δ_C (175 MHz; $CDCl_3$) : 140.2 (Ar-***C***), 137.1 (Ar-***C***) 129.3 (Ar-***C***), 128.7 (Ar-***C***), 128.5 (2 × Ar-***C***), 127.6 (Ar-***C***), 126.1 (Ar-

C), 101.2 (***C***-2'), 70.8 (***C***-1), 63.9 (***C***-4', ***C***-6'), 35.9 (***C***-5'), 35.7 (5'-***C***H_2Ph). *m/z* (ES^+) : 348 ($[M+Na+CH_3CN]^+$, 10%), 307 ($[M+Na]^+$, 65), 137 (100). HRMS (ES^+) found: 285.1486 ($C_{18}H_{21}O_3$ requires $[M+H]^+$ 285.1485). Anal. [Found: C, 75.8; H, 7.0. $C_{18}H_{20}O_3$ 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.

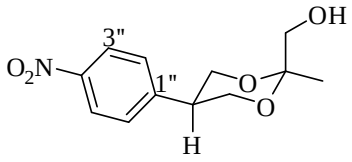


mp.: 106-107 ^oC. ν_{max} (ATR) : 3472 (***OH***), 1491, 1446, 1395, 1268, 1167, 1025, 758, 699, 610 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.45-7.42 (4H, m, Ar-***H***), 7.38-7.36 (1H, m, Ar-***H***), 7.25 (2H, t, *J* 7.2, Ar-***H***), 7.18 (1H, t, *J* 7.2, Ar-***H***), 7.05 (2H, d, *J* 7.2, Ar-***H***), 3.85 (2H, dd, *J* 11.7, 4.4, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.51-3.48 (4H, m, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$,1-$\boldsymbol{H}_2$), 2.45-2.38 (1H, m, 5'-***H***), 2.22 (2H, d, *J* 7.6, 5'-C$\boldsymbol{H}_2$Ph), 2.01 (1H, bs, O***H***). δ_C (175 MHz; $CDCl_3$) : 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'-***C***H_2Ph). *m/z* (ES^+) : 592 ($[2M+Na]^+$, 10%), 348 ($[M+Na+CH_3CN]^+$, 40), 285 ($[M+H]^+$, 100). HRMS (ES^+) found: 285.1485 ($C_{18}H_{21}O_3$ requires $[M+H]^+$ 285.1485).

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

Major isomer **172** :

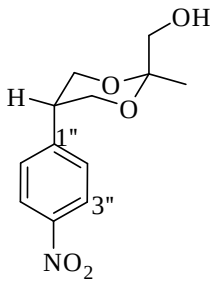
Similar to procedure **A4**, DIBAL (13.7 ml of a 1.0 M solution in hexane, 13.7 mmol) was added to a solution of **159** (1.28 g, 4.56 mmol) in THF (16.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal **172** (1.13 g, 98%) as a yellow 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; $CDCl_3$) : 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'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 4.02 (2H, dd, *J* 12.1, 4.5, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 3.67 (2H, d, *J* 6.5, 1-$\boldsymbol{H}_2$), 2.99-2.97 (1H, m, 5'-***H***), 1.84 (1H, t, *J* 6.5, O***H***), 1.52 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 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'-***C***H_3). *m/z* (ES^+) : 317 ($[M+Na+CH_3CN]^+$, 100%), 276 ($[M+Na]^+$, 40), 254 ($[M+H]^+$, 80). Anal. [Found: C, 56.9; H, 6.0; N, 5.5. $C_{12}H_{15}O_5N$ 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.

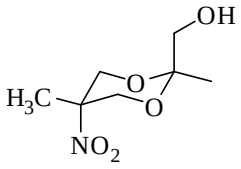


mp.: 58-59 °C. ν_{max} (ATR) : 3520-3310 (***OH***), 2872, 1737, 1601, 1513+1344 (***NO₂***), 1236, 1151, 1111, 1060, 938, 844, 744, 695 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 8.21 (2H, d, *J* 8.7, 3''-***H***), 7.41 (2H, d, *J* 8.7, 2''-***H***), 4.09 (2H, t, *J* 11.7, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 4.06 (2H, dd, *J* 11.7, 5.4, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.61 (2H, d, *J* 6.6, 1-$\boldsymbol{H}_2$), 3.33-3.29 (1H, m, 5'-***H***), 2.00 (1H, t, *J* 6.6, O***H***), 1.55 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 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'-***C***H_3). *m/z* (ES^+) : 317 ($[M+Na+CH_3CN]^+$, 100%), 276 ($[M+Na]^+$, 60). Anal. [Found: C, 56.6; H, 6.2; N, 5.1. $C_{12}H_{15}O_5N$ 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** :

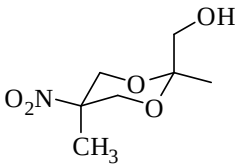
Similar to procedure **A4**, DIBAL (77.8 ml of a 1.0 M solution in hexane, 77.8 mmol) was added to a solution of **149** (4.68 g, 25.9 mmol) in THF (80.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title carbinol acetal **174** (4.01 g, 81%) as a white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



mp.: 62-63 °C. ν_{max} (ATR) : 3312 (***OH***), 2881, 1534+1346 (***NO₂***), 1445, 1279, 1173, 1084, 1058, 937, 847, 748, 663 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 4.45 (2H, d, *J* 12.3, 4'-***H***$_{eq}$, 6'-***H***$_{eq}$), 3.96 (2H, d, *J* 12.3, 4'-***H***$_{ax}$, 6'-***H***$_{ax}$), 3.65 (2H, d, *J* 6.6, 1-***H***$_2$), 1.72 (1H, t, *J* 6.6, O***H***), 1.66 (3H, s, 5'-C***H***$_3$), 1.42 (3H, s, 2'-C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 99.3 (***C***-2'), 82.1 (***C***-5'), 65.1 (***C***-4', ***C***-6'), 64.9 (***C***-1), 21.3 (5'-***C***H_3), 18.4 (2'-***C***H_3). *m/z* (ES^+) : 405 ($[2M+Na]^+$, 100%), 255 ($[M+Na+CH_3CN]^+$, 40). Anal. [Found: C, 43.9; H, 6.8; N, 7.3. $C_7H_{13}O_5N$ requires C, 44.0; H, 6.9; N, 7.3%].

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.



mp.: 122-123 °C. ν_{max} (ATR) : 3152 (***OH***), 2998, 2948, 2878, 1534+1347 (***NO₂***), 1445, 1253, 1190, 1148, 1101, 931, 850, 738, 668 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 4.65 (2H, d, *J* 13.1, 4'-***H***$_{eq}$, 6'-***H***$_{eq}$), 3.95 (2H, d, *J* 13.1, 4'-***H***$_{ax}$, 6'-***H***$_{ax}$), 3.49 (2H, d, *J* 6.7, 1-***H***$_2$), 1.82 (1H, t, *J* 6.7, O***H***), 1.46 (3H, s, 2'-C***H***$_3$), 1.42 (3H, s, 5'-C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 98.7 (***C***-2'), 83.1 (***C***-5'),

68.3 (***C***-1), 64.9 (***C***-4', ***C***-6'), 19.8 (5'-***C***H_3), 14.7 (2'-***C***H_3). *m/z* (ES^+) : 255 ($[M+Na+CH_3CN]^+$, 100%). Anal. [Found: C, 43.9; H, 6.8; N, 7.2. $C_7H_{13}O_5N$ requires C, 44.0; H, 6.9; N, 7.3%].

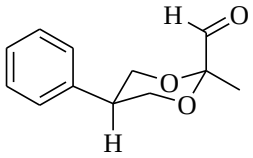
Typical procedure for aldehyde acetal synthesis (A5) :

To a stirred solution of oxalyl chloride (1.2 eq) in DCM maintained at -78 ^oC 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 ^oC 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 × 20.0 ml). The combined organic extracts were then washed with brine, dried using $MgSO_4$, 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.

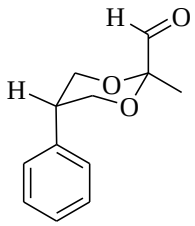


mp.: 41-42 ^oC. ν_{max} (ATR) : 1744 (***CHO***), 1604, 1515, 1218, 1133, 1049, 918, 795, 671 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 9.63 (1H, s, C***H***O), 7.28-7.24 (2H, m, Ar-***H***), 7.22-7.19 (1H, m, Ar-***H***), 7.08-7.05 (2H, m, Ar-***H***), 4.05 (2H, dd, *J* 12.0, 4.7, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 3.88 (2H, t, *J* 12.0, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 3.24-3.17 (1H, m, 5-***H***), 1.38 (3H, s, 2-C$\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 201.4 (***C***HO), 137.3 (***C***-1'), 129.1 (Ar-***C***), 127.9 (Ar-***C***), 127.8 (Ar-***C***), 99.8 (***C***-2), 68.3 (***C***-4, ***C***-6), 41.0 (***C***-5), 22.3 (2-***C***H_3). *m/z* (ES^+) : 453 ($[2M+CH_3CN]^+$, 100%), 437 (65), 261 (15), 217 (30), 104 (25). *m/z*

(EI) : 177 (M^+-CHO, 30 %), 117 (60), 77 (Ph^+, 30), 43 (100). Anal. [Found: C, 69.4; H, 6.8. $C_{12}H_{14}O_3$ 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.

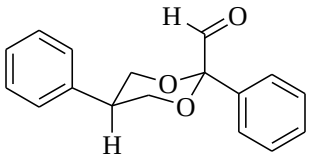


ν_{max} (ATR) : 1747 (***CHO***), 1604, 1495, 1453, 1374, 1051, 994, 865, 631 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 9.55 (1H, s, C***H***O), 7.42-7.40 (2H, m, Ar-***H***), 7.37-7.33 (2H, m, Ar-***H***), 7.31-7.27 (1H, m, Ar-***H***), 4.21 (2H, dd, *J* 12.0, 4.8, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 4.14 (2H, dd, *J* 12.0, 4.8, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 2.94-2.90 (1H, m, 5-***H***), 1.49 (3H, s, 2-C$\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 199.2 (***C***HO), 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-***C***H_3). *m/z* (ES^+) : 453 ($[2M+CH_3CN]^+$, 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** :

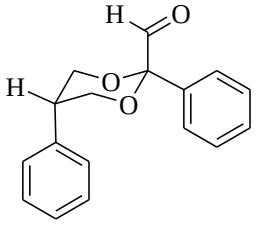
Similar to procedure **A5**, dimethylsulphoxide (0.55 ml, 7.56 mmol) was added to a solution of oxalyl chloride (0.30 ml, 3.78 mmol) in DCM (12.0 ml), then after a solution of **168** (0.85 g, 3.15 mmol) in DCM (5.00 ml) was added before finally adding triethylamine (2.10 ml, 14.8 mmol). Purification 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. ν_{max} (ATR) : 1729 (***CHO***), 1603, 1496, 1450, 1250, 1147, 1025, 854, 657 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 9.54 (1H, s, C***H***O), 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-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 4.17 (2H, t, *J* 11.7, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 3.31-3.25 (1H, m, 5-***H***). δ_C (125 MHz; $CDCl_3$) : 197.6 (***C***HO), 137.8 (Ar-***C***), 134.7 (Ar-***C***) 129.9 (Ar-***C***), 129.1 (Ar-***C***), 129.0 (Ar-***C***), 128.0 (Ar-***C***), 127.8 (Ar-***C***), 126.8 (Ar-***C***), 100.4 (***C***-2), 68.1 (***C***-4, ***C***-6), 41.1 (***C***-5). *m/z* (ES^+) : 291 ($[M+Na]^+$, 30%), 269 ($[M+H]^+$, 100). HRMS (ES^+) found: 269.1172 ($C_{17}H_{17}O_3$ requires $[M+H]^+$ 269.1172).

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.



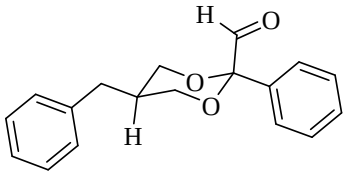
mp.: 83-86. ν_{max} (ATR) : 1727 (***CHO***), 1600, 1494, 1453, 1272, 1134, 1025, 915, 698 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 9.35 (1H, s, C***H***O), 7.62-7.56 (2H, m, Ar-***H***), 7.54-7.37 (3H, m, Ar-***H***), 7.33-7.20 (3H, m, Ar-***H***), 7.08-6.96 (2H, m, Ar-***H***), 4.21 (1H, dd, *J* 11.5, 4.6, 4-$\boldsymbol{H}_{ax}$), 4.16-4.10 (1H, m, 6-$\boldsymbol{H}_{ax}$), 4.05 (1H, t, *J* 11.5, 4-$\boldsymbol{H}_{eq}$), 3.97-3.83 (1H, m, 6-$\boldsymbol{H}_{eq}$), 3.43-3.34 (1H, m, 5-***H***). δ_C (125 MHz; $CDCl_3$) : 192.3 (***C***HO), 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),

40.8 (***C***-5). *m/z* (EI) : 239 (M^+-CHO, 100), 117 (40), 91 ($PhCH_2^+$, 5), 77 (Ph^+, 15). HRMS ($ASAP^+$) found: 269.1168 ($C_{17}H_{17}O_3$ requires $[M+H]^+$ 269.1172).

5-benzyl-2-phenyl-1,3-dioxane-2-carbaldehyde (180, 181) :

Major isomer **180** :

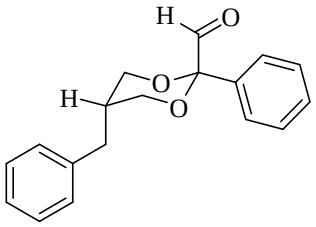
Similar to procedure **A5**, dimethylsulphoxide (1.86 ml, 26.3 mmol) was added to a solution of oxalyl chloride (1.15 ml, 13.1 mmol) in DCM (31.0 ml), then after a solution of **170** (3.11 g, 11.0 mmol) in DCM (20.0 ml) was added before finally adding triethylamine (7.18 ml, 51.5 mmol). Purification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



ν_{max} (ATR) : 1736 (***CHO***), 1451, 1253, 1145, 1028, 751, 698, 660 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 9.42 (1H, s, C***H***O), 7.54 (2H, d, *J* 7.4, Ar-***H***), 7.41 (2H, t, *J* 7.4, Ar-***H***), 7.38 (1H, t, *J* 7.4, Ar-***H***), 7.30 (2H, t, *J* 7.3, Ar-***H***), 7.22 (1H, t, *J* 7.3, Ar-***H***), 7.16 (2H, d, *J* 7.3, Ar-***H***), 4.08 (2H, dd, *J* 11.7, 4.0, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 3.79 (2H, dd, *J* 11.7, 7.7, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 2.67 (2H, d, *J* 7.7, 5-C***H***$_2$Ph), 2.17-2.12 (1H, m, 5-***H***). δ_C (175 MHz; $CDCl_3$) : 196.0 (***C***HO), 138.5 (Ar-***C***), 134.1 (Ar-***C***) 129.5 (Ar-***C***), 128.88 (Ar-***C***), 128.87 (Ar-***C***), 128.6 (Ar-***C***), 126.9 (Ar-***C***), 126.4 (Ar-***C***), 100.2 (***C***-2), 66.7 (***C***-4, ***C***-6), 36.0 (***C***-5), 34.9 (5-***C***H_2Ph). *m/z* (ES^+) : 305 ($[M+Na]^+$, 10%), 283 ($[M+H]^+$, 100). HRMS (ES^+) found: 283.1331 ($C_{18}H_{19}O_3$ requires $[M+H]^+$ 283.1332).

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.

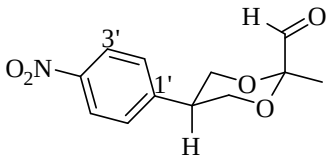


ν_{max} (ATR) : 1733 (***CHO***), 1371, 1231, 1134, 1027, 751, 701, 633 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 9.30 (1H, s, C***H***O), 7.54 (2H, d, *J* 7.1, Ar-***H***), 7.47 (2H, t, *J* 7.1, Ar-***H***), 7.43 (1H, t, *J* 7.1, Ar-***H***), 7.28 (2H, t, *J* 7.1, Ar-***H***), 7.21 (1H, t, *J* 7.1, Ar-***H***), 7.10 (2H, d, *J* 7.1, Ar-***H***), 4.01 (2H, dd, *J* 11.5, 4.1, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 3.69 (2H, t, *J* 11.5, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 2.47 (2H, d, *J* 7.8, 5-C$\boldsymbol{H}_2$Ph), 2.34-2.23 (1H, m, 5-***H***). δ_C (175 MHz; $CDCl_3$) : 193.6 (***C***HO), 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-***C***H_2Ph). *m/z* (ES^+) : 346 ($[M+Na+CH_3CN]^+$, 10%), 283 ($[M+H]^+$, 100). HRMS (ES^+) found: 283.1329 ($C_{18}H_{19}O_3$ requires $[M+H]^+$ 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.

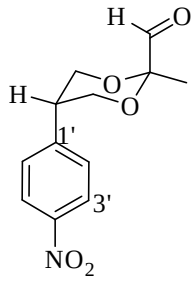


mp.: 98-99 °C. ν_{max} (ATR) : 2857, 1737 (***CHO***), 1602, 1511+1343 (***NO_2***), 1195, 1129, 1050, 1021, 919, 844, 769, 691 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 9.63 (1H, s, C***H***O), 8.15 (2H, d, *J* 8.6, 3'-***H***), 7.30 (2H, d, *J* 8.6, 2'-***H***), 4.11 (2H, dd, *J* 11.9, 4.7, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 3.94 (2H, t, *J* 11.9, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 3.38-3.34 (1H, m, 5-***H***), 1.43 (3H, s, 2-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 200.2 (***C***HO), 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-***C***H_3). *m/z* (ES^+) : 543 ($[2M+CH_3CN]^+$, 40%), 333 (100), 315

([M+Na+CH_3CN]$^+$, 30). Anal. [Found: C, 57.3; H, 5.2; N, 5.5. $C_{12}H_{13}O_5N$ 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.

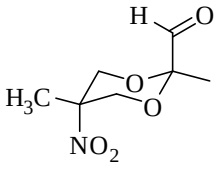


ν_{max} (ATR) : 2948, 1741 (***CHO***), 1601, 1514+1343 (***NO₂***), 1245, 1153, 1100, 1036, 919, 846, 770, 744, 696 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 9.61 (1H, s, C***H***O), 8.22 (2H, d, *J* 8.9, 2'-***H***), 7.68 (2H, d, *J* 8.9, 3'-***H***), 4.31 (2H, dd, *J* 12.4, 3.7, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 4.14 (2H, dd, *J* 12.4, 2.6, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 2.89-2.87 (1H, m, 5-***H***), 1.45 (3H, s, 2-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 199.5 (***C***HO), 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-***C***H_3). *m/z* (EI) : 236 (M$^+$-Me, 6%), 222 (M$^+$-CHO, 100), 207 (M$^+$-Me-CHO, 5), 116 (70), 91 ($PhCH_2^+$, 6), 77 (Ph^+, 15). *m/z* (ES$^+$) : 543 ([2M+CH_3CN]$^+$, 100%), 252 ([M+H]$^+$, 20). HRMS (ES$^+$) found: 252.0872 ($C_{12}H_{14}O_5N$ requires [M+H]$^+$ 252.0869).

2,5-dimethyl-5-nitro-1,3-dioxane-2-carbaldehyde (184, 185) :

Major isomer **184** :

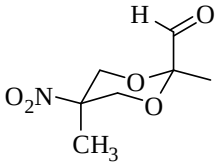
Similar to procedure **A5**, dimethylsulphoxide (3.00 ml, 42.2 mmol) was added to a solution of oxalyl chloride (1.85 ml, 21.1 mmol) in DCM (50.0 ml), thenafter a solution of **174** (3.36 g, 17.6 mmol) in DCM (50.0 ml) was added before finally adding triethylamine (11.6 ml, 82.7 mmol). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title aldehyde acetal **184** (2.64 g, 79%) as a white solid.



mp.: 47-48 °C. ν_{max} (ATR) : 2838, 1741 (***CHO***), 1543+1348 (***NO₂***), 1445, 1301, 1199, 1127, 1074, 1041, 900, 766, 628, 571 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 9.52 (1H, s, C***H***O), 4.72 (2H, d, *J* 12.9, 4-***H***$_{eq}$, 6-***H***$_{eq}$), 3.83 (2H, d, *J* 12.9, 4-***H***$_{ax}$, 6-***H***$_{ax}$), 1.35 (3H, s, 2-C***H***$_3$), 1.34 (3H, s, 5-C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 198.6 (***C***HO), 99.5 (***C***-2), 82.4 (***C***-5), 67.2 (***C***-4, ***C***-6), 21.3 (2-***C***H_3), 19.3 (5-***C***H_3). *m/z* (ES^+) : 533 (50%), 242 (100), 232 (30), 173 (60). Anal. [Found: C, 44.2; H,5.8; N, 7.3. $C_7H_{11}O_5N$ 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.



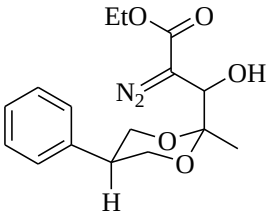
mp.: 49-50 °C. ν_{max} (ATR) : 2837, 1759 (***CHO***), 1541+1352 (***NO₂***), 1459, 1378, 1164, 1112, 1066, 1041, 990, 849, 759, 681 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 9.40 (1H, s, C***H***O), 4.35 (2H, d, *J* 12.3, 4-***H***$_{eq}$, 6-***H***$_{eq}$), 4.06 (2H, d, *J* 12.3, 4-***H***$_{ax}$, 6-***H***$_{ax}$), 1.71 (3H, s, 5-C***H***$_3$), 1.44 (3H, s, 2-C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 196.7 (***C***HO), 98.8 (***C***-2), 80.6 (***C***-5), 66.6 (***C***-4, ***C***-6), 20.8 (5-***C***H_3), 18.2 (2-***C***H_3). *m/z* (ES^+) : 419 ($[2M+CH_3CN]^+$, 100%), 401 ($[2M+Na]^+$, 30), 190 ($[M+H]^+$, 10). Anal. [Found: C, 44.0; H,6.2; N, 7.0. $C_7H_{11}O_5N$ requires C, 44.5; H, 5.9; N, 7.4%].

Typical procedure for diazoketol synthesis (A6) :

To a solution of ethyl diazoacetate (12 eq) in anhydrous CH_3CN 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_3CN and aldehyde acetal (10 eq) in anhydrous CH_3CN *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** :

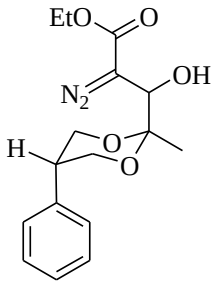
Similar to procedure **A6**, DBU (0.08 ml, 0.52 mmol) in anhydrous CH_3CN (6.00 ml) and **176** (1.06 g, 5.15 mmol) in CH_3CN (12.0 ml) were added successively to a solution of ethyl diazoacetate (0.65 ml, 6.17 mmol) in anhydrous CH_3CN (12.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol **194** (1.37 g, 86%) as a shiny yellow oil.



ν_{max} (ATR) : 3520-3410 (***OH*** br), 2980, 2875, 2096 (***C*=*N*₂**), 1683 (***C*=*O***), 1496, 1394, 1107, 1050, 870, 701 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.41 (2H, d, *J* 7.6, Ar-***H***), 7.35 (2H, t, *J* 7.6, Ar-***H***), 7.27 (1H, t, *J* 7.6, Ar-***H***), 4.85 (1H, bs, 3-***H***), 4.27 (2H, q, *J* 7.0, OC***H***$_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}$), 2.94-2.90 (1H, m, 5'-***H***), 2.84 (1H, bs, O***H***), 1.50 (3H, s, 2'-C***H***$_3$), 1.28 (3H, t, *J* 7.0, OCH_2C***H***$_3$). δ_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 (O***C***H_2CH_3), 57.9 (***C***-2), 39.1 (***C***-5'), 17.6 (2'-***C***H_3), 14.4 (OCH_2***C***H_3). *m/z* (ES^+) : 663 ($[2M+Na]^+$, 35%), 417 (100), 343 ($[M+Na]^+$, 60). HRMS (ES^+) found: 343.1262 ($C_{16}H_{20}O_5N_2Na$ requires $[M+Na]^+$ 343.1264).

Minor isomer **195** :

Similar to procedure **A6**, DBU (0.01 ml, 0.06 mmol) in anhydrous CH_3CN (1.00 ml) and **177** (0.13 g, 0.63 mmol) in CH_3CN (2.00 ml) were added successively to a solution of ethyl diazoacetate (0.08 ml, 0.76 mmol) in anhydrous CH_3CN (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.

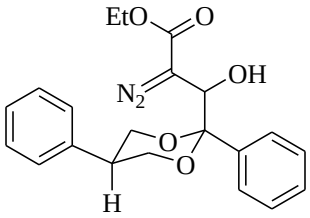


ν_{max} (ATR) : 3620-3390 (***OH*** br), 2981, 2875, 2103 (***C=N₂***), 1682 (***C=O***), 1496, 1394, 1126, 1056, 877, 701, 621 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.34 (2H, t, *J* 7.5, Ar-***H***), 7.30-7.26 (2H, m, Ar-***H***), 7.20 (1H, t, *J* 7.5, Ar-***H***), 4.56 (1H, d, *J* 4.2, 3-***H***), 4.30-4.21 (2H, q, *J* 7.2, $OC\boldsymbol{H}_2CH_3$), 4.12-4.06 (2H, m, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 4.04-3.99 (2H, m, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.24-3.16 (1H, m, 5'-***H***), 3.07 (1H, bs, O***H***), 1.61 (3H, s, 2'-$C\boldsymbol{H}_3$), 1.29 (3H, t, *J* 7.2, $OCH_2C\boldsymbol{H}_3$) . δ_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 ($O\boldsymbol{C}H_2CH_3$), 57.3 (***C***-2), 40.9 (***C***-5'), 15.3 (2'-$\boldsymbol{C}H_3$), 14.5 ($OCH_2\boldsymbol{C}H_3$). *m/z* (ES^+) : 663 ($[2M+Na]^+$, 45%), 384 ($[M+Na+CH_3CN]^+$, 100). HRMS (ES^+) found: 343.1261 ($C_{16}H_{20}O_5N_2Na$ requires $[M+Na]^+$ 343.1264).

Ethyl-2-diazo-3-(2',5'-diphenyl-1',3'-dioxan-2'-yl)-3-hydroxypropanoate (196, 197) :

Major isomer **196** :

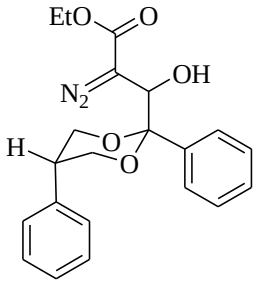
Similar to procedure **A6**, DBU (0.05 ml, 0.30 mmol) in anhydrous CH_3CN (4.00 ml) and **178** (0.80 g, 2.99 mmol) in CH_3CN (7.00 ml) were added successively to a solution of ethyl diazoacetate (0.38 ml, 3.58 mmol) in anhydrous CH_3CN (7.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol **196** (0.91 g, 80%) as a yellow solid.



mp.: 128-130 °C. ν_{max} (ATR) : 3504 (***OH***), 2868, 2114 (***C*=*N*₂**), 1666 (***C*=*O***), 1497, 1397, 1244, 1111, 1010, 917, 834, 702, 617 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.59 (2H, d, *J* 7.8, Ar-***H***), 7.50 (2H, d, *J* 7.5, Ar-***H***), 7.44 (2H, t, *J* 7.5, Ar-***H***), 7.40-7.37 (2H, m, Ar-***H***), 7.30-7.29 (2H, m, Ar-***H***), 4.54 (1H, s, 3-***H***), 4.31-4.23 (3H, m, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$, 4'-$\boldsymbol{H}_{ax}$), 4.13 (1H, d, *J* 11.5, 6'-$\boldsymbol{H}_{ax}$), 3.99 (2H, bs, OC$\boldsymbol{H}_2$$CH_3$), 3.04 (1H, s, O***H***), 2.60 (1H, s, 5'-***H***), 1.09 (3H, bs, $OCH_2C\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 166.1 (***C***-1), 142.1 (Ar-***C***), 135.5 (Ar-***C***) 129.0 (Ar-***C***), 128.7 (Ar-***C***), 128.6 (2 × Ar-***C***), 128.1 (Ar-***C***), 126.7 (Ar-***C***), 103.0 (***C***-2'), 72.8 (***C***-3), 65.8 (***C***-4'), 64.9 (***C***-6'), 60.5 (O***C***H_2CH_3), 56.2 (***C***-2), 38.6 (***C***-5'), 14.3 ($OCH_2\boldsymbol{C}H_3$). *m/z* (ES^+) : 787 ($[2M+Na]^+$, 20%), 405 ($[M+Na]^+$, 100). HRMS (ES^+) found: 405.1415 ($C_{21}H_{22}O_5N_2Na$ requires $[M+Na]^+$ 405.1421).

Minor isomer **197 :**

Similar to procedure **A6**, DBU (0.01 ml, 0.03 mmol) in anhydrous CH_3CN (0.50 ml) and **179** (0.08 g, 0.30 mmol) in CH_3CN (1.00 ml) were added successively to a solution of ethyl diazoacetate (0.04 ml, 0.36 mmol) in anhydrous CH_3CN (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.

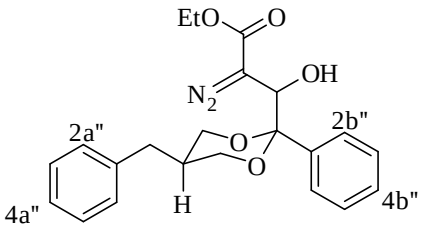


mp.: 103-105 °C. ν_{max} (ATR) : 3493-3413 (***OH*** br), 2980, 2960, 2870, 2103 (***C*=*N*₂**), 1682 (***C*=*O***), 1493, 1396, 1269, 1141, 1000, 918, 878, 702, 609 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.51 (2H, d, *J* 7.0, Ar-***H***), 7.44 (2H, t, *J* 7.7, Ar-***H***), 7.41-7.39 (1H, m, Ar-***H***), 7.23-7.20 (3H, m, Ar-

H), 6.98 (2H, t, *J* 7.0, Ar-***H***), 4.58 (1H, s, 3-***H***), 4.08 (2H, d, *J* 12.1, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 4.01 (2H, bs, OC$\boldsymbol{H}_2$CH$_3$), 3.94-3.88 (2H, m, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.36-3.34 (1H, m, 5'-***H***), 3.11 (1H, s, O***H***), 1.11 (3H, bs, OCH$_2$C$\boldsymbol{H}_3$). δ_C (125 MHz; CDCl$_3$) : 166.0 (***C***-1), 137.3 (Ar-***C***), 131.8 (Ar-***C***) 129.0 (Ar-***C***), 128.8 (Ar-***C***), 128.7 (2 × 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 (O***C***H$_2$CH$_3$), 56.0 (***C***-2), 40.9 (***C***-5'), 14.3 (OCH$_2$***C***H$_3$). *m/z* (ES$^+$) : 787 ([2M+Na]$^+$, 100%), 446 ([M+Na+CH$_3$CN]$^+$, 20), 405 ([M+Na]$^+$, 10). HRMS (ES$^+$) found: 787.2953 ($C_{42}H_{44}O_{10}N_4Na$ requires [2M+Na]$^+$ 787.2950).

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

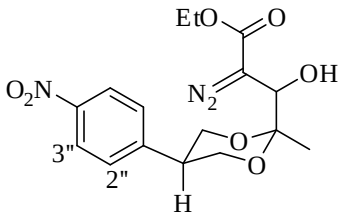
Similar to procedure **A6**, DBU (0.02 ml, 0.11 mmol) in anhydrous CH$_3$CN (2.00 ml) and **180** (0.30 g, 1.06 mmol) in CH$_3$CN (4.00 ml) were added successively to a solution of ethyl diazoacetate (0.13 ml, 1.28 mmol) in anhydrous CH$_3$CN (6.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol **198** (0.27 g, 64%) as a yellow solid.



ν_{max} (ATR) : 3434 (***OH***), 2871, 2098 (***C=N$_2$***), 1679 (***C=O***), 1451, 1371, 1290, 1136, 1041, 958, 740, 701, 663 cm^{-1}. δ_H (700 MHz; CDCl$_3$) : 7.47 (2H, d, *J* 7.4, 2b''-***H***), 7.42 (2H, t, *J* 7.4, 3b''-***H***), 7.37 (1H, t, *J* 7.4, 4b''-***H***), 7.33 (2H, t, *J* 7.7, 3a''-***H***), 7.24 (3H, m, 2a''-***H***, 4a''-***H***), 4.54 (1H, s, 3-***H***), 4.13 (2H, bq, *J* 7.1, OC$\boldsymbol{H}_2$CH$_3$), 3.92 (2H, d, *J* 11.3, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.76 (2H, d, *J* 11.3, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.30 (1H, bs, O***H***), 3.14 (1H, dd, *J* 13.6, 8.3, 5'-C***H***HPh), 3.10 (1H, dd, *J* 13.6, 8.3, 5'-CH***H***Ph), 1.53(1H, t, *J* 8.3, 5'-***H***), 1.20 (3H, bt, *J* 7.1, OCH$_2$C$\boldsymbol{H}_3$). δ_C (175 MHz; CDCl$_3$) : 166.0 (***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 (O***C***H$_2$CH$_3$), 57.1 (***C***-2), 35.7 (***C***-5'), 35.6 (5'-***C***H$_2$Ph), 14.3 (OCH$_2$***C***H$_3$). *m/z* (ES$^+$) : 419 ([M+Na]$^+$, 40%), 387 (50), 351 (100). HRMS (ES$^+$) found: 419.1574 ($C_{22}H_{24}O_5N_2Na$ requires [M+Na]$^+$ 419.1577).

Ethyl-2-diazo-3-hydroxy-3-(2'-methyl-5'-(4''-nitrophenyl)-1',3'-dioxan-2'-yl)propanoate (199) :

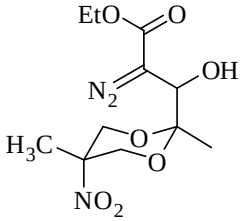
Similar to procedure **A6**, DBU (0.02 ml, 0.12 mmol) in anhydrous CH_3CN (2.00 ml) and **182** (0.30 g, 1.20 mmol) in CH_3CN (4.00 ml) were added successively to a solution of ethyl diazoacetate (0.15 ml, 1.43 mmol) in anhydrous CH_3CN (5.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol **199** (0.41 g, 94%) as a shiny yellow oil.



ν_{max} (ATR) : 3458-3410 (***OH*** br), 2982, 2880, 2099 (***C*=*N*~2~**), 1678 (***C*=*O***), 1517+1343 (***NO*~2~**), 1268, 1047, 849, 742 cm^{-1}. δ_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'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 4.25 (2H, q, *J* 7.0, OC$\boldsymbol{H}_2$$CH_3$), 4.13 (2H, ddd, *J* 12.2, 2.8, 2.0, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 2.92 (1H, tt, *J* 3.5, 2.8, 5'-***H***), 1.56 (3H, s, 2'-C$\boldsymbol{H}_3$), 1.29 (3H, t, *J* 7.0, $OCH_2C\boldsymbol{H}_3$). δ_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 (O***C***H_2CH_3), 38.9 (***C***-5'), 16.0 (2'-***C***H_3), 14.5 ($OCH_2\boldsymbol{C}H_3$). *m/z* (ES^+) : 222 (100%), 429 ($[M+Na+CH_3CN]^+$, 15%).

Ethyl-2-diazo-3-(2',5'-dimethyl-5-nitro-1',3'-dioxan-2'-yl)-3-hydroxypropanoate (200) :

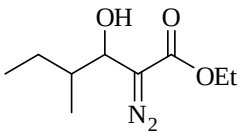
Similar to procedure **A6**, DBU (0.04 ml, 0.28 mmol) in anhydrous CH_3CN (4.00 ml) and **184** (0.52 g, 2.75 mmol) in CH_3CN (7.00 ml) were added successively to a solution of ethyl diazoacetate (0.35 ml, 3.30 mmol) in anhydrous CH_3CN (9.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol **200** (0.80 g, 96%) as a yellow solid.



mp.: 73-74 °C. ν_{max} (ATR) : 3397 (***OH***), 2987, 2107 (***C=N₂***), 1650 (***C=O***), 1544+1303 (***NO₂***), 1180, 1156, 1049, 867, 848, 776, 753 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 4.76 (1H, s, 3-***H***), 4.42 (2H, d, *J* 12.3, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 4.25 (2H, q, *J* 7.8, OC$\boldsymbol{H}_2$$CH_3$), 4.12 (1H, d, *J* 12.3, 4'-$\boldsymbol{H}_{eq}$), 4.04 (1H, d, *J* 12.3, 6'-$\boldsymbol{H}_{eq}$), 2.83 (1H, bs, O***H***), 1.68 (3H, s, 5'-C$\boldsymbol{H}_3$), 1.43 (3H, s, 2'-C$\boldsymbol{H}_3$), 1.29 (3H, t, *J* 7.8, $OCH_2C\boldsymbol{H}_3$). δ_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 (O***C***H_2CH_3), 21.3 (5'-***C***H_3), 16.9 (2'-***C***H_3), 14.4 (OCH_2***C***H_3). *m/z* (ES^+) : 629 ($[2M+Na]^+$, 20%), 326 ($[M+Na]^+$, 60%), 304 ($[M+H]^+$, 100%). Anal. [Found: C, 43.6; H,5.7; N, 13.1. $C_{11}H_{17}O_7N_3$ 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_3CN (6.00 ml) and 2-methylbutanal **214** (0.50 g, 5.81 mmol) in CH_3CN (12.0 ml) were added successively to a solution of ethyl diazoacetate (0.73 ml, 6.97 mmol) in anhydrous CH_3CN (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.

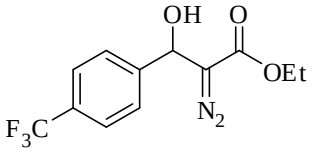


ν_{max} (ATR) : 3520-3410 (***OH*** br), 2965, 2089 (***C=N₂***), 1663 (***C=O***), 1461, 1373, 1286, 1012, 914, 744 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 4.38 (1H, d, *J* 7.5, 3-***H***), 4.24 (2H, q, *J* 7.2, OC$\boldsymbol{H}_2$$CH_3$), 2.50 (1H, bs, O***H***), 1.76-1.61 (1H, m, 4-***H***), 1.54-1.50 (1H, m, 5-***H***H), 1.28 (3H, t, *J* 7.2, $OCH_2C\boldsymbol{H}_3$), 1.26-1.10 (1H, m, 5-H***H***), 1.03 (3H, d, *J* 6.7, 4-C$\boldsymbol{H}_3$), 0.95-0.91 (3H, m, 6-$\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 166.8 (***C***-1), 71.1 (***C***-2), 70.7 (***C***-3), 60.9 (O***C***H_2CH_3), 39.2 (***C***-4), 25.7 (***C***-5), 14.9 (4- ***C***H_3), 14.4 (OCH_2***C***H_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_3CN (2.00 ml) and 4-(trifluoromethyl)benzaldehyde **215** (0.39 ml, 2.87 mmol) in CH_3CN (4.00 ml) were added successively to a solution of ethyl diazoacetate (0.36 ml, 3.45 mmol) in anhydrous CH_3CN

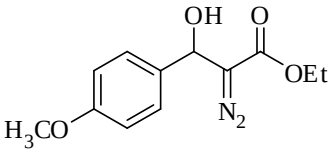
(4.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol **221** (0.77 g, 93%) as a yellow solid.



mp.: 51-53 ^{o}C. ν_{max} (ATR) : 3520-3367 (***OH*** br), 2989, 2092 (***C*=*N*$_2$**), 1653 (***C*=*O***), 1402, 1310, 1111, 1013, 807, 706, 599 cm^{-1}. δ_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, OC***H***$_2$CH$_3$), 2.90 (1H, d, *J* 3.6, O***H***), 1.31 (3H, t, *J* 7.1, OCH$_2$C***H***$_3$***)*** . δ_F (376.3 MHz; $CDCl_3$) : -63.03. δ_C (125 MHz; $CDCl_3$) : 166.0 (***C***-1), 142.7 (Ar-***C***), 130.4 (t, ^{2}*J* 32.5, **C**F$_3$), 126.2 (Ar-***C***), 125.78 (Ar-***C***), 125.75 (Ar-***C***), 77.21 (***C***-2), 68.3 (***C***-3), 61.4 (O***C***H$_2$CH$_3$), 14.5 (OCH$_2$***C***H$_3$***)***. *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. $C_{12}H_{11}O_3N_2F_3$ 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_3CN (4.00 ml) and 4-methoxybenzaldehyde **216** (0.45 ml, 3.67 mmol) in CH_3CN (7.00 ml) were added successively to a solution of ethyl diazoacetate (0.46 ml, 4.41 mmol) in anhydrous CH_3CN (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.

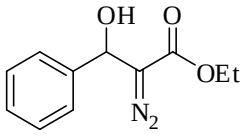


ν_{max} (ATR) : 3680-3443 (***OH*** br), 2980, 2091 (***C*=*N*$_2$**), 1665 (***C*=*O***), 1511, 1244, 1103, 1025, 780, 568, 525 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.35 (2H, d, *J* 8.7, Ar-***H***), 6.91 (2H, d, *J* 8.7, Ar-***H***), 5.87 (1H, d, *J* 3.3, 3-***H***), 4.27 (2H, q, *J* 7.1, OC***H***$_2$CH$_3$), 3.81 (3H, s, OC***H***$_3$), 2.96 (1H, bs, O***H***), 1.30 (3H, t, *J* 7.1, OCH$_2$C***H***$_3$***)***. δ_C (125 MHz; $CDCl_3$) : 166.4 (***C***-1), 159.5 (***C***=N$_2$), 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 (O***C***H$_2$CH$_3$),

55.3 (O***C***H_3), 14.5 (OCH_2***C***H_3). *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) :

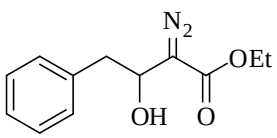
Similar to procedure **A6**, DBU (0.07 ml, 0.47 mmol) in anhydrous CH_3CN (4.00 ml) and benzaldehyde **217** (0.48 ml, 4.71 mmol) in CH_3CN (6.00 ml) were added successively to a solution of ethyl diazoacetate (0.59 ml, 5.65 mmol) in anhydrous CH_3CN (6.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazoketol **223** (0.84 g, 81%) as a yellow oil.



ν_{max} (ATR) : 3643-3317 (***OH*** br), 2093 (***C*=*N*₂**), 1665 (***C*=*O***), 1451, 1373, 1289, 1107, 1018, 721, 533 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 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, OC***H***$_2CH_3$), 2.96 (1H, bs, O***H***), 1.30 (3H, t, *J* 7.2, OCH_2C***H***$_3$***)***. δ_C (125 MHz; $CDCl_3$) : 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 (O***C***H_2CH_3), 14.5 (OCH_2***C***H_3). *m/z* (ES^+) : 645 (40%), 519 (75), 453 (35), 415 (100), 317 (30), 284 ($[M+Na+CH_3CN]^+$, 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 CH_3CN (4.00 ml) and 2-phenylacetaldehyde **218** (0.47 ml, 4.17 mmol) in CH_3CN (6.00 ml) were added successively to a solution of ethyl diazoacetate (0.53 ml, 5.00 mmol) in anhydrous CH_3CN (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.



ν_{max} (ATR) : 3601-3311 (***OH*** br), 2091 (***C=N₂***), 1666 (***C=O***), 1451, 1373, 1289, 1109, 1021, 741, 698 cm^{-1}. δ_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, OC***H***$_2CH_3$), 3.04 (1H, dd, *J* 13.7, 6.9, 4-***H***H), 2.98 (1H, dd, *J* 13.7, 6.9, 4-H***H***), 2.51 (1H, bs, O***H***), 1.27 (3H, t, *J* 7.2, OCH_2C***H***$_3$***)***. δ_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 (O***C***H_2CH_3), 41.0 (***C***-4), 14.4 (OCH_2***C***H_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®. The filtrate was concentrated *in vacuo* and purified by flash column chromatography using silica gel.

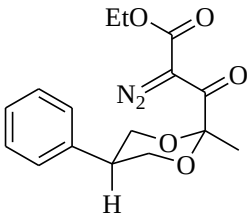
A typical procedure for iodoxybenzoic acid (IBX) oxidation (A8). IBX (1.5 eq) was dissolved in DMSO over 20 min at room temperature. To this was added a solution of the diazoketol (1 eq) in DMSO *via* cannular and the reaction mixture was stirred for 4 h at room temperature. It was then quenched with aqueous $NaHCO_3$ and then extracted with DCM (3 × 20.0 ml), the combined organic layer was copiously washed with aqueous $NaHCO_3$ (3 × 10.0 ml) and finally with water, it was subsequently dried with MgSO4, 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

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 ^{o}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 ^{o}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 $MgSO_4$, 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.

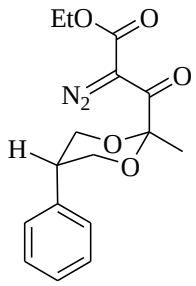


mp.: 60-62 ^{o}C. ν_{max} (ATR) : 2127 (***C*=*N*$_2$**), 1732 (***CO*C=N$_2$), 1666 (***CO*OEt), 1305, 1186, 1015, 856, 702, 629 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.28-7.25 (2H, t, *J* 7.4, Ar-***H***), 7.23-7.19 (1H, t, *J* 7.4, Ar-***H***), 7.08 (2H, d, *J* 7.4, Ar-***H***), 4.31 (2H, q, *J* 7.4, OC***H***$_2$CH$_3$), 4.06 (2H, dd, *J* 11.9, 4.8, 4'-***H***$_{eq}$, 6'-***H***$_{eq}$), 3.91 (2H, t, *J* 11.9, 4'-***H***$_{ax}$, 6'-***H***$_{ax}$), 3.25-3.18 (1H, m, 5'-***H***), 1.53 (3H, s, 2'-C***H***$_3$), 1.31 (3H, t, *J* 7.4, OCH$_2$C***H***$_3$***)***. δ_C (125 MHz; $CDCl_3$) : 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 (O***C***H$_2$CH$_3$), 40.1 (***C***-5'), 25.0 (2'-***C***H$_3$), 14.3 (OCH$_2$***C***H$_3$***)***. *m/z* (ES$^+$) : 382 ([M+Na+CH$_3$CN]$^+$, 20%), 341 ([M+Na]$^+$, 100), 319 ([M+H]$^+$, 30). Anal. [Found: C, 60.8; H, 5.7; N, 7.3. $C_{16}H_{18}O_5N_2$ requires C, 60.4; H, 5.7; N, 8.8%].

Minor isomer **210** :

Similar to procedure **A7**, MnO_2 (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.

Alternatively, to a stirred solution of oxalyl chloride (0.05 ml, 0.53 mmol, 1.2 eq) in DCM maintained at -78 ^{o}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 ^{o}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 $MgSO_4$, 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.



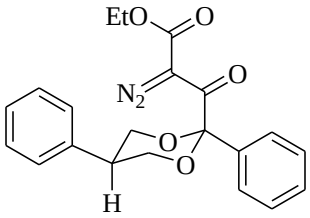
ν_{max} (ATR) : 2130 (***C*=*N*$_2$**), 1733 (***CO*C=N$_2$**), 1684 (***CO*OEt**), 1293, 1159, 1093, 1017, 918, 869, 748, 691 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.28-7.23 (3H, m, Ar-***H***), 7.20-7.15 (2H, m, Ar-***H***), 4.24 (2H, q, *J* 7.2, OC***H***$_2$CH$_3$), 4.12 (2H, dd, *J* 11.9, 5.5, 4'-***H***$_{eq}$, 6'-***H***$_{eq}$), 4.04 (2H, dd, *J* 11.9, 5.5, 4'-***H***$_{ax}$, 6'-***H***$_{ax}$), 2.88-2.84 (1H, m, 5'-***H***), 1.55 (3H, s, 2'-C***H***$_3$), 1.24 (3H, t, *J* 7.2, OCH$_2$C***H***$_3$***)*** . δ_C (125 MHz; $CDCl_3$) : 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 (OC***H***$_2$CH$_3$), 38.9 (***C***-5'), 19.7 (2'-***C***H$_3$), 14.3 (OCH$_2$***C***H$_3$***)***. *m/z* (ES$^+$) : 382 ([M+Na+CH$_3$CN]$^+$, 30%), 341 ([M+Na]$^+$, 100), 319 ([M+H]$^+$, 45). HRMS (ES$^+$) found: 341.1109 ($C_{16}H_{18}O_5N_2Na$ 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**, MnO_2 (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.

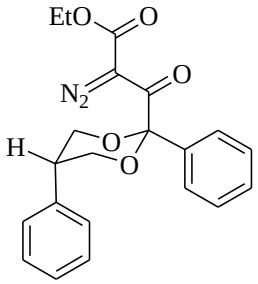
Similar to procedure **A8**, to a solution of IBX (0.29 g, 1.02 mmol) in DMSO (5.00 ml) was added a solution of **196** (0.26 g, 0.68 mmol) in DMSO (7.00 ml). Purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone **206** (0.24 g, 93%) as a clear oil.



mp.: 138-140 °C. ν_{max} (ATR) : 2922, 2130 (***C*=*N*₂**), 1727 (***CO*C=N₂), 1695, 1667 (***CO*OEt), 1599, 1494, 1394, 1249, 1134, 1038, 892, 753, 704, 668, 618 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 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, OC***H***$_2$CH$_3$, 4'-***H*$_{eq}$**, 6'-***H*$_{eq}$**, 4'-***H*$_{ax}$**, 6'-***H*$_{ax}$**), 3.39-3.33 (1H, m, 5'-***H***), 1.29 (3H, t, *J* 7.1, OCH$_2$C***H***$_3$). δ_C (125 MHz; $CDCl_3$) : 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 (O***C***H$_2$CH$_3$), 40.3 (***C***-5'), 14.2 (OCH$_2$***C***H$_3$). *m/z* (ES^+) : 783 ($[2M+Na]^+$, 90%), 381 ($[M+H]^+$, 100). HRMS (ES^+) found: 403.1262 ($C_{21}H_{20}O_5N_2Na$ requires $[M+Na]^+$ 403.1264).

Minor isomer **211** :

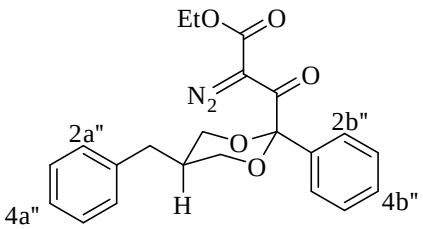
Similar to procedure **A7**, MnO_2 (0.30 g, 3.40 mmol) was added to a solution of **197** (0.13 g, 0.34 mmol) in DCM (5.00 ml). Purification by flash column chromatography (DCM/EtOAc : 9/1) afforded the title diazodiketone **211** (0.08 g, 62%) as a yellow oil.



ν_{max} (ATR) : 2980, 2131 (***C*=*N*$_2$**), 1738 (***CO*C=N$_2$**), 1694 (***CO*OEt**), 1452, 1367, 1293, 1225, 1122, 1042, 887, 750, 701, 624 cm^{-1}. δ_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, OC***H***$_2$CH$_3$, 4'-***H*$_{eq}$**, 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$_2$C***H***$_3$). δ_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 (O***C***H$_2$CH$_3$), 39.6 (***C***-5'), 14.3 (OCH$_2$***C***H$_3$). *m/z* (ES$^+$) : 783 ([2M+Na]$^+$, 100%). HRMS (ES$^+$) found: 403.1264 ($C_{21}H_{20}O_5N_2Na$ requires [M+Na]$^+$ 403.1264).

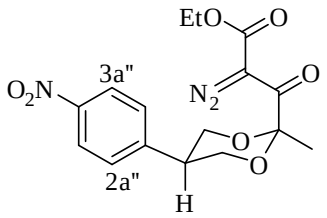
Ethyl-3-(5'-benzyl-2'-phenyl-1',3'-dioxan-2'-yl)-2-diazo-3-oxopropanoate (207) :

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.



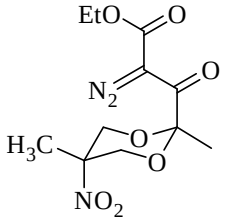
ν_{max} (ATR) : 2978, 2127 (***C*=*N*$_2$**), 1735 (***CO*C=N$_2$**), 1684 (***CO*OEt**), 1451, 1368, 1299, 1176, 1032, 889, 747, 700, 667 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.51 (2H, d, *J* 7.0, 2b''-***H***), 7.37 (3H, m, 3b''-***H***, 4b''-***H***), 7.29 (2H, t, *J* 7.7, 3a''), 7.22 (1H, t, *J* 7.7, 4a''-***H***), 7.12 (2H, d, *J* 7.7, 2a''-***H***), 4.27 (2H, q, *J* 7.2, OC***H***$_2$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'-C***H***$_2$Ph), 2.42-2.40 (1H, m, 5'-***H***), 1.29 (3H, t, *J* 7.2, OCH$_2$C***H***$_3$). δ_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 (O***C***H$_2$CH$_3$), 35.2 (***C***-5'), 34.6 (5'-***C***H$_2$Ph), 14.2 (OCH$_2$***C***H$_3$). *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 ($C_{22}H_{23}O_5N_2$ requires [M+H]$^+$ 395.1602).

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.



mp.: 148-150 ^{o}C. ν_{max} (ATR) : 2989, 2133 (***C*=*N*$_2$**), 1723 (***CO*C=N$_2$**), 1654 (***CO*OEt**), 1513+1323 (***NO*$_2$**), 1188, 1134, 1019, 889, 849, 747, 650 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 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, OC***H***$_2$CH$_3$), 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'-C***H***$_3$), 1.36 (3H, t, *J* 7.1, OCH$_2$C***H***$_3$). δ_C (125 MHz; $CDCl_3$) : 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 (O***C***H$_2$CH$_3$), 40.2 (***C***-5'), 24.9 (2'-***C***H$_3$), 14.3 (OCH$_2$***C***H$_3$). *m/z* (ES$^+$) : 427 ([M+Na+CH$_3$CN]$^+$, 20%), 364 ([M+H]$^+$, 10), 222 (100). HRMS (ES$^+$) found: 386.0956 ($C_{16}H_{17}O_7N_3Na$ requires [M+Na]$^+$ 386.0959). Anal. [Found: C, 52.3; H, 4.7; N, 11.4. $C_{16}H_{17}O_7N_3$ requires C, 52.9; H, 4.7; N, 11.6%].

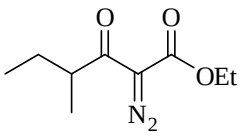
Ethyl-2-diazo-3-(2',5'-dimethyl-5'-nitro-1',3'-dioxan-2'-yl)-3-oxopropanoate (209) :
Similar to procedure **A8**, to a solution of IBX (1.11 g, 3.96 mmol) in DMSO (15.0 ml) was added a solution of **200** (0.80 g, 2.64 mmol) in DMSO (10.0 ml). Purification by flash column chromatography (petroleum ether/EtOAc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



mp.: 116-118 °C. ν_{max} (ATR) : 2993, 2132 (***C*=*N*$_2$**), 1735 (***CO*C=N$_2$**), 1659 (***CO*OEt**), 1547+1447 (***NO*$_2$**), 1306, 1187, 1134, 1071, 1011, 857, 757, 663 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 4.74 (2H, d, *J* 13.3, 4'-***H***$_{eq}$, 6'-***H***$_{eq}$), 4.34 (2H, q, *J* 7.1, OC***H***$_2$CH$_3$), 3.90 (2H, d, *J* 13.3, 4'-***H***$_{ax}$, 6'-***H***$_{ax}$), 1.51 (3H, s, 2'-C***H***$_3$), 1.34 (3H, s, 5'-C***H***$_3$), 1.33 (3H, t, *J* 7.1, OCH$_2$C***H***$_3$). δ_C (125 MHz; $CDCl_3$) : 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 (O***C***H$_2$CH$_3$), 24.3 (2'-***C***H$_3$), 19.3 (5'-***C***H$_3$), 14.3 (OCH$_2$***C***H$_3$). *m/z* (ES$^+$) : 365 ([M+Na+CH$_3$CN]$^+$, 100%), 342 ([M+CH$_3$CN]$^+$, 30), 324 ([M+Na]$^+$, 20). HRMS (ES$^+$) found: 324.0800 ($C_{11}H_{15}O_7N_3Na$ requires [M+Na]$^+$ 324.0802). Anal. [Found: C, 43.8; H, 5.0; N, 13.8. $C_{11}H_{15}O_7N_3$ requires C, 43.9; H, 5.0; N, 13.9%].

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

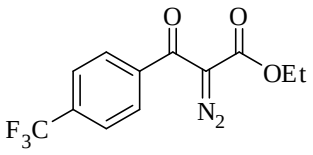
Similar to procedure **A8**, to a solution of IBX (1.72 g, 6.15 mmol) in DMSO (15.0 ml) was added a solution of the alcohol **220** (0.82 g, 4.10 mmol) in DMSO (5.00 ml). Subsequent purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone **226** (0.65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



ν_{max} (ATR) : 2970, 2130 (***C*=*N*$_2$**), 1712 (***CO*C=N$_2$**), 1663 (***CO*OEt**), 1458, 1372, 1292, 1021, 977, 751 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 4.26 (2H, q, *J* 7.2, OC***H***$_2$CH$_3$), 3.42 (1H, q, *J* 6.9, 4-***H***), 1.73-1.66 (1H, m, 5-***H***H), 1.39-1.32 (1H, m, 5-H***H***), 1.29 (3H, t, *J* 7.2, OCH$_2$C***H***$_3$), 1.06 (3H, d, *J* 6.9, 4-C***H***$_3$), 0.87 (3H, t, *J* 7.6, 6-***H***$_3$). δ_C (125 MHz; $CDCl_3$) : 196.7 (***C***-3), 161.1 (***C***-1), 75.6 (***C***-2), 61.2 (O***C***H$_2$CH$_3$), 43.2 (***C***-4), 26.2 (***C***-5), 16.0 (4- ***C***H$_3$), 14.2 (OCH$_2$***C***H$_3$), 11.5 (***C***-6). *m/z* (ES$^+$) : 418 ([2M+Na]$^+$, 40%), 262 ([M+Na+CH$_3$CN]$^+$, 85), 221 ([M+Na]$^+$, 100). HRMS (ES$^+$) found: 221.0898 ($C_9H_{14}O_3N_2Na$ requires [M+Na]$^+$ 221.0897).

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

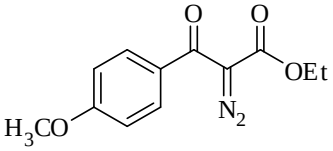
Similar to procedure **A8**, to a solution of IBX (0.55 g, 1.98 mmol) in DMSO (10.0 ml) was added a solution of the alcohol **221** (0.38 g, 1.32 mmol) in DMSO (5.00 ml). Subsequent purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone **227** (0.38 g, 100%) as a yellow oil.



ν_{max} (ATR) : 2985, 2146 (***C*=*N*$_2$**), 1719 (***CO*C=N$_2$), 1630 (***CO*OEt), 1512, 1407, 1304, 1266, 1115, 1014, 933, 764, 707, 683, 539 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.70 (2H, d, *J* 8.3, Ar-***H***), 7.66 (2H, d, *J* 8.3, Ar-***H***), 4.22 (2H, q, *J* 7.2, OC***H***$_2$CH$_3$), 1.23 (3H, t, *J* 7.2, OCH$_2$C***H***$_3$***)*** . δ_F (376.3 MHz; $CDCl_3$) : -63.50. δ_C (125 MHz; $CDCl_3$) : 186.0 (***C***-3), 160.5 (***C***-1), 140.3 (***C***-4'), 133.5 (q, ^2J 32.6, **C**F$_3$), 128.6 (***C***-1'), 124.8 (Ar-***C***), 124.4 (Ar-***C***), 123.9 (q, ^3J 271.3, **C**F$_3$), 77.3 (***C***-2), 61.8 (O***C***H$_2$CH$_3$), 14.1 (OCH$_2$***C***H$_3$***)***. *m/z* (ES$^+$) : 649 (75%), 595 ([2M+Na]$^+$, 5), 483 (100), 350 ([M+Na+CH$_3$CN]$^+$, 80), 309 ([M+Na]$^+$, 30). HRMS (ES$^+$) found: 309.0460 ($C_{12}H_9O_3N_2F_3Na$ requires [M+Na]$^+$ 309.0458).

Ethyl-2-diazo-3-(4'-methoxyphenyl)-3-oxopropanoate (228) :

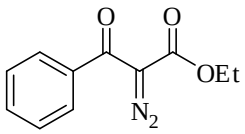
Similar to procedure **A8**, to a solution of IBX (0.12 g, 0.42 mmol) in DMSO (10.0 ml) was added a solution of the alcohol **222** (0.07 g, 0.28 mmol) in DMSO (5.00 ml). Subsequent purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone **228** (65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



ν_{max} (ATR) : 2980, 2840, 2139 (***C*=*N*$_2$**), 1715 (***CO*CN$_2$), 1598 (***CO*OEt), 1460, 1367, 1249, 1107, 1018, 839, 757, 692, 613 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.66 (2H, d, *J* 8.7, Ar-***H***), 6.91 (2H, d, *J* 8.7, Ar-***H***), 4.26 (2H, q, *J* 7.1, OC***H***$_2$CH$_3$), 3.85 (3H, s, OC***H***$_3$), 1.28 (3H, t, *J* 7.1, OCH$_2$C***H***$_3$***)***. δ_C (125 MHz; $CDCl_3$) : 185.3 (***C***-3), 163.1 (***C***-1), 161.3 (***C***-4'), 131.0 (***C***-1'), 129.3 (Ar-***C***), 113.1 (Ar-***C***), 75.6 (***C***-2), 61.5 (O***C***H$_2$CH$_3$), 55.4 (O***C***H$_3$), 14.2 (OCH$_2$***C***H$_3$). *m/z* (ES$^+$) : 519 ([2M+Na]$^+$, 100%), 312 ([M+Na+CH$_3$CN]$^+$, 55), 271 ([M+Na]$^+$, 65). HRMS (ES$^+$) found: 271.0692 ($C_{12}H_{12}O_4N_2Na$ requires [M+Na]$^+$ 271.0689).

Ethyl-2-diazo-3-oxo -3-phenylpropanoate (229) :

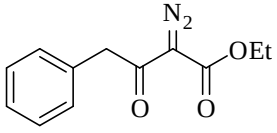
Similar to procedure **A8**, to a solution of IBX (0.73 g, 2.59 mmol) in DMSO (18.0 ml) was added a solution of the alcohol **223** (0.38 g, 1.73 mmol) in DMSO (8.00 ml). Subsequent purification by flash column chromatography (petroleum ether/EtOAc : 8/2) afforded the title diazodiketone **229** (0.36 g, 96%) as a yellow oil.



ν_{max} (ATR) : 2983, 2139 (***C*=*N*$_2$**), 1717 (***CO*CN_2), 1625 (***CO*OEt), 1447, 1368, 1291, 1109, 1010, 931, 786, 744, 697, 536 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.62 (2H, d, *J* 7.3, Ar-***H***), 7.52 (1H, t, *J* 7.3, Ar-***H***), 7.41 (2H, t, *J* 7.3, Ar-***H***), 4.24 (2H, q, *J* 7.0, O***C*H**$_2$$CH_3$), 1.24 (3H, t, *J* 7.0, OCH_2C***H*$_3$*)**. δ_C (125 MHz; $CDCl_3$) : 186.8 (***C***-3), 160.9 (***C***-1), 137.1 (Ar-***C***), 132.2 (Ar-***C***), 128.3 (Ar-***C***), 127.8 (Ar-***C***), 76.1 (***C***-2), 61.5 (O***C***H_2CH_3), 14.1 (OCH_2***C***H_3). *m/z* (ES^+) : 459 ($[2M+Na]^+$, 100%), 282 ($[M+Na+CH_3CN]^+$, 75), 241 ($[M+Na]^+$, 80). HRMS (ES^+) found: 241.0586 ($C_{11}H_{10}O_3N_2Na$ 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.

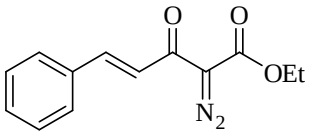


ν_{max} (ATR) : 2982, 2133 (***C*=*N*$_2$**), 1709 (***CO*CN_2), 1649 (***CO*OEt), 1493, 1369, 1293, 1120, 1028, 854, 743, 711, 630, 532 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.35-7.23 (5H, m, Ar-***H***), 4.33 (2H, q, *J* 7.2, O***C*H**$_2$$CH_3$), 4.21 (2H, s, 4-***H***$_2$), 1.35 (3H, t, *J* 7.2, OCH_2C***H*$_3$*)**. δ_C (125 MHz; $CDCl_3$) : 190.2 (***C***-3), 161.2 (***C***-1), 134.0 (Ar-***C***), 129.7 (Ar-***C***), 128.5 (Ar-***C***), 127.0 (Ar-***C***), 76.2 (***C***-2), 61.5 (O***C***H_2CH_3), 45.7 (***C***-4), 14.3 (OCH_2***C***H_3). *m/z* (ES^+) : 479 (100%), 296

([M+Na+CH_3CN]$^+$, 75), 255 ([M+Na]$^+$, 55). HRMS (ES$^+$) found: 255.0742 ($C_{12}H_{12}O_3N_2Na$ requires [M+Na]$^+$ 255.0740).

(*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 $NaHCO_3$ (15.0 ml) and then extracted with DCM (3 × 20.0 ml). The combined organic layers were copiously washed with aqueous $NaHCO_3$ (3 × 40.0 ml) and water, dried over $MgSO_4$, 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.

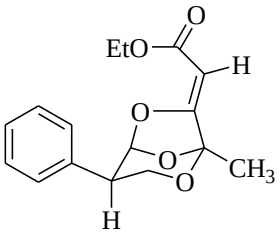


mp.: 96-98 ^oC. ν_{max} (ATR) : 2979, 2145 (***C*=*N*$_2$**), 1695 (***CO*CN_2), 1637 (***CO*OEt), 1580 (***C*=*C***), 1445, 1336, 1207, 1138, 1044, 869, 756, 699, 540, 480 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.87 (1H, d, *J* 15.6, 4-***H***), 7.77 (1H, d, *J* 15.6, 5-***H***), 7.63-7.62 (2H, m, Ar-***H***), 7.39-7.38 (3H, m, Ar-***H***), 4.35 (2H, q, *J* 7.2, OC***H***$_2$$CH_3$), 1.37 (3H, t, *J* 7.2, OCH_2C***H***$_3$***)***. δ_C (175 MHz; $CDCl_3$) : 181.5 (***C***-3), 161.5 (***C***-1), 142.8 (***C***-5), 134.7 (***C***-1'), 130.5 (***C***-4'), 128.9 (***C***-3'), 128.7 (***C***-2'), 121.8 (***C***-4), 77.4 (***C***-2), 61.5 (O***C***H_2CH_3), 14.4 (OCH_2***C***H_3). *m/z* (ES$^+$) : 511 ([2M+Na]$^+$, 10%), 308 ([M+Na+CH_3CN]$^+$, 100), 245 ([M+H]$^+$, 55). Anal. [Found: C, 63.6; H, 5.0; N, 11.1. $C_{13}H_{12}O_3N_2$ requires C, 63.9; H, 5.0; N, 11.5%].

(Z)-ethyl-2-(1'-methyl-4'-phenyl-2',6',8'-trioxa-bicyclo[3.2.1]octan-7'-ylidene)acetate (235):

To a solution of rhodium (II) perfluorobutyrate catalyst, $Rh_2(CO_2C_3F_7)_4$ (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

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%)

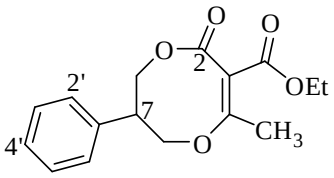


ν_{max} (ATR) : 1705 (***C*-*O***),1656 (***CO***OEt), 1495, 1304, 1238, 1113, 1019, 948, 823, 702, 617 cm^{-1}. δ_H (500 MHz, $CDCl_3$) : 7.41 (2H, d, *J* 7.2, Ar-***H***), 7.35 (2H, t, *J* 7.2, Ar-***H***), 7.31 (1H, d, *J* 7.2, Ar-***H***), 6.00 (1H, s, 5'-***H***), 5.16 (1H, s, 2-***H***), 4.33 (1H, q, *J* 7.2, OC***H***HCH_3), 4.25 (1H, q, *J* 7.2, OCH***H***CH_3), 4.08-4.00 (2H, m, 3'-$\boldsymbol{H}_{ax}$, 3'-$\boldsymbol{H}_{eq}$), 3.49-3.45 (1H, m, 4'-***H***), 1.67 (3H, s, 1'-C***H***$_3$), 1.36 (3H, t, *J* 7.2, $OCH_2C\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 165.6 (***C***-1), 162.7 (***C***-7', enol ether), 135.0 (***C***-1''), 128.8 (Ar-***C***), 128.7 (Ar-***C***), 128.0 (Ar-***C***), 106.3 (***C***-5'), 103.5 (***C***-1'), 88.5 (***C***-2), 66.6 (***C***-3'), 60.2 ($OC\boldsymbol{H}_2CH_3$), 45.5 (***C***-4'), 20.0 (1'-***C***H_3), 14.3 ($OCH_2\boldsymbol{C}H_3$). *m/z* (ES^+) : 354 ($[M+Na+CH_3CN]^+$, 20%), 313 ($[M+Na]^+$, 70), 291 ($[M+H]^+$, 100). HRMS (ES^+) found: 313.1044 ($C_{16}H_{18}O_5Na$ requires $[M+Na]^+$ 313.1047).

(*Z*)-ethyl-4-methyl-2-oxo-7-phenyl-2,6,7,8-tetrahydro-1,5-dioxocine-3-carboxylate (248) :
Rhodium (II) perfluorobutyrate, $Rh_2(CO_2C_3F_7)_4$ (5 mol%) solution in benzene (18.0 ml) was maintained at 75 ^oC 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) perfluorobutyrate, $Rh_2(CO_2C_3F_7)_4$ (5 mol%) solution in toluene (10.0 ml) placed in a microwave vial (20.0 ml) was argon flushed and maintained at 70 ^oC. After 2 min, a solution of diazodiketone 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 ^oC for 15 min. The

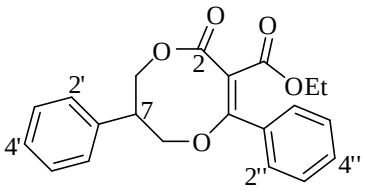
reaction mixture was then allowed to attain room temperature, silica gel was added and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8) to give the title lactone **248** as an oil (0.03 g, 40%).



ν_{max} (ATR) : 2982, 1722 (***C*=*O***), 1606 (***C*=*C***), 1468, 1391, 1310, 1233, 1168, 1102, 1076, 1032, 908, 770, 706, 636 cm^{-1}. δ_H (500 MHz, $CDCl_3$) : 7.37 (2H, d, *J* 7.1, 2'-***H***), 7.32 (3H, m, 3'-***H***, 4'-***H***), 4.55 (2H, d, *J* 7.0, 8-$\boldsymbol{H}_2$), 4.42 (1H, dd, *J* 13.4, 3.1, 6-***H***H), 4.32 (1H, dd, *J* 13.4, 6.2, 6-H***H***), 4.22 (2H, q, *J* 7.2, 3-$CO_2C\boldsymbol{H}_2CH_3$), 3.36-3.32 (1H, m, 7-***H***), 2.29 (3H, s, 4-$C\boldsymbol{H}_3$), 1.29 (3H, t, *J* 7.2, 3-$CO_2CH_2C\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 168.5 (***C***-4, enol ether), 168.1 (***C***-2), 166.2 (3-$\boldsymbol{C}O_2CH_2CH_3$), 137.0 (***C***-1'), 129.0 (***C***-2'), 128.1 (***C***-3'), 128.0 (***C***-4'), 100.2 (***C***-3), 68.3 (***C***-6), 67.9 (***C***-8), 61.5 (3-$CO_2\boldsymbol{C}H_2CH_3$), 46.6 (***C***-7), 21.6 (4-$\boldsymbol{C}H_3$), 14.0 (3-$CO_2CH_2\boldsymbol{C}H_3$). *m/z* (EI) : 290 ($M^+$, 30%), 275 ($M^+$-Me, 45), 244 ($M^+$-OEt, 30), 218 ($M^+$-$CO_2$Et, 5), 117 (100), 104 (70), 91 ($PhCH_2^+$,40). HRMS (GCMS, EI) found: 290.1146 ($C_{16}H_{18}O_5$ requires M^+ 290.1149).

(*Z*)-ethyl-2-oxo-4,7-diphenyl-2,6,7,8-tetrahydro-1,5-dioxocine-3-carboxylate (249) :

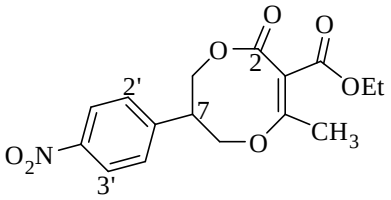
Rhodium (II) perfluorobutyrate, $Rh_2(CO_2C_3F_7)_4$ (5 mol%) solution in toluene (10.0 ml) placed in a microwave vial (20.0 ml) was argon flushed and maintained at 70 ^oC. After 2 min, a solution of diazodiketone acetal **206** (0.07 g, 0.18 mmol) in toluene (5.00 ml) was added and the vial was immediately placed into the reactor at 70 ^oC 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%).



ν_{max} (ATR) : 2967, 1724 (***C*=*O***), 1606 (***C*=*C***), 1490, 1453, 1363, 1233, 1135, 1100, 1074, 1025, 978, 907, 867, 753 cm^{-1}. δ_H (400 MHz, $CDCl_3$) : 7.47-7.40 (5H, m, Ar-***H***), 7.31-7.20 (5H, m, Ar-***H***), 4.76 (1H, dd, *J* 12.0, 7.8, 8-***H***H), 4.54 (1H, dd, *J* 12.0, 3.4, 8-H***H***), 4.26 (1H, dd, *J* 12.6, 4.8, 6-***H***H), 4.01 (1H, dd, *J* 12.6, 8.4, 6-H***H***), 4.22 (2H, q, *J* 7.2, 3-$CO_2C\boldsymbol{H}_2CH_3$), 3.46-3.40 (1H, m, 7-***H***), 1.29 (3H, t, *J* 7.2, 3-$CO_2CH_2C\boldsymbol{H}_3$). δ_C (100 MHz; $CDCl_3$) : 168.3 (***C***-4), 168.1 (***C***-2), 165.2 (3-$\boldsymbol{C}O_2CH_2CH_3$), 137.5 (***C***-1'), 135.2 (***C***-1''), 129.5 (***C***-2''), 128.8 (***C***-2'), 128.52 (***C***-3'), 128.49 (***C***-4'), 127.9 (***C***-3''), 127.6 (***C***-4''), 99.8 (***C***-3), 69.5 (***C***-6), 68.7 (***C***-8), 61.3 (3-$CO_2\boldsymbol{C}H_2CH_3$), 46.4 (***C***-7), 14.2 (3-$CO_2CH_2\boldsymbol{C}H_3$). *m/z* (EI) : 352 ($M^+$, 5%), 336 ($M^+$-Me, 20), 306 ($M^+$-OEt, 30), 279 ($M^+$-$CO_2$Et, 5), 117 (100), 104 (80), 91 ($PhCH_2^+$,30).

(*Z*)-ethyl-4-methyl-7-(4-nitrophenyl)-2-oxo-2,6,7,8-tetrahydro-1,5-dioxocine-3-carboxylate (250) :

Rhodium (II) perfluorobutyrate, $Rh_2(CO_2C_3F_7)_4$ (5 mol%) solution in toluene (10.0 ml) placed in a microwave vial (20.0 ml) was argon flushed and maintained at 70 ^oC. 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 ^oC 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%).

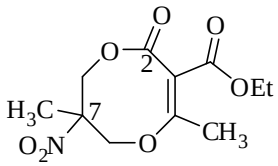


ν_{max} (ATR) : 2978, 1724 (***C*=*O***), 1608 (***C*=*C***), 1520+1350(***NO₂***), 1350, 1180, 1116, 1030, 946, 852, 812, 752, 706 cm^{-1}. δ_H (400 MHz, $CDCl_3$) : 8.17 (2H, d, *J* 8.7, 3'-***H***), 7.57 (2H, d, *J* 8.7, 2'-***H***), 4.31 (2H, d, *J* 7.1, 8-$\boldsymbol{H}_2$), 4.21 (2H, q, *J* 7.1, 3-$CO_2C\boldsymbol{H}_2CH_3$), 4.03 (1H, dd, *J* 11.5, 2.2, 6-***H***H), 3.94 (1H, dd, *J* 11.5, 4.8, 6-H***H***), , 3.28-3.23 (1H, m, 7-***H***), 2.43 (3H, s, 4-C$\boldsymbol{H}_3$), 1.27 (3H, t, *J* 7.1, 3-$CO_2CH_2C\boldsymbol{H}_3$). δ_C (100 MHz; $CDCl_3$) : 168.7 (***C***-4, enol ether), 167.9 (***C***-2), 166.0 (3-$\boldsymbol{C}O_2CH_2CH_3$), 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-$CO_2\boldsymbol{C}H_2CH_3$), 45.4 (***C***-7), 19.9 (4-$\boldsymbol{C}H_3$), 14.3 (3-$CO_2CH_2\boldsymbol{C}H_3$).

m/z (EI) : 335 (M^+, 10%), 320 (M^+-Me, 5), 290 (M^+-OEt, 20), 262 (M^+-CO_2Et, 5), 149 (100), 104 (20). HRMS ($ASAP^+$) found: 336.1071 ($C_{16}H_{18}O_7N$ 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, $Rh_2(CO_2C_3F_7)_4$ (5 mol%) solution in toluene (10.0 ml) placed in a microwave vial (20.0 ml) was argon flushed and maintained at 75 ^oC. 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 ^oC 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%).

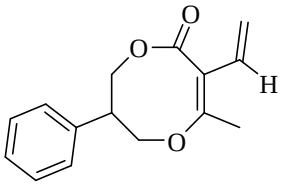


ν_{max} (ATR) : 2985, 1720 (***C*=*O***), 1607 (***C*=*C***), 1549+1458 (***NO₂***), 1380, 1299, 1244, 1155, 1067, 907, 864, 820, 766, 637 cm^{-1}. δ_H (700 MHz, $CDCl_3$) : 4.91 (1H, d, *J* 12.9, 8-***H***H), 4.70 (1H, d, *J* 13.9, 6-***H***H), 4.45 (1H, d, *J* 12.9, 8-H***H***), 4.28 (1H, d, *J* 13.9, 6-H***H***), 4.21 (2H, q, *J* 7.1, 3-CO_2C***H***$_2CH_3$), 2.21 (3H, s, 4-C***H***$_3$), 1.68 (3H, s, 7-C***H***$_3$), 1.27 (3H, t, *J* 7.1, 3-CO_2CH_2C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 167.4 (***C***-4, enol ether), 165.9 (***C***-2), 165.4 (3-***C***$O_2CH_2CH_3$), 101.0 (***C***-3), 87.4 (***C***-7), 68.3 (***C***-6), 67.1 (***C***-8), 61.9 (3-CO_2***C***H_2CH_3), 21.2 (4-***C***H_3), 20.2 (7-***C***H_3), 13.9 (3-CO_2CH_2***C***H_3). *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 ($C_{11}H_{15}O_7N$ requires M^+ 273.0843).

(*Z*)-4-methyl-7-phenyl-3-ethenyl-7,8-dihydro-1,5-dioxocin-2(6H)-one (284) :

Rhodium (II) perfluorobutyrate, $Rh_2(CO_2C_3F_7)_4$ (5 mol%) solution in toluene (10.0 ml) placed in a microwave vial (20.0 ml) was argon flushed and maintained at 70 ^oC. After 2 min, a solution of vinyldiazoketone 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 ^oC for 15 min. The reaction mixture was then allowed to attain room temperature, silica gel was added and the solvent was

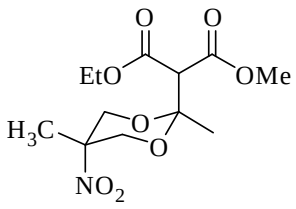
evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether : 2/8) to give the title lactone **284** as an oil (0.04 g, 45%).



ν_{max} (ATR) : 1714 (***C*=*O***), 1617 (***C*=*C***), 1494, 1390, 1302, 1258, 1173, 1012, 896, 764, 700, 616 cm^{-1}. δ_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-C***H***=CH_2), 5.27 (1H, d, *J* 17.1, CH=C***H***H), 5.13 (1H, d, *J* 11.1, CH=CH***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-C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 169.7 (***C***-2), 157.4 (***C***-4, enol ether), 137.6 (***C***-1'), 131.0 (3-***C***H=CH_2), 128.9 (Ar-***C***), 128.1 (Ar-***C***), 127.8 (Ar-***C***), 114.2 (3-CH=***C***H_2), 105.3 (***C***-3), 68.0 (***C***-8), 67.4 (***C***-6), 47.2 (***C***-7), 19.0 (4-***C***H_3). *m/z* (ES^+) : 308 ($[M+Na+CH_3CN]^+$, 20%), 267 ($[M+Na]^+$, 20), 245 ($[M+H]^+$, 60). HRMS (ES^+) found: 267.0993 ($C_{15}H_{16}O_3Na$ 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, $Rh_2(CO_2C_3F_7)_4$ (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 ^oC. After 2 min, a solution of vinyldiazoketone **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 ^oC 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**.

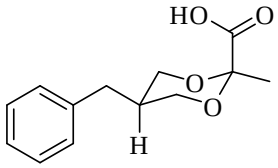


ν_{max} (ATR) : 2987, 2953, 1756+1731 (***C*=*O***), 1547+1454 (***NO*$_2$**), 1383, 1295, 1245, 1112, 1036, 878, 754, 618 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 4.54 (2H, d, *J* 13.0, 4'-***H***$_{ax}$,6'-***H***$_{ax}$), 4.24 (1H, s, 2-***H***), 4.21 (3H, q, *J* 7.1, OC***H***$_2$CH$_3$), 3.97 (2H, d, *J* 13.0, 4'-***H***$_{eq}$, 6'-***H***$_{eq}$), 3.75 (3H, s, OC***H***$_3$), 1.65 (3H, s, 5'-C***H***$_3$), 1.56 (3H, s, 2'-C***H***$_3$), 1.27 (3H, t, *J* 7.1, OCH$_2$C***H***$_3$). δ_C (125 MHz; $CDCl_3$) : 165.9 (***C***-3), 165.3 (***C***-1), 99.1 (***C***-2'), 82.2 (***C***-5'), 64.7 (***C***-4',***C***-6'), 61.8 (O***C***H$_2$CH$_3$), 54.1 (***C***-2), 52.7 (O***C***H$_3$), 20.8 (5'-***C***H$_3$), 20.7 (2'-***C***H$_3$), 14.0 (OCH$_2$***C***H$_3$). *m/z* (ASAP$^+$) : 306 ([M+H]$^+$, 20%), 290 ([M+H-CH$_4$]$^+$, 20), 173 (15), 160 (100). HRMS (ASAP$^+$) found: 306.1187 ($C_{12}H_{20}O_8N$ requires [M+H]$^+$ 306.1189).

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

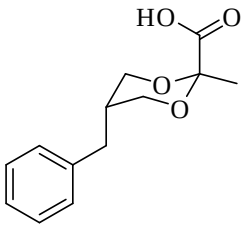
To a solution of an isomeric mixture of **147** and **148** (7:3 ratio) (8.50 g, 36.0 mmol) in THF/H_2O (1:1, 75.0 ml) was added sodium hydroxide (6.40 g, 0.16 mmol). The reaction was left to stir at room temperature overnight, then it was cooled to 0 ^{o}C and treated using a cold 5 M solution of aqueous 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** :



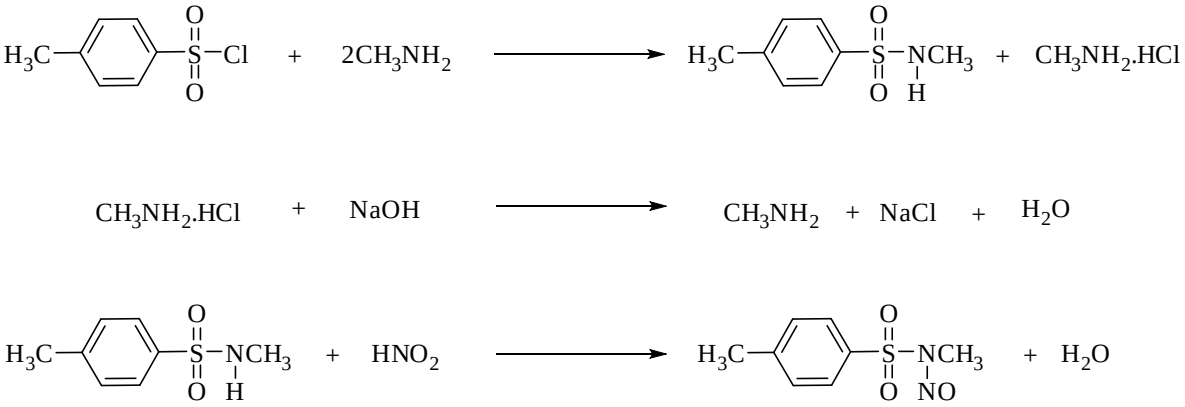
mp.: 99-101 ^{o}C. ν_{max} (ATR) : 3200-2700 (CO***OH***), 1718 (***C*=*O***), 1142, 1032, 750, 672 cm^{-1}. δ_H (400 MHz; $CDCl_3$) : 8.10 (1H, s, COO***H***), 7.30-7.23 (2H, m, Ar-***H***), 7.23-7.20 (1H, m, Ar-***H***), 7.20-7.05 (2H, m, Ar-***H***), 3.98 (2H, dd, *J* 11.5, 4.2, 4-***H***$_{eq}$, 6-***H***$_{eq}$), 3.58 (2H, dd, *J* 11.5, 10.8, 4-***H***$_{ax}$, 6-***H***$_{ax}$), 2.40-2.30 (3H, m, 5-***H***, 5-C***H***$_2$Ph), 1.60 (3H, s, 2-C***H***$_3$). δ_C (100.5 MHz; $CDCl_3$) : 174.0 (***C***O), 137.9 (***C***-1'), 129.2 (Ar-***C***), 128.8 (Ar-***C***), 126.7 (Ar-***C***), 98.2 (***C***-2), 68.3 (***C***-4, ***C***-6), 35.1 (***C***-5), 34.8 (5-C***H***$_2$Ph), 25.9 (2-C***H***$_3$). *m/z* (ES$^+$) : 259.1 ([M+Na]$^+$, 100 %). Anal. [Found: C, 66.0; H, 6.8. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%].

Minor isomer **391** : (as a mixture with the major isomer)



δ_H (400 MHz; $CDCl_3$) : 7.95 (1H, s, COO***H***), 7.40-7.30 (2H, m, Ar-***H***), 7.30-7.20 (2H, m, Ar-***H***), 7.15-7.05 (1H, m, Ar-***H***), 4.04 (2H, dd, *J* 12.2, 2.8, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 3.84 (2H, dd, *J* 12.2, 2.6, 4-$\boldsymbol{H}_{ax}$, 6-$\boldsymbol{H}_{ax}$), 3.05 (2H, d, *J* 7.8, 5-C$\boldsymbol{H}_2$Ph), 1.70-1.60 (1H, m, 5-***H***) 1.68 (3H, s, 2-C$\boldsymbol{H}_3$). δ_C (100.5 MHz; $CDCl_3$) : 175.2 (***C***O), 139.9 (***C***-1'), 129.3 (Ar-***C***), 128.6 (Ar-***C***), 126.6 (Ar-***C***), 98.4 (***C***-2), 66.0 (***C***-4, ***C***-6), 35.2 (***C***-5), 35.1 (5-***C***H_2Ph), 25.6 (2-***C***H_3). *m/z* (ES^+) : 259.1 ($[M+Na]^+$, 100 %). HRMS (ES^+) found: 259.0937 ($C_{13}H_{16}O_4Na$ requires $[M+Na]^+$ 259.0946).

Diazald® (*p*-Tolylsulfonylmethylnitrosamide) (394) preparation :[4]



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_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 ^oC in order to maintain the sulfonylmethylamine (m.p. 78 ^oC) in molten condition. The reaction mixture was stirred for a while.

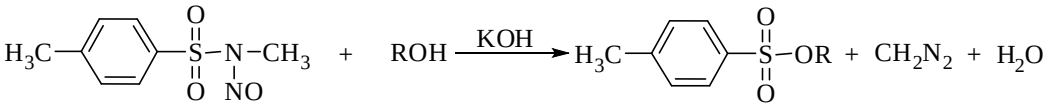
Once the mixture had become acidic, indicated by taking the pH using an indicator paper, 3.10 ml of the alkali solution was added, followed by the immediate addition of the second portion (5.60 g) of the *p*-toluenesulfonyl chloride **392**. Once the solution had become acidic again, 1.60 ml of the alkali 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_2O and the mixture was heated at 100 ^oC 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 ^oC and a solution of 7.75 g of $NaNO_2$ dissolved in 15.6 ml of H_2O was added slowly *via* a dropping funnel over 45 min. Temperature was kept below 10 ^oC. 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_2O was added to the mixture and the product was separated by suction filtration and washed with 31.0 ml H_2O. 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]

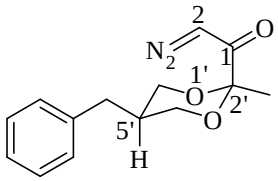


R=$CH_3O(CH_2CH_2)_2O$

A solution of Diazald® **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_2O/ether placed at a temperature of 60 ^oC. 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%)

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 ^{o}C was added triethylamine, (Et_3N, 0.45 ml, 3.30 mmol) and isobutylchloroformate, (^{i}BuOCOCl, 0.36 ml, 2.80 mmol). After 2 h (reaction followed by TLC), an excess of an ethereal solution of diazomethane **395** (CH_2N_2, 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 (NH_4Cl), sodium bicarbonate ($NaHCO_3$) and brine. The organic phase was dried over magnesium sulphate ($MgSO_4$), 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.

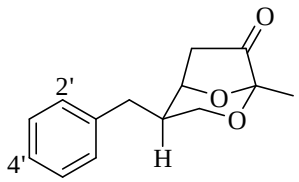


mp.: 63-65 ^{o}C. ν_{max} (ATR) : 3131, 2974-2871, 2107 (***C*=*N*$_2$**), 1626 (***C*=*O***), 1335,1331, 1023, 829, 730, 700, 670 cm^{-1}. δ_H (400 MHz; $CDCl_3$) : 7.32-7.28 (2H, m, Ar-***H***), 7.23-7.10 (3H, m, Ar-***H***), 5.70 (1H, s, 2-***H***), 3.85 (2H, dd, *J* 11.6, 4.5, 4'-***H***$_{eq}$, 6'-***H***$_{eq}$), 3.52 (2H, t, *J* 11.6, 4'-***H***$_{ax}$, 6'-***H***$_{ax}$), 2.40-2.30 (3H, m, 5'-***H***, 5'-C***H***$_2$Ph), 1.40 (3H, s, 2'-C***H***$_3$). δ_C (100.5 MHz; $CDCl_3$) : 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'-***C***H$_2$Ph), 26.1 (2'-***C***H$_3$). *m/z* (ES$^+$) : 283.1 ([M+Na]$^+$, 100 %). Anal. [Found : C, 64.2; H, 6.3; N, 10.4. $C_{14}H_{16}N_2O_3$ 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, $Rh_2(OAc)_4$ (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

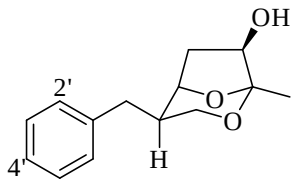
chromatography (petroleum ether/EtOAc : 9/1), to give the C-H insertion product **398** (0.10 g, 50%) as a white solid.



mp.: 80-82 ^{o}C. ν_{max} (ATR) : 3062, 3000-2842, 1752 (***C*=*O***), 1180, 1095, 1020, 858, 742, 702, 550 cm^{-1}. δ_H (400 MHz; $CDCl_3$) : 7.30-7.25 (2H, m, 3'-***H***), 7.22-7.15 (1H, m, 4'-***H***), 7.12 (2H, d, *J* 7.2, 2'-***H***), 4.55 (1H, ddd, *J* 7.5, 3.4, 1.0, 5-***H***), 3.88 (1H, ddd, *J* 12.1, 5.8, 1.0, 3-$\boldsymbol{H}_{eq}$***)***, 3.63 (1H, t, *J* 12.1, 3-$\boldsymbol{H}_{ax}$***)***, 2.85-2.80 (1H, m, 4-***H)***, 2.63 (1H, dd, *J* 18.4, 7.5, 6-***H***H), 2.48 (1H, d, *J* 18.4, 6-H***H***), 2.38 (2H, d, *J* 8.1, 4-C$\boldsymbol{H}_2$Ph), 1.35 (3H, s, 1-C$\boldsymbol{H}_3$). δ_C (100.5 MHz; $CDCl_3$) : 211.0 (***C***-7), 137.4 (***C***-1'), 128.9 (Ar-***C***), 128.6 (Ar-***C***), 126.8 (Ar-***C***), 98.0 (***C***-1), 74.5 (***C***-5), 66.0 (***C***-3), 38.8 (***C***-4), 35.9 (***C***-6), 34.8 (4-***C***H_2Ph), 18.2 (1-***C***H_3). *m/z* (CI, NH_3) : 250 ($[M+NH_4]^+$, 29%), 233 ($[M+H]^+$, 100), 217 (12), 203 (20), 187 (10), 144 (25), 129 (10), 91 ($PhCH^+$, 18), 77 (Ph^+, 5). HRMS (ES^+) found: 255.1223 ($C_{14}H_{16}O_3Na$ requires $[M+Na]^+$ 255.1259). Anal. [Found: C, 71.3; H, 7.0. $C_{14}H_{16}O_3$ requires C, 71.4; H, 6.9%].

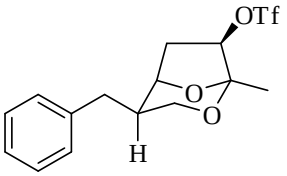
(7*R*)-4-benzyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (399) :

$NaBH_4$ (0.02g, 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_4Cl) was added and the organic layer was then separated and washed with brine (NaCl). The organic extracts were dried over magnesium sulphate ($MgSO_4$), filtered and concentrated *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%).



ν_{max} (ATR) : 3670-2950 (broad ***OH***), 1632, 1262, 1160, 1068, 1050, 745, 700, 702, 550 cm^{-1}. δ_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-$\boldsymbol{H}_{ax}$***)***, 3.77 (1H, ddd, *J* 11.7, 5.8, 1.4, 3-$\boldsymbol{H}_{eq}$), 2.52-2.45 (1H, m, 4-***H***), 2.43 (1H, ddd, *J* 13.6, 11.0, 7.7, 6-***H***H), 2.28 (2H, m, 4-C$\boldsymbol{H}_2$Ph), 1.93 (1H, bs, O***H***), 1.79 (1H, dd, *J* 13.6, 3.8, 6-H***H***), 1.31 (3H, s, 1-C$\boldsymbol{H}_3$). δ_C (100.5 MHz; $CDCl_3$) : 138.2 (***C***-1'), 128.8 (***C***-2', ***C***-3'), 126.6 (***C***-4'), 102.7 (***C***-1), 77.1 (***C***-5), 75.4 (***C***-7), 65.7 (***C***-3), 38.9 (***C***-4), 35.0 (4-***C***H_2Ph), 32.7 (***C***-6), 22.2 (1-***C***H_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%].

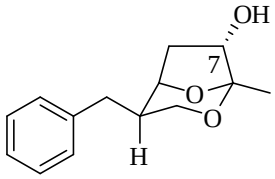
(7*R*)-4-benzyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-7-yltrifluoromethanesulfonate (412):
To a solution of the bicyclic alcohol **399** (0.18 g, 0.77 mmol) in DCM (10.0 ml), maintained at 0 ^oC was added 2,6-lutidine (0.28 ml, 2.31 mmol), after 30 min trifluoromethane sulfonic anhydride (Tf_2O, 0.40 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 1.M $CuSO_4$ (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.



ν_{max} (ATR) : 1454, 1413+1202 (**OSO**$_2$), 1391, 1246, 1142, 1035, 977, 949, 883, 734 cm^{-1}. δ_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, dd, *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-$\boldsymbol{H}_{eq}$), 3.78 (1H, t, *J* 12.0, 3-$\boldsymbol{H}_{ax}$), 2.71 (1H, dd, *J* 14.5, 10.9, 6-H***H***), 2.63-2.56 (1H, m, 4-***H)***, 2.41-2.32 (2H, m, 4-C$\boldsymbol{H}_2$Ph), 2.12 (1H, dd, *J* 14.5, 3.7, 6-***H***H), 1.45 (3H, s, 1-C$\boldsymbol{H}_3$). δ_F (376.3 MHz; $CDCl_3$) : -74.79. δ_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, **C**F_3), 100.9 (***C***-1), 86.4 (***C***-7), 76.6 (***C***-5), 65.2 (***C***-3), 38.4 (***C***-4), 34.7 (4-***C***H_2Ph), 30.1 (***C***-6), 21.9 (1-***C***H_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).

(7*S*)-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 $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc : 7/3) to yield as an inseperable 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.

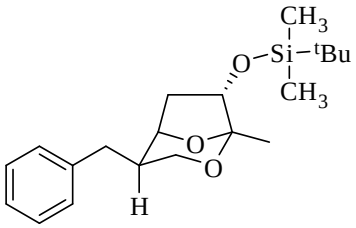


ν_{max} (ATR) : 3620-3170 (broad ***OH***), 2942, 1604, 1495, 1386, 1269, 1212, 1162, 1034, 990, 740, 700, 662, 629 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.28 (2H, t, *J* 7.7, 3'-***H***), 7.21 (1H, t, *J* 7.7, 4'-***H***), 7.10 (2H, d, *J* 7.7, 2'-***H***), 4.33 (1H, d, *J* 7.4, 7-***H***), 4.25 (1H, dd, *J* 7.4, 3.0, 5-***H)***, 3.75 (1H, dd, *J* 11.7, 5.4, 3-$\boldsymbol{H}_{eq}$), 3.39 (1H, t, *J* 11.7, 3-$\boldsymbol{H}_{ax}$), 2.49 (1H, dd, *J* 13.8, 7.4, 6-***H***H), 2.47-2.42 (1H, m, 4-***H***), 2.34 (1H, dd, *J* 14.0, 7.8, 4-C***H***HPh), 2.28 (1H, dd, *J* 14.0, 7.8, 4-CH***H***Ph), 2.10 (1H, bs, O***H***), 1.83 (1H, ddd, *J* 13.8, 7.4, 3.0, 6-H***H***), 1.43 (3H, s, 1-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 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-***C***H_2Ph), 19.6 (1-***C***H_3). *m/z* (EI) : 234 (M^+, 2%), 216 (M^+-H_2O, 5), 157 (M^+-Ph, 10), 143 (M^+-CH_2Ph, 10), 91 (CH_2Ph^+, 100), 77 (Ph^+, 5). HRMS ($ASAP^+$) found: 235.1323 ($C_{14}H_{19}O_3$ requires $[M+H]^+$ 235.1334).

[(7*S*)-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).



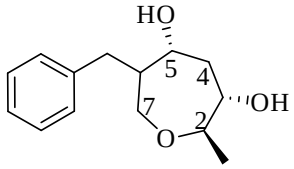
ν_{max} (ATR) : 3020-2855 (***CH***-OSi), 1496, 1472, 1387, 1258+837 (***Si-C***H_3), 1210, 1165, 1088, 836, 699 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.27 (2H, t, *J* 7.3, 3'-***H***), 7.20 (1H, t, *J* 7.3, 4'-***H***), 7.10 (2H, d, *J* 7.3, 2'-***H***), 4.33 (1H, d, *J* 7.5, 5-***H***), 4.24 (1H, dd, *J* 7.5, 3.1, 7-***H)***, 3.74 (1H, dd, *J* 11.5, 5.1, 3-$\boldsymbol{H}_{eq}$), 3.39 (1H, t, *J* 11.5, 3-$\boldsymbol{H}_{ax}$), 2.47-2.40 (1H, m, 4-***H***), 2.39-2.25 (3H, m, 4-C$\boldsymbol{H}_2$Ph, 6-***H***H), 1.87 (1H, ddd, *J* 13.4, 7.5, 3.1, 6-H***H***), 1.37 (3H, s, 1-C$\boldsymbol{H}_3$), 0.91 (9H, s, SiC(C$\boldsymbol{H}_3$)$_3$), 0.10 (3H, s, Si(C$\boldsymbol{H}_3$)$_2$), 0.07 (3H, s, Si(C$\boldsymbol{H}_3$)$_2$). δ_C (125 MHz; $CDCl_3$) : 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***H_2Ph), 25.8 (SiC(***C***H_3)$_3$), 20.0 (1-***C***H_3), 18.1 (Si***C***$(CH_3)_3$), -4.6 (SiC(***C***H_3)$_2$), -4.9 (SiC(***C***H_3)$_2$). *m/z* (ES^+) : 371 ($[M+Na]^+$, 50%), 349 ($[M+H]^+$, 100). HRMS (ES^+) found: 371.2017 ($C_{20}H_{32}O_3NaSi$ requires $[M+Na]^+$ 371.2013).

(2*R*,3*S*,5*R*)-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_3SiH, 0.08 ml, 0.51 mmol) was added at -78 ^oC 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 ^oC. 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.

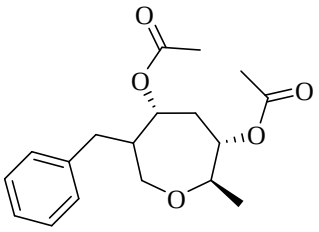


ν_{max} (ATR) : 3604-3160 (broad ***OH***), 2928, 1602, 1496, 1375, 1081, 1030, 868, 745, 699 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.28 (2H, t, *J* 7.7, 3'-***H***), 7.21-7.19 (3H, m, Ar-***H***), 4.33-4.30 (1H, m, 5-***H***), 4.01-3.99 (1H, m, 3-***H)***, 3.81 (1H, qd, *J* 6.5, 3.7, 2-***H***), 3.65 (1H, dd, *J* 11.1, 7.0, 7-***H***H), 3.58 (1H, dd, *J* 11.1, 3.5, 7-H***H***), 2.64 (1H, dd, *J* 13.8, 5.7, 6-C***H***HPh), 2.58 (1H, dd, *J* 13.8, 9.1, 6-CH***H***Ph), 2.23-2.19 (1H, m, 6-***H***), 2.11-2.06 (1H, m, 4-***H***H), 1.84 (1H, ddd, *J* 13.2, 5.9, 2.8, 4-H***H***), 1.26 (3H, d, *J* 6.5, 2-C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 139.8 (***C***-1'), 128.9 (***C***-2'), 128.4 (***C***-3'), 126.1 (***C***-4'), 82.4 (***C***-2), 80.5 (***C***-5), 77.4 (***C***-3), 63.0 (***C***-7), 44.6 (***C***-6), 36.4 (***C***-4), 33.2 (6-***C***H_2Ph), 19.4 (2-***C***H_3). *m/z* (ES^+) : 259 ($[M+Na]^+$, 100%), 243 (30), 237 ($[M+H]^+$, 15). HRMS (ES^+) found: 259.1303 ($C_{14}H_{20}O_3Na$ requires $[M+Na]^+$ 259.1305).

(2*R*,3*S*,5*R*)-6-benzyl-2-methyloxepane-3,5-diyl 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 $NaHCO_3$, extracted with DCM (2 × 10.0 ml) and the combined organic extracts were washed with brine, dried over $MgSO_4$, 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 coloueless 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.

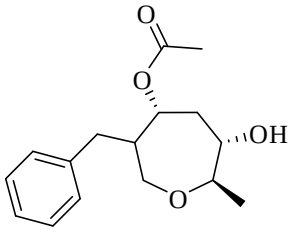


ν_{max} (ATR) : 2974, 1733 (***C*=*O***), 1604, 1546, 1364, 1230, 1067, 1023, 907, 748, 701, 606 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.28 (2H, t, *J* 7.4,3'-***H***), 7.21-7.18 (3H, m, Ar-***H***), 4.84-4.83 (1H, m, 3-***H***), 4.02-3.93 (4H, m, 2-***H***, 5-***H***, 7-$\boldsymbol{H}_2$), 2.96 (1H, dd, *J* 13.9, 4.7, 6-C***H***HPh), 2.64 (1H, dd, *J* 13.9, 9.0, CH***H***Ph), 2.14-2.11 (1H, m, 6-***H***), 2.06 (3H, s, C$\boldsymbol{H}_3$CO), 2.02 (3H, s, C$\boldsymbol{H}_3$CO), 1.98 (1H, dd, *J* 13.7, 6.5, 4-***H***H), 1.94 (1H, dd, *J* 13.7, 5.6, 4-H***H***), 1.29 (3H, d, *J* 6.5, 2-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 170.9 (5-CH_3***C***OO), 170.7 (3-CH_3***C***OO), 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-***C***H_2Ph), 21.1 (***C***H_3COO), 20.9 (***C***H_3COO), 19.7 (2-***C***H_3). *m/z* (ES^+) : 343 ($[M+Na]^+$, 100%), 321 ($[M+H]^+$, 30), 201 (10), 183 (5). HRMS (ES^+) found: 343.1518 ($C_{18}H_{24}O_5Na$ requires $[M+Na]^+$ 343.1516).

(4*R*,6*S*,7*R*)-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.

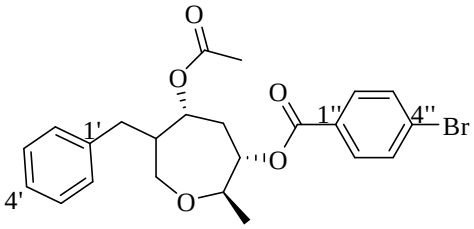


ν_{max} (ATR) : 3480-3308 (broad ***OH***), 2962, 1725 (***C*=*O***), 1496, 1454, 1388, 1230, 1067, 1023, 907, 748, 701, 606 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.29-7.26 (2H, m, Ar-***H***), 7.20-7.18 (3H, m, Ar-***H***), 4.11-4.08 (1H, m, 6-***H***), 4.01-3.96 (3H, m, 2-$\boldsymbol{H}_2$, 4-***H***), 3.85-3.82 (1H, m, 7-***H***), 2.94 (1H, dd, *J* 13.8, 5.1, 3-C***H***HPh), 2.66 (1H, dd, *J* 13.8, 9.1, 3-CH***H***Ph), 2.12-2.09 (1H, m, 3-***H***), 2.01 (3H, s, C$\boldsymbol{H}_3$CO), 1.97-1.92 (1H, m, 5-***H***H), 1.90-1.87 (1H, m, 5-H***H***), 1.60 (1H, bs, O***H***), 1.25 (3H, d, *J* 6.4, 7-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 171.0 (4-CH_3***C***OO), 139.6 (***C***-1'), 129.2 (***C***-2'), 128.4 (***C***-3'), 126.1 (***C***-4'), 82.2 (***C***-7), 77.9 (***C***-6), 77.8 (***C***-4), 63.7 (***C***-2), 44.2 (***C***-3), 38.4 (***C***-5), 34.1 (3-***C***H_2Ph), 20.9 (4-***C***H_3COO), 19.6 (7-***C***H_3). *m/z* (ES^+) : 342 ($[M+Na+CH_3CN]^+$, 100%), 301, ($[M+Na]^+$, 20), 279 ($[M+H]^+$, 80), 201 (40), 183 (10).

(2*R*,3*S*,5*R*)-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 $NaHCO_3$, and then extracted with DCM (2 × 10.0 ml) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered 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 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.

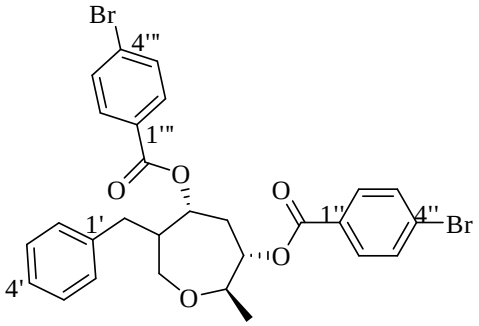


ν_{max} (ATR) : 1718 (***C*=*O***), 1590, 1484, 1453, 1398, 1268, 1234, 1172, 1034, 847, 756, 701 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.88 (2H, d, *J* 8.6, 2''-***H***), 7.59 (2H, d, *J* 8.6, 3''-***H***), 7.29 (2H, t, *J* 7.7, 3'-***H***), 7.20 (3H, m, 2'-***H***, 4'-***H***), 5.08-5.07 (1H, m, 3-***H***), 4.13-4.07 (2H, m, 2-***H***, 5-***H***), 4.04 (1H, dd, *J* 11.4, 5.1, 7-***H***H), 4.00 (1H, dd, *J* 11.4, 5.9, 7-H***H***), 2.98 (1H, dd, *J* 14.0, 5.0, 6-C***H***HPh), 2.68 (1H, dd, *J* 14.0, 8.7, 6-CH***H***Ph), 2.20-2.16 (1H, m, 6-***H***), 2.13-2.07 (2H, m, 4-$\boldsymbol{H}_2$), 2.02 (3H, s, 5-C$\boldsymbol{H}_3$CO), 1.36 (3H, d, *J* 6.5, 2-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 170.9 (5-CH_3***C***OO), 165.5 (3-Ar***C***OO), 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-***C***H_2Ph), 20.9 (5-***C***H_3COO), 19.8 (2-***C***H_3). *m/z* (EI) : 460 (M^+, 6%), 200 (65), 185 (65), 109 (80), 96 (100), 83 (100), 55 ($CH_3CO_2^+$, 2). HRMS ($ASAP^+$) found: 461.0948 ($C_{23}H_{26}O_5{}^{79}Br$ requires $[M+H]^+$ 461.0964).

(2*R*,3*S*,5*R*)-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 × 10.0 ml) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered 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 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.

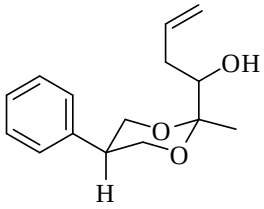


ν_{max} (ATR) : 2974, 2930, 1713 (***C*=*O***), 1592, 1486, 1456, 1398, 1265, 1178, 1102, 1011, 845, 756, 701 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.85 (2H, d, *J* 8.4, 2''-***H***), 7.80 (2H, d, *J* 8.4, 3''-***H***), 7.57 (4H, t, *J* 7.7, 2'''-***H***, 3'''-***H***), 7.28 (2H, t, *J* 7.5, 3'-***H***), 7.21 (3H, m, 2'-***H***, 4'-***H***), 5.10-5.09 (1H, m, 3-***H***), 4.27 (2H, d, *J* 5.4, 7-$\boldsymbol{H}_2$), 4.17 (1H, q, *J* 7.7, 5-***H***), 4.13 (1H, dq, *J* 6.5, 2.9, 2-***H***), 3.09 (1H, dd, *J* 14.0, 4.8, 6-C***H***HPh), 2.77 (1H, dd, *J* 14.0, 9.5, 6-CH***H***Ph), 2.34-2.30 (1H, m, 6-***H***), 2.15 (2H, dd, *J* 7.7, 4.2, 4-$\boldsymbol{H}_2$), 1.37 (3H, d, *J* 6.5, 2-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 165.6 (Ar***C***OO), 165.4 (Ar***C***OO), 139.4 (***C***-1'), 131.8 (***C***-2''', ***C***-3'''), 131.1 (***C***-2''), 131.0 (***C***-3''), 129.2 (***C***-2'), 129.0 (***C***-4'''), 128.8 (***C***-4''), 128.5 (***C***-3'), 128.4 (***C***-1'''), 128.2 (***C***-1''), 126.3 (***C***-4'), 80.7 (***C***-3), 80.0 (***C***-2), 78.8 (***C***-5), 64.5 (***C***-7), 44.3 (***C***-6), 35.9 (***C***-4), 34.5 (6-***C***H_2Ph), 19.8 (2-***C***H_3). *m/z* (EI) : 418 (M^+-BrPhCO, 6%), 235 (M^+-2 × BrPhCO, 18), 198 (100), 185 (80), 91 ($PhCH_2^+$, 20), 77 (Ph^+, 28). HRMS ($ASAP^+$) found: 601.0200 ($C_{28}H_{26}O_5{}^{79}Br_2$ requires $[M+H]^+$ 601.0225).

1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-3-en-1-ol (259, **260) :**

Major isomer **259** :

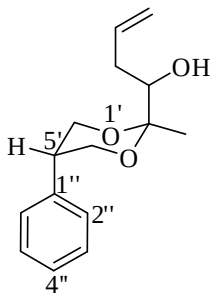
To a stirred solution of aldehyde **176** (2.70 g, 13.1 mmol) in THF (70.0 ml) at -78 ^oC was added allylmagnesium bromide, 1 M in diethylether (21.0 ml, 21.0 mmol). The cooling bath was removed after the addition and the reaction was stirred at room temperature overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride (NH_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 **259** as a clear oil (3.04 g, 94%).



ν_{max} (ATR) : 3620-3310 (***OH*** br), 2874, 1641 (***C*=*C***), 1496, 1452, 1136, 1073, 868, 756 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.36-7.32 (4H, m, Ar-***H***), 7.29-7.25 (1H, m, Ar-***H***), 5.99-5.91 (1H, m, 3-***H***), 5.19 (1H, dd, *J* 17.1, 1.6, 4-***H***H), 5.13 (1H, dd, *J* 10.2, 1.6, 4-H***H***), 4.20 (1H, dd, *J* 11.7, 4.6, 4'-$\boldsymbol{H}_{eq}$), 4.16 (1H, dd, *J* 11.7, 4.6, 6'-$\boldsymbol{H}_{eq}$), 4.12 (1H, td, *J* 9.6, 2.5, 1-***H***), 4.09 (1H, dd, *J* 11.7, 7.1, 4'-$\boldsymbol{H}_{ax}$), 4.01 (1H, dd, *J* 11.7, 7.1, 6'-$\boldsymbol{H}_{ax}$), 3.04-2.99 (1H, dd, *J* 7.1, 4.6, 5'-***H***), 2.42 (1H, m, 2-***H***H), 2.23-2.18 (1H, m, 2-H***H***), 2.15 (1H, bs, O***H***), 1.43 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 140.3 (***C***-1''), 135.6 (***C***-3), 128.6 (Ar-***C***), 127.8 (Ar-***C***), 127.1 (Ar-***C***), 117.1 (***C***-4), 99.8 (***C***-2'), 70.8 (***C***-1), 64.7 (***C***-4'***)***, 64.2 (***C***-6'), 39.9 (***C***-5'), 35.4 (***C***-2), 17.3 (2'-$\boldsymbol{C}H_3$). *m/z* (ES^+) : 312 ($[M+Na+CH_3CN]^+$, 10%), 271 ($[M+Na]^+$, 100), 249 ($[M+H]^+$, 5). HRMS (ES^+) found: 271.1305 ($C_{15}H_{20}O_3Na$ requires $[M+Na]^+$ 271.1305).

Minor isomer **260** :

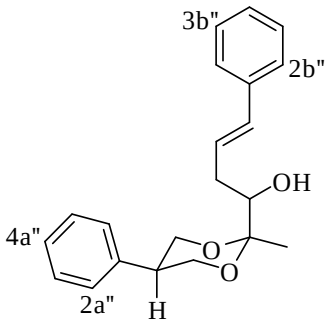
To a solution of aldehyde **177** (0.72 g, 3.50 mmol) stirred in THF (20.0 ml) at -78 ^oC was added a solution of allylmagnesium bromide, 1 M in diethylether (6.00 ml, 5.59 mmol). The cooling bath was removed after the addition and reaction was stirred at room temperature overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride (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, then 8:2) to give the title alcohol **260** as a clear oil (0.80 g, 92%).



ν_{max} (ATR) : 3570-3304 (***OH*** br), 2873, 1641 (***C*=*C***), 1495, 1449, 1375, 1247, 1147, 1071, 911, 873, 755, 697 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.34 (2H, t, *J* 7.7, 3''-***H***), 7.28 (1H, d, *J* 7.7, 4''-***H***), 7.21 (2H, d, *J* 7.7, 2''-***H***), 5.98-5.92 (1H, m, 3-***H***), 5.18 (1H, dd, *J* 17.0, 1.6, 4-***H***H), 5.12 (1H, dd, *J* 10.1, 1.6, 4-H***H***), 4.07 (2H, t, *J* 11.5, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 4.02-3.98 (2H, m, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.60 (1H, td, *J* 10.1, 3.5, 1-***H***), 3.20-3.16 (1H, m, 5'-***H***), 2.48 (1H, m, 2-***H***H), 2.36 (1H, d, *J* 3.5, O***H***), 2.27-2.22 (1H, m, 2-H***H***), 1.53 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (175 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'-***C***H_3). *m/z* (ES^+) : 312 ($[M+Na+CH_3CN]^+$, 100%), 271 ($[M+Na]^+$, 20), 249 ($[M+H]^+$, 5). HRMS (ES^+) found: 271.1299 ($C_{15}H_{20}O_3Na$ requires $[M+Na]^+$ 271.1305).

(*E*)-1-(2'-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 ^oC followed by the immediate addition of Grubbs's 2nd 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 *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%).

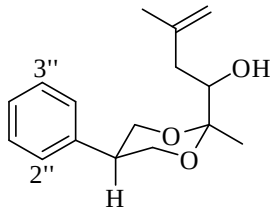


mp.: 121-123 ^oC. ν_{max} (ATR) : 3491-3350 (***OH***), 2910, 1598 (***C*=*C***), 1493, 1451, 1382, 1145, 1076, 970, 864, 755, 696 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.38 (2H, d, *J* 7.7, 2a''-***H***), 7.36-7.33 (4H, m), 7.30 (2H, t, *J* 7.7, 3a''-***H***), 7.27 (1H, t, *J* 6.9, 4b''-***H***), 7.21 (1H, t, *J* 7.7, 4a''-***H***), 6.52 (1H, d, *J* 15.9, 4-***H***), 6.37 (1H, td, *J* 15.9, 7.3, 3-***H***), 4.22-4.17 (3H, m, 1-***H***, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 4.10 (1H, dd, *J* 11.7, 6.9, 4'-$\boldsymbol{H}_{eq}$), 4.04 (1H, dd, *J* 11.7, 6.9, 6'-$\boldsymbol{H}_{eq}$), 3.04-3.01 (1H, m, 5'-***H***), 2.57 (1H, dd, *J* 14.6, 7.3, 2-***H***H), 2.39-2.34 (1H, m, 2-H***H***), 2.19 (1H, s, O***H***), 1.47 (3H, s, 2'-

C***H***$_3$). δ_C (175 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'-***C***H_3). *m/z* (EI) : 324 (M^+, 2%), 306 (M^+-H_2O, 6), 291 (M^+-H_2O-Me, 2), 177 (100), 117 (70), 91 ($PhCH_2^+$, 20), 77 (Ph^+, 40). Anal. [Found: C, 77.2; H, 7.5. $C_{21}H_{24}O_3$ 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 ^oC 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%).

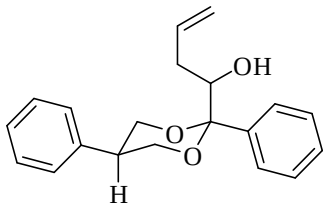


ν_{max} (ATR) : 3510-3488 (***OH*** br), 2874, 1648 (***C=C***), 1496, 1452, 1393, 1143, 1076, 881, 756 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.34 (4H, sd, *J* 2.4, 2''-***H***, 3''-***H***), 7.28-7.25 (1H, m, 4''-***H***), 4.88 (1H, s, 4-***H***H), 4.87 (1H, s, 4-H***H***), 4.24 (1H, d, *J* 10.8, 1-***H***), 4.21 (1H, dd, *J* 11.6, 4.6, 4'-$\boldsymbol{H}_{eq}$), 4.17 (1H, dd, *J* 11.6, 4.6, 6'-$\boldsymbol{H}_{eq}$), 4.11 (1H, dd, *J* 11.6, 7.0, 4'-$\boldsymbol{H}_{ax}$), 4.02 (1H, dd, *J* 11.6, 7.0, 6'-$\boldsymbol{H}_{ax}$), 3.04-3.01 (1H, dd, *J* 7.0, 4.6, 5'-***H***), 2.35 (1H, d, *J* 14.6, 2-***H***H), 2.15 (1H, dd, *J* 14.6, 10.8, 2-H***H***), 2.08 (1H, bs, O***H***), 1.84 (3H, s, 3-C$\boldsymbol{H}_3$), 1.44 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (175 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-***C***H_3), 17.4 (2'-***C***H_3). *m/z* (ES^+) : 285 ($[M+Na]^+$, 10%), 263 ($[M+H]^+$, 10), 245 ($[M+H+H_2O]^+$, 100).

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 ^{o}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 (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 **261** as a white solid (2.23 g, 72%).

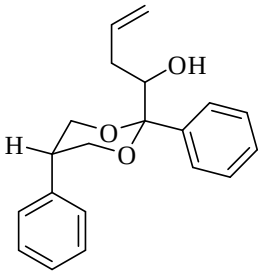


mp.: 110-112 ^{o}C. ν_{max} (ATR) : 3521 (***OH***), 1641 (***C*=*C***), 1493, 1450, 1393, 1169, 1027, 969, 759 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.63 (2H, d, *J* 8.4, Ar-***H***), 7.48-7.44 (4H, m, Ar-***H***), 7.38 (3H, m, Ar-***H***), 7.28 (1H, t, *J* 7.4, Ar-***H***), 5.79 (1H, m, 3-***H***), 5.03 (1H, dd, *J* 17.1, 1.7, 4-***H***H), 5.01 (1H, dd, *J* 6.9, 1.7, 4-H***H***), 4.26 (1H, dd, *J* 11.7, 3.7, 4'-$\boldsymbol{H}_{ax}$), 4.24 (1H, dd, *J* 11.7, 3.7, 6'-$\boldsymbol{H}_{ax}$), 4.15 (1H, ddd, *J* 11.7, 2.3, 1.6, 4'-$\boldsymbol{H}_{eq}$), 4.09 (1H, ddd, *J* 11.7, 2.3, 1.6, 6'-$\boldsymbol{H}_{eq}$), 3.72 (1H, dd, *J* 10.4, 2.5, 1-***H***), 2.55 (1H, m, 5'-***H***), 2.28-2.23 (1H, m, 2-***H***H), 2.10 (1H, d, *J* 2.5, O***H***), 2.00-1.94 (1H, m, 2-H***H***). δ_C (125 MHz; $CDCl_3$) : 142.7 (Ar-***C***), 135.6 (***C***-3), 135.5 (Ar-***C***), 128.6 (Ar-***C***), 128.49 (Ar-***C***), 128.45 (2 × Ar-***C***), 128.2 (Ar-***C***), 126.6 (Ar-***C***), 116.7 (***C***-4), 102.1 (***C***-2'), 77.2 (***C***-1), 65.2 (***C***-4'***)***, 65.1 (***C***-6'), 38.8 (***C***-5'), 34.7 (***C***-2). *m/z* (ES$^+$) : 311 ([M+H]$^+$, 40%), 177 (100), 131 (5). HRMS (ES$^+$) found: 311.1643 ($C_{20}H_{23}O_3$ requires [M+H]$^+$ 311.1645). Anal. [Found: C, 76.9; H, 7.2. $C_{20}H_{22}O_3$ requires C, 77.4; H, 7.1%].

Minor isomer **262** :

To a stirred solution of aldehyde **179** (0.89 g, 3.32 mmol) in THF (22.0 ml) at -78 ^{o}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 (NH_4Cl)

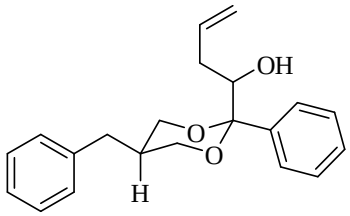
solution and extracted with diethylether (3 × 30.0 ml). Combined organic extracts were dried over $MgSO_4$ and filtrate concentrated in *vacuo.* The crude residue was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 9:1) to give the title alcohol **262** as a clear oil (0.67 g, 65%).



ν_{max} (ATR) : 3503 (***OH***), 1640 (***C*=*C***), 1494, 1446, 1390, 1134, 1027, 912, 756 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.48-7.45 (4H, m, Ar-***H***), 7.40 (1H, t, *J* 6.8, Ar-***H***), 7.23 (2H, t, *J* 7.2, Ar-***H***), 7.19 (1H, t, *J* 7.2, Ar-***H***), 6.98 (2H, d, *J* 7.2, Ar-***H***), 5.85-5.79 (1H, m, 3-***H***), 5.05 (1H, dd, *J* 17.2, 1.3, 4-***H***H), 5.02 (1H, dd, *J* 10.3, 1.3, 4-H***H***), 4.08-4.02 (2H, m, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.88 (1H, t, *J* 11.7, 4'-$\boldsymbol{H}_{ax}$), 3.85 (1H, t, *J* 11.7, 6'-$\boldsymbol{H}_{ax}$), 3.69 (1H, dt, *J* 10.2, 3.0, 1-***H***), 3.43-3.30 (1H, m, 5'-***H***), 2.51 (1H, d, *J* 3.0, O***H***), 2.29-2.26 (1H, m, 2-***H***H), 2.12-2.07 (1H, m, 2-H***H***). δ_C (175 MHz; $CDCl_3$) : 137.6 (Ar-***C***), 135.8 (Ar-***C***), 135.5 (***C***-3), 128.7 (Ar-***C***), 128.64 (Ar-***C***), 128.60 (Ar-***C***), 128.5 (Ar-***C***), 127.5 (Ar-***C***), 127.3 (Ar-***C***), 116.9 (***C***-4), 101.8 (***C***-2'), 77.3 (***C***-1), 66.3 (***C***-4'***)***, 66.1 (***C***-6'), 41.2 (***C***-5'), 34.7 (***C***-2). *m/z* (ES^+) : 643 ($[2M+Na]^+$, 10%), 374 ($[M+Na+CH_3CN]^+$, 100), 333 ($[M+Na]^+$,10). HRMS (ES^+) found: 311.1642 ($C_{20}H_{23}O_3$ requires $[M+H]^+$ 311.1642).

1-(5'-benzyl-2'-phenyl-1',3'-dioxan-2'-yl)but-3-en-1-ol (263) :

To a solution of aldehyde **180** (2.80 g, 9.93 mmol) stirred in THF (15.0 ml) at -78 ^oC was added allylmagnesium bromide, 1 M in diethylether (16.0 ml, 15.9 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 (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 **363** as a white solid (2.61 g, 81%).



mp.: 110-112 ^{o}C. ν_{max} (ATR) : 3560 (***OH***), 2915, 1641 (***C*=*C***), 1494, 1449, 1375, 1142, 1019, 914, 746, 701 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.43-7.41 (4H, m, Ar-***H***), 7.37-7.35 (1H, m, Ar-***H***), 7.31 (2H, t, *J* 7.5, Ar-***H***), 7.25-7.21 (3H, m, Ar-***H***), 5.89-5.83 (1H, m, 3-***H***), 5.09 (1H, dd, *J* 17.2, 1.6, 4-***H***H), 5.05 (1H, dd, *J* 10.2, 1.6, 4-H***H***), 3.91 (2H, dd, *J* 9.4, 2.7, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.72 (2H, t, *J* 9.4, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.68 (1H, dd, *J* 3.9, 2.7, 1-***H***), 3.12 (2H, d, *J* 8.0, 5'-C$\boldsymbol{H}_2$Ph), 2.44-2.41 (1H, m, 2-***H***H), 2.33 (1H, d, *J* 3.9, O***H***), 2.15-2.10 (1H, m, 2-H***H***), 1.51-1.49 (1H, m, 5'-***H***). δ_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'-***C***H_2Ph), 34.7 (***C***-2). *m/z* (EI) : 324 (M^+, 5%), 253 (M^+-$CHOHCH_2CH{=}CH_2$, 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).

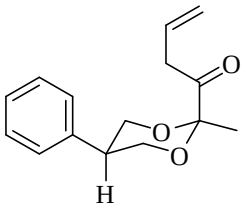
1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-3-en-1-one (264, 265) and (*E*)-1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-2-en-1-one (268, 269) :

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®, washed with DCM (3 × 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%).

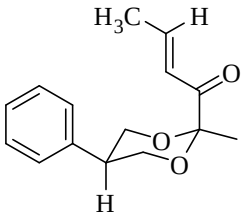
Careful separation of fractions enabled small analytical samples of each isomer to be obtained.

Isomer **264** :



ν_{max} (ATR) : 2965, 1728 (***C*=*O***), 1702, 1630 (***C*=*C***), 1496, 1453, 1372, 1241, 1133, 1026, 880, 756, 625 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.30 (2H, t, *J* 7.4, Ar-***H***), 7.25 (1H, t, *J* 7.4, Ar-***H***), 7.10 (2H, d, *J* 7.4, Ar-***H***), 6.05-5.99 (1H, m, 3-***H***), 5.23 (1H, dd, *J* 10.2, 1.3, 4-***H***H), 5.19 (1H, dd, *J* 17.2, 1.3, 4-H***H***), 4.06 (2H, dd, *J* 11.5, 4.7, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.80 (2H, t, *J* 11.5, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.41 (2H, d, *J* 6.9, 2-$\boldsymbol{H}_2$), 3.24-3.20 (1H, m, 5'-***H***), 1.49 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 208.1 (***C***-1), 137.2 (***C***-1''), 130.4 (***C***-3), 128.8 (Ar-***C***), 127.6 (Ar-***C***), 127.5 (Ar-***C***), 119.0 (***C***-4), 100.8 (***C***-2'), 67.9 (***C***-4', ***C***-6'), 41.9 (***C***-2), 40.3 (***C***-5'), 24.7 (2'-***C***H_3). *m/z* (ES^+) : 515 ($[2M+Na]^+$, 10%), 310 ($[M+Na+CH_3CN]^+$, 70), 307 (100), 269 ($[M+Na]^+$, 90), 247 ($[M+H]^+$, 70). HRMS (ES^+) found: 269.1150 ($C_{15}H_{18}O_3Na$ requires $[M+Na]^+$ 269.1148).

Isomer **268** :

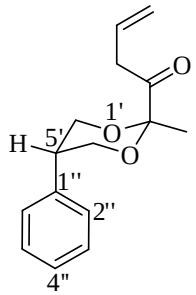


ν_{max} (ATR) : 2964, 1705 (***C*=*O***), 1627 (***C*=*C***), 1495, 1443, 1369, 1296, 1190, 1043, 881, 755, 667, 529 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.27-7.19 (4H, m, Ar-***H***, 3-***H***), 7.07 (2H, d, *J* 7.3, Ar-***H***), 6.63 (1H, d, *J* 15.4, 2-***H***), 4.02 (2H, dd, *J* 12.2, 4.7, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.81 (2H, t, *J* 12.2, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.25-3.20 (1H, m, 5'-***H***), 1.95 (3H, d, *J* 6.9, 4-$\boldsymbol{H}_3$), 1.44 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 198.2 (***C***-1), 146.3 (***C***-3), 137.4 (***C***-1''), 128.7 (Ar-***C***), 127.6 (Ar-***C***), 127.4 (Ar-***C***), 125.9 (***C***-2), 100.7 (***C***-2'), 67.8 (***C***-4', ***C***-6'), 40.5 (***C***-5'), 24.9 (2'-***C***H_3), 18.6 (***C***-4). *m/z* (ES^+) : 575 (40%), 413 (15), 269 ($[M+Na]^+$, 100), 229 (45). HRMS (ES^+) found: 269.1150 ($C_{15}H_{18}O_3Na$ requires $[M+Na]^+$ 269.1148).

Minor isomer **265**, **269** :

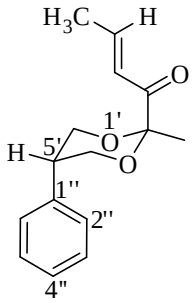
To a stirred mixture of powdered 4Å molecular sieves (17.0 g) and PDC (2.77 g, 7.36 mmol) in dry DCM (100 ml) under argon at room temperature was added a solution of alcohol **260** (0.44 g, 1.77 mmol) in DCM (20.0 ml). After stirring at room temperature for 4 h, the reaction mixture was filtered through 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** :



ν_{max} (ATR) : 2877, 1729 (***C*=*O***), 1641 (***C*=*C***), 1496, 1451, 1392, 1319, 1247, 1171, 1023, 919, 869, 755, 632 cm^{-1}. δ_H (700 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, 4***H***H), 5.18 (1H, dd, *J* 17.0, 1.4, 4-H***H***), 4.13-4.09 (4H, m, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.49 (2H, d, *J* 6.8, 2-$\boldsymbol{H}_2$), 2.98-2.95 (1H, m, 5'-***H***), 1.56 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (175 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'-***C***H_3). *m/z* (ES^+) : 310 ($[M+Na+CH_3CN]^+$, 80%), 269 ($[M+Na]^+$, 100). HRMS (ES^+) found: 269.1144 ($C_{15}H_{18}O_3Na$ requires $[M+Na]^+$ 269.1148).

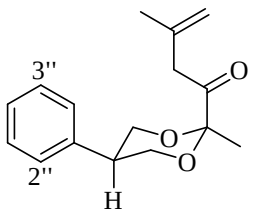
Isomer **269** :



ν_{max} (ATR) : 2965, 1703 (***C*=*O***), 1627 (***C*=*C***), 1495, 1444, 1372, 1293, 1179, 1110, 1029, 972, 876, 753, 698, 629 cm^{-1}. δ_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'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 4.10 (2H, dd, *J* 12.0, 4.0, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 2.79-2.78 (1H, m, 5'-***H***), 1.97 (3H, d, *J* 7.0, 4-$\boldsymbol{H}_3$), 1.51 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_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'-***C***H_3), 18.6 (***C***-4). *m/z* (ES^+) : 310 ($[M+Na+CH_3CN]^+$, 70%), 269 ($[M+Na]^+$, 80), 242 (100). HRMS (ES^+) found: 269.1149 ($C_{15}H_{18}O_3Na$ 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%).



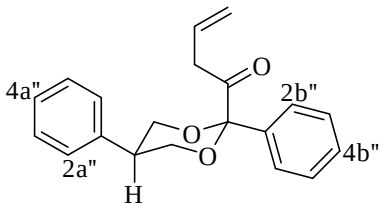
ν_{max} (ATR) : 2966, 1726 (***C*=*O***), 1648 (***C*=*C***), 1495, 1448, 1372, 1242, 1193, 1131, 1039, 884, 755, 698 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.30 (2H, t, *J* 7.7, 3''-***H***), 7.25 (1H, t, *J* 7.7, 4''-***H***), 7.10 (2H, d, *J* 7.7, 2''-***H***), 5.01 (1H, t, *J* 1.6, 4-***H***H), 4.87 (1H, dd, *J* 1.6, 0.9, 4-H***H***), 4.07 (2H, dd, *J* 11.9, 4.7, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.84 (2H, t, *J* 11.9, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.37 (2H, s, 2-$\boldsymbol{H}_2$), 3.24 (1H, tt, *J* 9.5, 4.7, 5'-***H***), 1.84 (3H, dd, *J* 1.6, 0.9, 3-C$\boldsymbol{H}_3$), 1.50 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (175 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'-***C***H_3), 22.9 (3-***C***H_3). *m/z* (ES^+) : 324 ($[M+Na+CH_3CN]^+$, 100%), 283 ($[M+Na]^+$, 10). HRMS (ES^+) found: 261.1480 ($C_{16}H_{21}O_3$ requires $[M+H]^+$ 261.1485).

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 mixtute 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** :



ν_{max} (ATR) : 2978, 1730 (***C*=*O***), 1700, 1638 (***C*=*C***), 1500, 1456, 1396, 1310, 1252, 1156, 1080, 1040, 976, 916, 753, 702 cm^{-1}. δ_H (500 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*

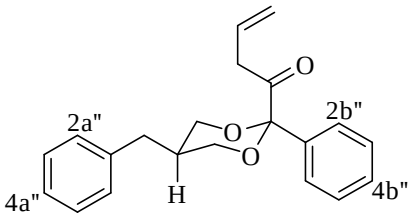
7.4, 2a''-***H***), 5.87-5.78 (1H, m, 3-***H***), 5.11 (1H, dd, *J* 10.1, 1.4, 4-***H***H), 5.02 (1H, dd, *J* 17.2, 1.4, 4-H***H***), 4.27 (2H, dd, *J* 12.1, 4.8, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 4.08 (2H, t, *J* 12.1, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.29 (2H, d, *J* 7.0, 2-$\boldsymbol{H}_2$), 3.27-3.22 (1H, m, 5'-***H***). δ_C (125 MHz; $CDCl_3$) : 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^+-$COCH_2CH{=}CH_2$, 100), 117 (60), 105 (70), 77 (Ph^+, 20). HRMS ($ASAP^+$) found: 309.1480 ($C_{15}H_{21}O_3Na$ 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 insepaprable mixture of the title ketones **267** and **271** as a coloueless oil (1.85 g, 71%).

Careful separation of fractions enabled small analytical sample of the major isomer **267** to be obtained.

Major isomer **267** :



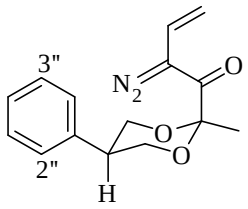
ν_{max} (ATR) : 2922, 2876, 1738 (***C***=***O***), 1640 (***C***=***C***), 1504, 1451, 1392, 1314, 1248, 1152, 1046, 1010, 980, 924, 756, 700 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.54 (2H, d, *J* 7.4, 2b''-***H***), 7.38 (2H, t, *J* 7.4, 3b''-***H***), 7.35 (1H, t, *J* 7.4, 4b''-***H***), 7.29 (2H, t, *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-***H***H), 5.03 (1H, dd, *J* 17.1, 1.4, 4-H***H***), 4.03 (2H, dd, *J* 11.7, 4.0, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.71 (2H, dd, *J* 11.7, 7.3, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.33 (2H, d, *J* 6.9, 2-$\boldsymbol{H}_2$), 2.67 (2H, d, *J* 7.8, 5'-C$\boldsymbol{H}_2$Ph), 2.11-2.06 (1H, m, 5'-

H). δ_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'-***C***H_2Ph). *m/z* (ES^+) : 667 ($[2M+Na]^+$, 20%), 386 ($[M+Na+CH_3CN]^+$, 50), 345 ($[M+Na]^+$, 100), 323 ($[M+H]^+$, 80). HRMS (ES^+) found: 323.1650 ($C_{21}H_{23}O_3Na$ requires $[M+H]^+$ 323.1647).

2-diazo-1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-3-en-1-one (279, 280) :

Major isomer **279** :

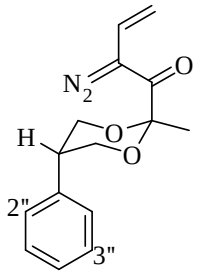
A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.40 ml, 2.68 mmol) in CH_3CN (2.00 ml) was added to a stirred mixture of the inseparable ketones of **264** and **268** (0.11 g, 0.45 mmol) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (0.21 g, 0.89 mmol) dissolved in CH_3CN (5.00 ml) at 0 ^oC. After stirring for 3 h at room temperature, a saturated ammonium chloride solution (NH_4Cl) (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 vinyldiazoketone **279** as a shiny orange oil (0.11 g, 90%).



ν_{max} (ATR) : 2924, 2082 (***C=N₂***), 1648 (***C=O***), 1609 (***C=C***), 1495, 1453, 1374, 1263, 1133, 1025, 981, 842, 755, 640 cm^{-1}. δ_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, dd, *J* 17.2, 11.2, 3-***H***), 5.27 (1H, d, *J* 11.2, 4-***H***H), 4.87 (1H, d, *J* 17.2, 4-H***H***), 4.10 (2H, dd, *J* 11.8, 4.0, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.92 (2H, t, *J* 11.8, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.28-3.25 (1H, tt, *J* 11.8, 4.0, 5'-***H***), 1.56 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_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'-***C***H_3). *m/z* (ES^+) : 567 ($[2M+Na]^+$, 85%), 336 ($[M+Na+CH_3CN]^+$, 70), 308 ($[M-N_2+Na+CH_3CN]^+$, 100), 267 ($[M-N_2+Na]^+$, 25). HRMS (ES^+) found: 295.1054 ($C_{15}H_{16}O_3N_2Na$ $[M+Na]^+$ requires 295.1053).

Minor isomer **280** :

A solution of DBU (4.40 ml, 29.3 mmol) in CH_3CN (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 CH_3CN (35.0 ml) at rt. After stirring for 3 h, a saturated ammonium chloride solution (NH_4Cl) (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 vinyldiazoketone **280** as shiny orange oil (0.72 g, 72%).

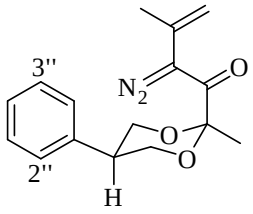


ν_{max} (ATR) : 2974, 2886, 2088 (***C*=*N*₂**), 1650 (***C*=*O***), 1614 (***C*=*C***), 1496, 1456, 1344, 1260, 1156, 1032, 990, 878, 760, 643 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.43 (2H, d, *J* 7.7, 2''-***H***), 7.35 (2H, t, *J* 7.7, 3''-***H***), 7.28 (1H, t, *J* 7.7, 4''-***H***), 6.50 (1H, dd, *J* 17.3, 9.9, 3-***H***), 5.23 (1H, d, *J* 9.9, 4-***H***H), 4.86 (1H, d, *J* 17.3, 4-H***H***), 4.24 (2H, dd, *J* 11.9, 3.5, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 4.15 (2H, dd, *J* 11.9, 5.2, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 2.89 (1H, tt, *J* 5.2, 3.5, 5'-***H***), 1.62 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (175 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'), 68.6 (***C***-2), 66.3 (***C***-4', ***C***-6'), 38.9 (***C***-5'), 21.5 (2'-***C***H_3). *m/z* (ES^+) : 567 ($[2M+Na]^+$, 30%), 336 ($[M+Na+CH_3CN]^+$, 80), 273 ($[M+H]^+$, 40), 245 ($[M+H-N_2]^+$, 100). HRMS (ES^+) found: 273.1230 ($C_{15}H_{17}O_3N_2$ 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 CH_3CN (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 CH_3CN (10.0 ml) at rt. After stirring for 3 h, a saturated ammonium chloride solution (NH_4Cl) (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

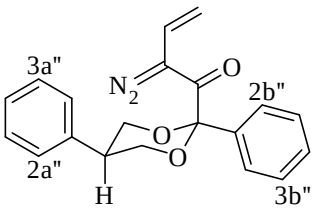
was then purified by flash column chromatography on silica gel (ether/petroleum ether : 1:9 then 2:8) to give the title vinyldiazoketone **315** as an orange oil (0.35 g, 57%).



ν_{max} (ATR) : 2964, 2077 (***C*=*N*$_2$**), 1649 (***C*=*O***), 1609 (***C*=*C***), 1496, 1452, 1375, 1332, 1187, 1135, 1044, 884, 817, 756, 699 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.30 (2H, t, *J* 7.7, 3''-***H***), 7.25 (1H, t, *J* 7.7, 4''-***H***), 7.12 (2H, d, *J* 7.7, 2''-***H***), 5.58 (1H, qd, *J* 1.0, 0.8, 4-***H***H), 5.15 (1H, qd, *J* 1.4, 1.0, 4-H***H***), 4.10 (2H, dd, *J* 11.9, 4.7, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.98 (2H, t, *J* 11.9, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.26 (1H, tt, *J* 11.9, 4.7, 5'-***H***), 2.02 (3H, dd, *J* 1.4, 0.8, 3-C$\boldsymbol{H}_3$), 1.57 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 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'-***C***H_3), 21.5 (3-***C***H_3). *m/z* (ES^+) : 322 ($[M-N_2+Na+CH_3CN]^+$, 100%), 177 (90). HRMS (ES^+) found: 287.1384 ($C_{16}H_{19}O_3N_2$ requires $[M+H]^+$ 287.1385).

2-diazo-1-(2',5'-diphenyl-1',3'-dioxan-2'-yl)but-3-en-1-one (281) :

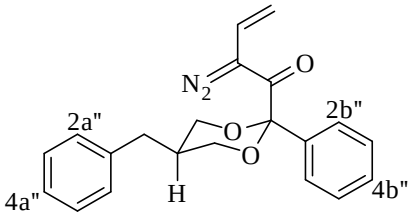
A solution of DBU (5.60 ml, 37.4 mmol) in CH_3CN (18.0 ml) was added to a stirred solution of the inseparable ketones **266** and **270** (1.44 g, 4.68 mmol) and *p*-ABSA (2.24 g, 9.35 mmol) dissolved in CH_3CN (30.0 ml) at rt. After stirring for 3 h, a saturated ammonium chloride solution (NH_4Cl) (30.0 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 vinyldiazoketone **281** as a bright orange oil (1.08 g, 69%).



ν_{max} (ATR) : 2923, 2884, 2081 (***C*=*N*~2~**), 1643 (***C*=*O***), 1606 (***C*=*C***), 1495, 1452, 1298, 1249, 1139, 1095, 1025, 981, 859, 757, 697 cm^{-1}. δ_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-***H***H), 4.74 (1H, d, *J* 17.2, 4-H***H***), 4.30 (2H, dd, *J* 11.7, 4.8, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 4.23 (2H, t, *J* 11.7, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 3.42-3.29 (1H, tt, *J* 11.7, 4.8, 5'-***H***). δ_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 ($C_{20}H_{19}O_3N_2$ 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_3CN (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_3CN (25.0 ml) at rt. After stirring for 3 h, a saturated ammonium chloride solution (NH_4Cl) (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 vinyldiazoketone **282** as an orange oil (0.75 g, 81%).



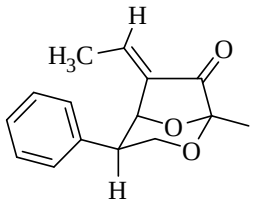
ν_{max} (ATR) : 2916, 2848, 2083 (***C*=*N*~2~**), 1646 (***C*=*O***), 1611 (***C*=*C***), 1493, 1448, 1297, 1240, 1138, 1102, 1050, 980, 866, 757, 697 cm^{-1}. δ_H (400 MHz; $CDCl_3$) : 7.52 (2H, d, *J* 8.0, 2b''-***H***), 7.39-7.34 (3H, m, 3b''-***H***, 4b''-***H***), 7.30 (2H, t, *J* 7.2, 3a''-***H***), 7.22 (1H, t, *J* 7.2, 4a''-***H***), 7.14 (2H, d, *J* 7.2, 2a''-***H***), 6.43 (1H, dd, *J* 17.2, 10.7, 3-***H***), 5.16 (1H, d, *J* 10.7, 4-***H***H), 4.74 (1H, d, *J* 17.2, 4-H***H***), 4.08 (2H, dd, *J* 11.9, 4.3, 4'-$\boldsymbol{H}_{eq}$, 6'-$\boldsymbol{H}_{eq}$), 3.79 (2H, t, *J* 11.9, 4'-$\boldsymbol{H}_{ax}$, 6'-$\boldsymbol{H}_{ax}$), 2.48 (2H, d, *J* 7.8, 5'-C$\boldsymbol{H}_2$Ph), 2.43-2.33 (1H, m, 5'-***H***). δ_C (100 MHz; $CDCl_3$) : 188.6 (***C***-1), 138.0 (***C***-1a''), 137.0 (***C***-1b''), 129.2 (***C***-4a''), 128.7 (***C***-2a''), 128.6 (***C***-3a''), 128.5 (***C***-3b''),

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'-***C***H_2Ph). *m/z* (ES^+) : 413 ($[M+Na+CH_3CN]^+$, 40%), 371 ($[M+Na]^+$, 70), 349 ($[M+H]^+$, 90), 321 ($[M+H-N_2]^+$, 100). HRMS (ES^+) found: 349.1547 ($C_{21}H_{21}O_3N_2$ 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) :

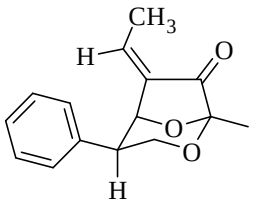
A solution of vinyldiazoketone **279** (0.11 g, 0.40 mmol, 100 mmol/L) in benzene (4.00 ml), was added *via* syringe pump over 20 h to a solution of rhodium (II) perfluorobutyrate, $Rh_2(CO_2C_3F_7)_4$ (5 mol%, 1 mmol/L) in benzene (20.0 ml) maintained at room temperature. Upon complete addition, silica 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 :



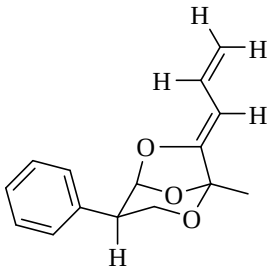
mp.: 95-97 °C. ν_{max} (ATR) : 2940, 2882, 1739 (***C***=***O***), 1664 (***C***=***C***), 1441, 1382, 1173, 1105, 1020, 874, 835, 759, 733, 700 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.31 (2H, t, *J* 7.4, Ar-***H***), 7.28 (1H, t, *J* 7.4, Ar-***H***), 7.13 (2H, d, *J* 7.4, Ar-***H***), 6.28 (1H, q, *J* 7.3, 6-C***H***CH_3), 5.09 (1H, bs, 5-***H***), 4.29 (1H, t, *J* 12.1, 3-$\boldsymbol{H}_{ax}$), 4.09 (1H, dd, *J* 12.1, 5.5, 3-$\boldsymbol{H}_{eq}$), 3.87-3.84 (1H, m, 4-***H***), 1.47 (3H, s, 1-C$\boldsymbol{H}_3$), 1.07 (3H, d, *J* 7.3, 6-CHC$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 199.3 (***C***-7), 135.9 (***C***-1'), 133.8 (6-***C***HCH_3), 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-***C***H_3), 14.9 (6-CH***C***H_3). *m/z* (EI) : 227 (2%), 214 (M^+-2 × Me, 6), 202 (M^+-Me-C_2H_4, 40), 104 (100), 91 ($PhCH_2^+$, 10), 77 (Ph^+, 5). Anal. [Found: C, 72.9; H, 6.7. $C_{15}H_{16}O_3$ requires C, 73.7; H, 6.6%].

(*Z*)-6-ethylidene-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one (286) :



mp.: 76-79 ^{o}C. ν_{max} (ATR) : 2948, 2878, 1739 (***C*=*O***), 1663 (***C*=*C***), 1496, 1439, 1383, 1284, 1173, 1021, 873, 758, 734, 638 cm^{-1}. δ_H (700 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***H***CH_3), 4.80 (1H, d, *J* 3.2, 5-***H***), 4.24 (1H, t, *J* 12.1, 3-$\boldsymbol{H}_{ax}$), 4.08 (1H, dd, *J* 12.1, 5.6, 3-$\boldsymbol{H}_{eq}$), 3.79 (1H, ddd, *J* 12.1, 5.6, 3.2, 4-***H***), 2.21 (3H, d, *J* 7.5, 6-CHC$\boldsymbol{H}_3$), 1.45 (3H, s, 1-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 201.6 (***C***-1), 138.7 (6-***C***HCH_3), 136.1 (***C***-6), 131.1 (***C***-1'), 128.7 (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***H_3), 14.3 (6-CH***C***H_3). *m/z* (EI) : 244 (M^+, 2%), 214 (M^+-2 × Me, 6), 202 (M^+-Me-C_2H_4, 40), 104 (100), 91 ($PhCH_2^+$, 5), 77 (Ph^+, 2). HRMS ($ASAP^+$) found: 245.1183 ($C_{15}H_{17}O_3$ requires $[M+H]^+$ 245.1178).

(*Z*)-7-allylidene-1-methyl-4-phenyl-2,6,8-trioxabicyclo[3.2.1]octane (287) :

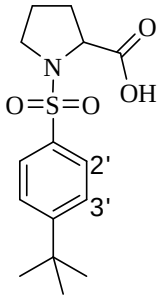


ν_{max} (ATR) : 1685 (***C*-*O***), 1656 (***C*=*C***), 1493, 1421, 1318, 1107, 1020, 932, 801, 756, 640 cm^{-1}. δ_H (700 MHz, $CDCl_3$) : 7.35 (4H, m, Ar-***H***), 7.30 (1H, m, Ar-***H***), 6.84 (1H, dt, *J* 17.2, 10.5, 7-CHC***H***=CH_2), 5.81 (1H, s, 5-***H***), 5.35 (1H, d, *J* 10.5, 7-C***H***CH=CH_2), 5.32 (1H, d, *J* 17.2, 7-CHCH=C***H***H), 5.19 (1H, d, *J* 10.5, 7-CHCH=CH***H***), 4.09 (1H, t, *J* 11.3, 3-$\boldsymbol{H}_{ax}$), 4.03 (1H, dd, *J* 11.3, 6.3, 3-$\boldsymbol{H}_{eq}$), 3.44 (1H, dd, *J* 11.3, 6.3, 4-***H***), 1.66 (3H, s, 1-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 151.1 (***C***-7, enol ether), 135.9 (***C***-1'), 130.0 (7-CH***C***H=CH_2), 128.7 (Ar-***C***), 128.6 (Ar-***C***), 127.8 (Ar-***C***), 115.0 (7-CHCH=***C***H_2), 104.1 (***C***-5), 102.2 (***C***-1), 98.2 (7-***C***HCH=CH_2), 66.1 (***C***-

3), 46.0 (***C***-4), 20.3 (1-***C***H_3). *m/z* (ES^+) : 267 ($[M+Na]^+$, 20%), 245 ($[M+H]^+$, 10), 227 (40), 115 (100).

1-(4'-*tert*-butylphenylsulfonyl)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*-butylbenzene-1-sulfonyl chloride **292** (2.43 g, 10.4 mmol). The mixture was stirred at 20 ^oC for 12 h, then washed with ether (3 × 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%).

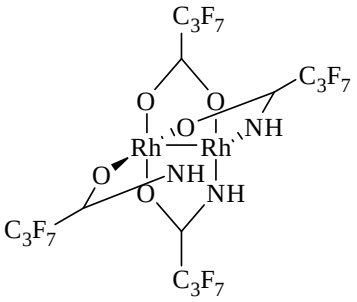


ν_{max} (ATR) : 2955, 1712 (***C=O***), 1594, 1435, 1328+1149 (***SO₂***), 1239, 1196, 1095, 1012, 937, 827, 755, 635 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.80 (2H, d, *J* 8.6, 2'-***H***), 7.57 (2H, d, *J* 8.6, 3'-***H***), 4.25 (1H, dd, *J* 8.8, 3.5, 2-***H***), 3.56 (1H, ddd, *J* 9.7, 6.8, 3.9, 5-***H***H), 3.25 (1H, ddd, *J* 9.4, 6.8, 3.2, 5-H***H***), 2.26-2.22 (1H, m, 3-***H***H), 1.95-1.90 (1H, m, 3-H***H***), 1.89-1.84 (1H, m, 4-***H***H), 1.79-1.74 (1H, m, 4-H***H***), 1.36 (9H, s, 6-C(C***H***$_3$)$_3$). δ_C (175 MHz; $CDCl_3$) : 174.3 (***C***O), 157.4 (***C***-4'), 133.4 (***C***-1'), 127.6 (***C***-2'), 126.4 (***C***-3'), 60.6 (***C***-2), 49.2 (***C***-5), 35.3 (***C***$(CH_3)_3$), 31.0 (C(***C***H_3)$_3$), 30.0 (***C***-3), 24.7 (***C***-4). *m/z* (ES^+) : 645 ($[2M+Na]^+$, 10%), 329 ($[M+H_2O]^+$, 20), 312 ($[M+H]^+$, 100), 266 (25).

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 Na_2CO_3/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%).

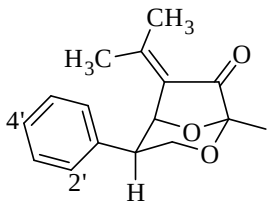


mp.: >250 ^{o}C. Anal. [Found: C, 18.7; H, 0.7; N, 5.8. $C_{16}H_4O_4F_{28}N_4Rh_2$ requires C, 18.2; H, 0.4; N, 5.3%].

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 vinyldiazoketone **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), Rh_2(*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%).

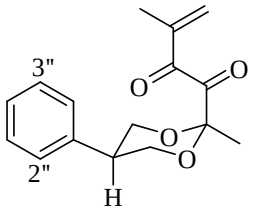
1-methyl-4-phenyl-6-(propan-2-ylidene)-2,8-dioxabicyclo[3.2.1]octan-7-one (316) :



ν_{max} (ATR) : 2990, 2906, 1734 (***C*=*O***), 1650 (***C*=*C***), 1476, 1388, 1184, 1097, 926, 890, 833, 745, 715 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.30 (2H, t, *J* 7.3, 3'-***H***), 7.25 (1H, t, *J* 7.3, 4'-***H***), 7.13

(2H, d, *J* 7.3, 2'-***H***), 5.05 (1H, d, *J* 3.9, 5-***H***), 4.33 (1H, t, *J* 11.7, 3-$\boldsymbol{H}_{ax}$), 4.06 (1H, dd, *J* 11.7, 5.7, 3-$\boldsymbol{H}_{eq}$), 3.83 (1H, ddd, *J* 11.7, 5.7, 3.9, 4-***H***), 2.26 (3H, s, 6-C(C$\boldsymbol{H}_3$)$_2$), 1.44 (3H, s, 1-C$\boldsymbol{H}_3$), 1.03 (3H, s, 6-C(C$\boldsymbol{H}_3$)$_2$). δ_C (175 MHz; $CDCl_3$) : 200.5 (***C***-7), 151.6 (***C***-6), 136.4 (***C***-1'), 128.8 (***C***-2'), 128.0 (***C***-3'), 126.9 (6-***C***(CH$_3$)$_2$), 100.6 (***C***-1), 80.1 (***C***-5), 64.3 (***C***-3), 44.8 (***C***-4), 23.6 (6-C(***C***H$_3$)$_2$), 20.3 (6-C(***C***H$_3$)$_2$), 18.8 (1-***C***H$_3$). *m/z* (GCMS, EI), t_R = 9.78 min : 216 (M^+-C_3H_6, 50%), 198 (10), 142 (40), 104 (100), 91 (10), 77 (Ph^+, 10). HRMS (ES^+) found: 259.1331 ($C_{16}H_{19}O_3$ requires $[M+H]^+$ 259.1329).

3-methyl-1-(2'-methyl-5'-phenyl-1',3'-dioxan-2'-yl)but-3-ene-1,2-dione (317) :



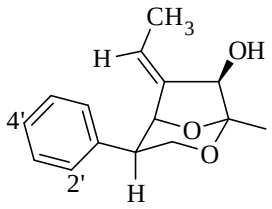
δ_H (700 MHz; $CDCl_3$) : 7.30 (2H, t, *J* 7.3, 3'-***H***), 7.25 (1H, t, *J* 7.3, 4'-***H***), 7.13 (2H, d, *J* 7.3, 2'-***H***), 6.23 (1H, s, 4-***H***H), 6.04 (1H, s, 4-H***H***), 4.09 (1H, dd, *J* 11.4, 5.0, 4'-$\boldsymbol{H}_{eq}$), 4.02 (1H, t, *J* 11.4, 4'-$\boldsymbol{H}_{ax}$), 3.24 (1H, tt, *J* 11.4, 5.0, 5'-***H***), 1.99 (3H, s, 3-C$\boldsymbol{H}_3$), 1.65 (3H, s, 2'-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 204.3 (***C***-1), 196.2 (***C***-2), 140.8 (***C***-3), 137.3 (***C***-1''), 131.9 (***C***-4), 127.7 (***C***-2''), 127.6 (***C***-3''), 100.3 (***C***-2'), 68.1 (***C***-4'), 40.2 (***C***-5'), 25.8 (2'***C***H$_3$), 16.4 (3-***C***H$_3$). *m/z* (GCMS, EI), t_R = 9.74 min : 274 (M^+, 10%), 177 (70), 117 (100), 104 (10), 91 (10), 77 (Ph^+, 10), 43 (100). HRMS (ES^+) found: 292.1546 ($C_{16}H_{22}O_4N$ requires $[M+NH_4]^+$ 292.1543).

(7*RS,E/Z*)-6-ethylidene-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (318, 319) :

A solution of vinyldiazoketone **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 $Rh_2(NHCOC_3F_7)_4$ (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

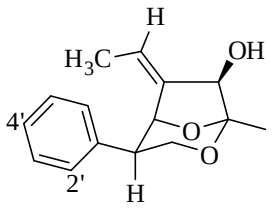
filtrate was concentrated *in vacuo*. The crude residue (which contained a 1:1/ **318**:**319** mixture of geometric isomeric enols) was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 9:1 then 8:2) to afford the title bicyclic enols **318** (17 mg, 24%) and **319** (13 mg, 18%) as clear oils.

(7*RS*,*E*)-6-ethylidene-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (318)



ν_{max} (ATR) : 3398 (***OH***), 2894, 1668 (***C*=*C***), 1610, 1500, 1448, 1389, 1262, 1146, 1098, 1028, 871, 831, 791, 756, 699 cm^{-1}. δ_H (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-C***H***CH_3), 4.53 (2H, bd, *J* 6.5, 5-***H***, 7-***H***), 4.42 (1H, t, *J* 12.2, 3-$\boldsymbol{H}_{ax}$), 4.05 (1H, ddd, *J* 12.2, 5.6, 1.6, 3-$\boldsymbol{H}_{eq}$), 3.52 (1H, ddd, *J* 12.2, 5.6, 3.1, 4-***H***), 2.16 (1H, d, *J* 6.5, O***H***), 1.80 (3H, d, *J* 7.1, 6-CHC$\boldsymbol{H}_3$), 1.52 (3H, s, 1-C$\boldsymbol{H}_3$). δ_C (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-***C***$CHCH_3$), 103.6 (***C***-1), 82.6 (***C***-5), 74.8 (***C***-7), 64.7 (***C***-3), 44.5 (***C***-4), 22.2 (1-***C***CH_3), 13.7 (6-CH***C***H_3). *m/z* ($ASAP^+$) : 247 ($[M+H]^+$, 100%), 229 ($[M+H-H_2O]^+$, 20). HRMS ($ASAP^+$) found: 247.1336 ($C_{15}H_{19}O_3$ requires $[M+H]^+$ 247.1334).

(7*RS*,*Z*)-6-ethylidene-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (319) :



ν_{max} (ATR) : 3406 (***OH***), 2894, 1665 (***C*=*C***), 1525, 1401, 1391, 1298, 1256, 1153, 1101, 1030, 971, 875, 755, 698, 647 cm^{-1}. δ_H (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-C***H***CH_3), 4.85 (1H, bs, 5-***H***), 4.59 (1H, t, *J* 11.8, 3-$\boldsymbol{H}_{ax}$), 4.32 (1H, s, 7-***H***), 4.06 (1H, ddd, *J* 11.8, 5.4, 1.4, 3-$\boldsymbol{H}_{eq}$), 3.61 (1H, dd, *J*

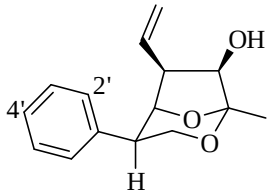
5.4, 3.4, 4-***H***), 2.23 (1H, s, O***H***), 1.49 (3H, s, 1-C$\boldsymbol{H}_3$), 0.82 (3H, d, *J* 7.0, 6-CHC$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 136.8 (***C***-1'), 128.8 (***C***-6), 128.6 (***C***-3'), 128.1 (***C***-2'), 127.4 (***C***-4'), 122.0 (6-***C***HCH_3), 102.9 (***C***-1), 80.3 (***C***-5), 76.6 (***C***-7), 64.0 (***C***-3), 44.4 (***C***-4), 22.3 (1-***C***H_3), 14.7 (6-CH***C***H_3). *m/z* ($ASAP^+$) : 247 ($[M+H]^+$, 100%), 229 ($[M+H-H_2O]^+$, 50). HRMS ($ASAP^+$) found: 247.1326 ($C_{15}H_{19}O_3$ requires $[M+H]^+$ 247.1334).

(6*SR*,7*RS*)-6-ethenyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (320, 322) :

Major isomer **320** :

A solution of vinyldiazoketone **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 Rh_2(*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-ethenyl-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 ^oC. 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 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 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 **320** (0.14 g, 45%) as a white solid, $[\alpha]^{20.1}_D$ = - 31.2^o (c = 0.4, $CDCl_3$).

Similarly, conducting the initial diazo decomposition step with the achiral $Rh_2(hfb)_4$ gave the title product **320** in 41% overall yield.



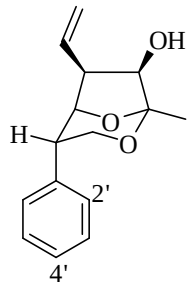
mp.: 108-110 ^oC. ν_{max} (ATR) : 3410 (***OH***), 2970, 2904, 1604 (***C***=***C***), 1504, 1394, 1332, 1258, 1112, 1027, 984, 882, 816, 756, 698, 666 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.26 (2H, t, *J* 7.6, 3'-***H***), 7.18 (1H, t, *J* 7.6, 4'-***H***), 7.08 (2H, d, *J* 7.6, 2'-***H***), 5.60 (1H, td, *J* 17.0, 10.3, 6-C***H***=CH_2), 4.93 (1H, dd, *J* 17.0, 1.6, 6-CH=C***H***H), 4.80 (1H, bd, *J* 7.1, 5-***H***), 4.72 (1H, t, *J* 11.1, 3-$\boldsymbol{H}_{ax}$),

4.71 (1H, dd, *J* 10.3, 1.6, 6-CH=CH***H***), 4.40 (1H, dd, *J* 11.1, 5.8, 3-$\boldsymbol{H}_{eq}$), 4.17 (1H, dd, *J* 10.3, 4.1, 7-***H***), 3.63-3.60 (1H, m, 4-***H***), 3.30 (1H, td, *J* 10.3, 7.1, 6-***H***), 2.25 (1H, d, *J* 4.1, O***H***), 1.53 (3H, s, 1-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 137.4 (***C***-1'), 131.0 (6-***C***H=CH_2), 128.2 (***C***-3'), 126.5 (***C***-4'), 126.2 (***C***-2'), 119.0 (6-CH=***C***H_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-***C***H_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 ^oC. 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® 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 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.

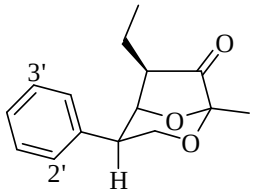


ν_{max} (ATR) : 3450 (***OH***), 2962, 2930, 1610 (***C=C***), 1493, 1390, 1116, 1086, 948, 869, 756, 702, 636, 540 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.47 (2H, d, *J* 7.4, 2'-***H***), 7.34 (2H, t, *J* 7.4, 3'-***H***), 7.25 (1H, t, *J* 7.4, 4'-***H***), 6.21-6.14 (1H, m, 6-C***H***=CH_2), 5.40 (1H, dd, *J* 10.4, 1.8, 6-CH=C***H***H), 5.34 (1H, dd, *J* 17.0, 1.8, 6-CH=CH***H***), 4.46 (1H, dd, *J* 11.8, 5.6, 3-$\boldsymbol{H}_{eq}$), 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-$\boldsymbol{H}_{ax}$), 3.30 (1H, td, *J* 10.4, 3.3, 6-***H***), 2.86-2.82 (1H, m, 4-***H***), 2.05 (1H, s, O***H***), 1.53 (3H, s, 1-C$\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 142.9 (***C***-1'), 131.3 (6-***C***H=CH_2), 128.4 (***C***-3'), 128.3 (***C***-4'), 126.5 (***C***-2'), 120.5 (6-CH=***C***H_2), 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-***C***H_3). *m/z* (EI) : 246 (M^+, 10%), 231 (M^+-Me, 20), 143 (30), 104 (100), 77 (Ph^+, 10). HRMS (ES^+) found: 247.1324 ($C_{15}H_{19}O_3$ requires $[M+H]^+$ 247.1334).

(6*RS*)-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-ethenyl-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 vinyldiazoketone **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%).

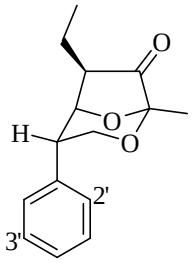


mp.: 69-71 °C. ν_{max} (ATR) : 2874, 1757 (***C=O***), 1670, 1455, 1382, 1174, 1016, 850, 811, 701, 627 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.32 (2H, t, *J* 7.6, 3'-***H***), 7.24 (1H, t, *J* 7.6, 4'-***H***), 7.12 (2H, d, *J* 7.6, 2'-***H***), 5.09 (1H, dd, *J* 6.9, 3.6, 5-***H***), 4.32 (2H, d, *J* 4.3, 3-$\boldsymbol{H}_2$), 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-C***H***HCH_3), 1.45 (3H, s, 1-

C***H***$_3$), 1.03-0.97 (1H, m, 6-CH***H***CH$_3$), 0.48 (3H, t, *J* 7.5, 6-CH$_2$C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 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-***C***H$_3$), 17.2 (6-***C***H$_2$CH$_3$), 12.0 (6-CH$_2$***C***H$_3$).). *m/z* (EI) : 246 (M^+, 2%), 218 (M^+-C_2H_4, 10), 158 (70), 145 (100), 129 (50), 91 ($PhCH_2^+$, 10), 77 (Ph^+, 5). HRMS ($ASAP^+$) found: 247.1327 ($C_{15}H_{19}O_3$ 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 $Rh_2(hfb)_4$ 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 proceeded 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 **437** as a white crystalline solid (85 mg, 37%).

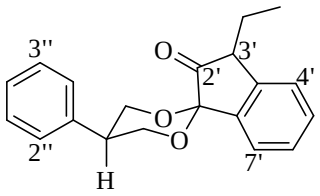


mp.: 81-82 °C. ν_{max} (ATR) : 2962, 2876, 1756 (***C*=*O***), 1601, 1457, 1381, 1171, 1074, 987, 844, 765, 741, 701 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.56 (2H, d, *J* 7.3, 2'-***H***), 7.38 (2H, t, *J* 7.3, 3'-***H***), 7.30 (1H, t, *J* 7.3, 4'-***H***), 4.70 (1H, d, *J* 7.2, 5-***H***), 4.19 (1H, dd, *J* 12.9, 4.8, 3-***H***$_{ax}$), 4.11 (1H, t, *J* 12.9, 3-***H***$_{eq}$), 2.73-2.70 (2H, m, 4-***H***, 6-***H***), 2.05-1.99 (1H, m, 6-C***H***HCH$_3$), 1.57-1.51 (1H, m, 6-CH***H***CH$_3$), 1.44 (3H, s, 1-C***H***$_3$), 1.17 (3H, t, *J* 7.5, 6-CH$_2$C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 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-***C***H$_3$), 16.9 (6-***C***H$_2$CH$_3$), 12.5 (6-CH$_2$***C***H$_3$). *m/z* (EI) : 246 (M^+, 2%), 218 (M^+-C_2H_4, 6), 158 (60), 145 (100), 91 ($PhCH_2^+$, 10), 77 (Ph^+, 5). HRMS

(ASAP$^+$) found: 247.1330 ($C_{15}H_{19}O_3$ requires $[M+H]^+$ 247.1334). Anal. [Found: C, 73.0; H, 7.4. $C_{15}H_{18}O_3$ requires C, 73.2; H, 7.3%].

3'-ethyl-5-phenylspiro[(1,3)-dioxane-2,1'-inden]-2'(3'H)-one (440):

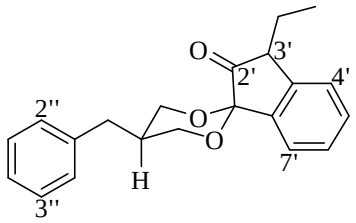
A two-neck flask filled with 10 wt % palladium-carbon (0.22 g) was argon purged before adding ethanol (7.00 ml). The flask was again argon purged after adding the crude solution containing 3'-ethenyl-5-phenylspiro[(1,3)-dioxane-2,1'-inden]-2'(3'H)-one **438** (1.08 g, 3.53 mmol) [prepared from a reaction between vinyldiazoketone **281** and $Rh_2(hfb)_4$ 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 $CHCl_3$, 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 **440** as a white crystalline solid (0.45 g, 41%).



mp.: 134-136 ^oC. ν_{max} (ATR) : 2968, 1736 (***C*=*O***), 1498, 1462, 1330, 1284, 1076, 1013, 984, 872, 756, 699 cm^{-1}. δ_H (700 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-$\boldsymbol{H}_{ax}$), 4.79 (1H, t, *J* 11.8, 6-$\boldsymbol{H}_{ax}$), 4.08 (2H, dd, *J* 11.8, 5.2, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 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'-C***H***HCH_3), 2.02-1.96 (1H, m, 3'-CH***H***CH_3), 0.95 (3H, t, *J* 7.5, 3'-$CH_2C\boldsymbol{H}_3$). δ_C (175 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'-$\boldsymbol{C}H_2CH_3$), 10.6 (3'-$CH_2\boldsymbol{C}H_3$).). *m/z* (ES^+) : 372 ($[M+Na+CH_3CN]^+$, 40%), 331 ($[M+Na]^+$, 10), 328 (100), 309 ($[M+H]^+$, 80). HRMS (ES^+) found: 309.1486 ($C_{20}H_{21}O_3$ requires $[M+H]^+$ 309.1491). Anal. [Found: C, 77.2; H, 6.5. $C_{20}H_{20}O_3$ 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 $Rh_2(hfb)_4$ 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 went on for 2 h at room temperature before diluting with $CHCl_3$, 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%).

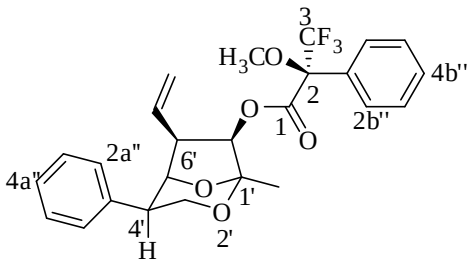


mp.: 153-155 ^{o}C. ν_{max} (ATR) : 2966, 1732 (***C*=*O***), 1478, 1461, 1325, 1281, 1070, 1010, 976, 860, 754, 654 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.52 (1H, d, *J* 7.9, 7'-***H***), 7.42 (1H, t, *J* 7.9, 6'-***H***), 7.36 (1H, t, *J* 7.9, 5'-***H***), 7.31 (2H, t, *J* 7.5, 3''-***H***), 7.28 (1H, 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-$\boldsymbol{H}_{ax}$), 4.38 (1H, t, *J* 11.5, 6-$\boldsymbol{H}_{ax}$), 3.91-3.88 (2H, m, 4-$\boldsymbol{H}_{eq}$, 6-$\boldsymbol{H}_{eq}$), 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-C$\boldsymbol{H}_2$Ph), 2.05-1.99 (1H, m, 3'-C***H***HCH_3), 1.97-1.91 (1H, m, 3'-CH***H***CH_3), 0.91 (3H, t, *J* 7.6, 3'-$CH_2C\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 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-***C***H_2Ph), 24.4 (3'-***C***H_2CH_3), 10.7 (3'-$CH_2\boldsymbol{C}H_3$).). *m/z* (ES^+) : 323 ($[M+H]^+$, 100). HRMS (ES^+) found: 323.1651 ($C_{21}H_{23}O_3$ requires $[M+H]^+$ 323.1647). Anal. [Found: C, 77.8; H, 6.9. $C_{21}H_{22}O_3$ requires C, 78.2; H, 6.9%].

(2*SR*)-((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 Rh_2(*S*-TBSP)$_4$ catalyst, triethylamine (36 µl, 0.26 mmol) and a catalytic amount of DMAP (3 mg, 0.02 mmol) in $CDCl_3$ (50 µl) were added to the residue. After 24 h, ^{1}NMR revealed complete conversion into the diastereomeric Mosher's esters. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with DCM (3 × 2.00 ml) and the combined organic extracts were washed with brine, dried over $MgSO_4$, 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 Rh_2(hfb)$_4$ catalyst led to an inseparable mixture of diastereomeric Mosher's esters **323** and **324** (60%) in ratio 1:1.



Major diastereoisomer **323** :

ν_{max} (ATR) : 2974, 1752 (***C*=*O***), 1649 (***C*=*C***), 1451, 1389, 1249, 1169, 1065, 1024, 990, 870, 757, 697 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 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'-C***H***=CH_2), 4.87 (1H, dd, *J* 16.7, 1.7, 6'-CH=C***H***H), 4.78 (1H, bd, *J* 4.5, 5'-***H***), 4.53 (1H, dd, *J* 10.3, 1.7, 6'-CH=CH***H***), 4.52 (1H, t, *J* 12.0, 3'-$\boldsymbol{H}_{ax}$), 4.29 (1H, dd, *J* 12.0, 5.7, 3'-$\boldsymbol{H}_{eq}$), 3.65-3.63 (1H, m, 4'-***H***), 3.62 (3H, s, 2-OC$\boldsymbol{H}_3$), 3.51-3.45 (1H, m, 6'-***H***), 1.57 (3H, s, 1'-C$\boldsymbol{H}_3$). δ_F (376.3 MHz; $CDCl_3$) : -71.26. δ_C (175 MHz; $CDCl_3$) : 165.6 (***C***-1), 136.9 (***C***-1a''), 132.4 (***C***-1b''), 129.6 (***C***-2b''), 128.9 (6'-***C***H=CH_2), 128.4 (***C***-4b''), 128.3 (***C***-3a''), 127.3 (***C***-2b''), 126.6 (***C***-4a''), 126.2 (***C***-2a''), 124.2

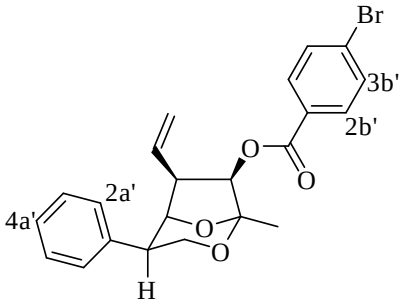
(**C**F_3), 122.6 (***C***-2), 119.8 (6'-CH=***C***H_2), 102.8 (***C***-1'), 81.7 (***C***-5'), 77.9 (***C***-7'), 63.6 (***C***-3'), 55.6 (2-O***C***H_3), 48.6 (***C***-6'), 39.8 (***C***-4'), 23.6 (1'-***C***H_3). *m/z* (GCMS, EI), t_R = 11.16 min : 462 (M^+, 5%), 434 (M^+-C_2H_4, 10), 229 (30), 189 (80), 104 (100), 91 (10), 77 (Ph^+,5). *m/z* (ASAP$^+$) : 463 ($[M+H]^+$, 20%), 446 ($[M-CH_4]^+$, 10), 214 ($[M-CH_4-PhC(CF_3)(OCH_3)COO]^+$, 90), 141 (100). HRMS (ASAP$^+$) found: 463.1725 ($C_{25}H_{26}O_5F_3$ requires $[M+H]^+$ 463.1732).

Minor diastereoisomer **324** :

δ_H (700 MHz; $CDCl_3$) : 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'-C***H***=CH_2), 4.95 (1H, dd, *J* 16.7, 1.7, 6'-CH=C***H***H), 4.78 (1H, bd, *J* 4.5, 5'-***H***), 4.66 (1H, dd, *J* 10.3, 1.7, 6'-CH=CH***H***), 4.33 (1H, t, *J* 12.0, 3'-$\boldsymbol{H}_{ax}$), 4.12 (1H, dd, *J* 12.0, 5.7, 3'-$\boldsymbol{H}_{eq}$), 3.60-3.57 (1H, m, 4'-***H***), 3.55 (3H, s, 2-OC$\boldsymbol{H}_3$), 3.41-3.39 (1H, m, 6'-***H***), 1.59 (3H, s, 1'-C$\boldsymbol{H}_3$). δ_F (376.3 MHz; $CDCl_3$) : -71.73. δ_C (175 MHz; $CDCl_3$) : 165.7 (***C***-1), 137.0 (***C***-1a''), 132.0 (***C***-1b''), 129.5 (***C***-2b''), 128.7 (6'-***C***H=CH_2), 128.3 (***C***-4b''), 128.3 (***C***-3a''), 127.6 (***C***-2b''), 126.6 (***C***-4a''), 126.2 (***C***-2a''), 124.1 (**C**F_3), 122.5 (***C***-2), 119.7 (6'-CH=***C***H_2), 103.0 (***C***-1'), 81.4 (***C***-5'), 78.4 (***C***-7'), 63.5 (***C***-3'), 55.5 (2-O***C***H_3), 48.5 (***C***-6'), 39.7 (***C***-4'), 23.7 (1'-***C***H_3). *m/z* (GCMS, EI), t_R = 11.21 min : 462 (M^+, 5%), 434 (M^+-C_2H_4, 10), 229 (20), 189 (70), 133 (20), 104 (100), 91 (10), 77 (Ph^+,5).

(6*RS*,7*RS*)-6-ethenyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octa-7-yl-4-bromobenzoate (361) :

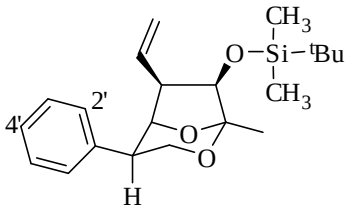
To a solution of bicyclic alcohol **320** (0.03 g, 0.12 mmol) in DCM (2.00 ml), triethylamine (0.09 ml, 0.61 mmol) and a catalytic amount of DMAP (7.4 mg, 0.06 mmol) were added at room temperature and the reaction mixture was stirred for 0.5 h. 4-bromobenzoyl chloride (0.05 g, 0.24 mmol) in DCM (1.00 ml) was added dropwise to the reaction mxture and further stirring continued at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with DCM (2 × 8.00 ml) and the combined organic extracts were washed with brine, dried over $MgSO_4$, 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%).



ν_{max} (ATR) : 2974, 2902, 1725 (***C*=*O***), 1589 (***C*=*C***), 1482, 1391, 1265, 1105, 1009, 920, 867, 753, 695 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.92 (2H, d, *J* 8.5, 2b'-***H***), 7.63 (2H, d, *J* 8.5, 3b'-***H***), 7.28 (2H, t, *J* 7.5, 3a'-***H***), 7.20 (1H, t, *J* 7.5, 4a'-***H***), 7.12 (2H, d, *J* 7.5, 2a'-***H***), 5.48 (1H, dt, *J* 16.9, 10.2, 6-C***H***=CH_2), 5.47 (1H, d, *J* 10.2, 7-***H***), 4.95 (1H, d, *J* 16.9, 6-CH=C***H***H), 4.91 (1H, bd, *J* 7.0, 5-***H***), 4.80 (1H, t, *J* 11.4, 3-$\boldsymbol{H}_{ax}$), 4.64 (1H, d, *J* 10.2, 6-CH=CH***H***), 4.53 (1H, ddd, *J* 11.4, 6.0, 1.2, 3-$\boldsymbol{H}_{eq}$), 3.74-3.71 (1H, m, 4-***H***), 3.59 (1H, td, *J* 10.2, 7.0, 6-***H***), 1.58 (3H, s, 1-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 164.8 (***C***=O), 137.2 (***C***-1a'), 131.9 (***C***-3b'), 131.2 (***C***-2b'), 129.2 (6-***C***H=CH_2), 128.6 (***C***-4b'), 128.5 (***C***-1b'), 128.4 (***C***-3a'), 126.7 (***C***-4a'), 126.1 (***C***-2a'), 120.1 (6-CH=***C***H_2), 103.0 (***C***-1), 81.2 (***C***-5), 76.8 (***C***-7), 64.3 (***C***-3), 48.3 (***C***-6), 40.0 (***C***-4), 23.4 (1-***C***H_3). *m/z* ($ASAP^+$) : 429 ($[M+H]^+$, 100%), 413 ($[M-CH_4]^+$, 20), 229 ($[M-CH_4$-BrPhCO$]^+$, 90). HRMS ($ASAP^+$) found: 429.0690 ($C_{22}H_{22}O_4{}^{79}Br$ requires $[M+H]^+$ 429.0701).

***tert*-butyldimethyl[(6*RS*,7*RS*)-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*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) (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 × 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%).

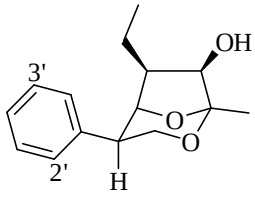


ν_{max} (ATR) : 2956, 2940-2862 (***CH***-OSi), 1468 (***C=C***), 1388, 1256+838 (***Si-C***H_3), 1188, 1130, 1040, 990, 906, 778, 760, 698, 664 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.26 (2H, t, *J* 7.5, 3'-***H***), 7.18 (1H, t, *J* 7.5, 4'-***H***), 7.08 (2H, d, *J* 7.5, 2'-***H***), 5.55 (1H, td, *J* 17.1, 10.2, 6-C***H***=CH_2), 4.89 (1H, t, *J* 11.3, 3-$\boldsymbol{H}_{ax}$), 4.82 (1H, dd, *J* 17.1, 2.0, 6-CH=C***H***H), 4.74 (1H, ddd, *J* 7.1, 3.3, 1.5, 5-***H***), 4.60 (1H, dd, *J* 10.2, 2.0, 6-CH=CH***H***), 4.32 (1H, ddd, *J* 11.3, 5.7, 1.5, 3-$\boldsymbol{H}_{eq}$), 4.14 (1H, d, *J* 10.2, 7-***H***), 3.61-3.58 (1H, m, 4-***H***), 3.27 (1H, td, *J* 10.2, 7.1, 6-***H***), 1.47 (3H, s, 1-C$\boldsymbol{H}_3$), 0.95 (9H, s, SiC(C$\boldsymbol{H}_3$)$_3$), 0.10 (3H, s, Si(C$\boldsymbol{H}_3$)$_2$), 0.01 (3H, s, Si(C$\boldsymbol{H}_3$)$_2$). δ_C (175 MHz; $CDCl_3$) : 137.9 (***C***-1'), 132.4 (6-***C***H=CH_2), 128.1 (***C***-3'), 126.3 (***C***-2'), 126.3 (***C***-4'), 117.8 (6-CH=***C***H_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(***C***H_3)$_3$), 23.2 (1-***C***H_3), 18.1 (Si***C***$(CH_3)_3$), -4.3 (Si(***C***H_3)$_2$), -4.6 (Si(***C***H_3)$_2$). *m/z* (ES^+) : 401 ($[M+Na+H_2O]^+$, 10%), 383 ($[M+Na]^+$, 5), 378 ($[M+H_2O]^+$, 30), 361 ($[M+H]^+$, 60), 360 (M^+, 70). HRMS (ES^+) found: 361.2195 ($C_{21}H_{33}O_3Si$ requires $[M+H]^+$ 361.2194).

(6*SR*,7*RS*)-6-ethyl-1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (370, 373) :

Major isomer **370** :

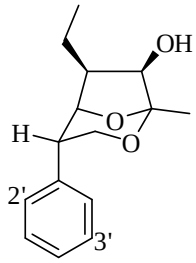
$NaBH_4$ (10 mg, 0.26 mmol) was added to a solution of bicyclic ketone **436** (0.04 g, 0.16 mmol) in MeOH (5.00 ml) at room temperature and the reaction mixture stirred at room temperature overnight. It was then diluted with DCM, saturated solution of ammonium chloride (NH_4Cl) was added and the organic 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%).



ν_{max} (ATR) : 3445-3231 (broad ***OH***), 1604, 1499, 1182, 1110, 1027, 881, 754, 698, 622 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.30 (2H, t, *J* 7.7, 3'-***H***), 7.21 (1H, t, *J* 7.7, 4'-***H***), 7.14 (2H, d, *J* 7.7, 2'-***H***), 4.77 (1H, t, *J* 11.5, 3-$\boldsymbol{H}_{ax}$), 4.67-4.65 (1H, bs, 5-***H***), 4.29 (1H, dd, *J* 11.5, 5.8, 3-$\boldsymbol{H}_{eq}$), 4.15 (1H, d, *J* 10.2, 7-***H***), 3.60-3.57 (1H, m, 4-***H***), 2.47-2.42 (1H, m, 6-***H***), 1.97-2.04 (1H, bs, O***H***), 1.51 (3H, s, 1-C$\boldsymbol{H}_3$), 1.39-1.33 (1H, m, 6-C***H***HCH_3), 0.87-0.81 (1H, m, 6-CH***H***CH_3), 0.56 (3H, t, *J* 7.2, 6-$CH_2C\boldsymbol{H}_3$). δ_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-***C***H_3), 16.5 (6-***C***H_2CH_3), 13.4 (6-CH_2***C***H_3). *m/z* (ES^+) : 303 (60%), 289 ($[M+CH_3CN]^+$, 20), 249 ($[M+H]^+$, 20). HRMS (ES^+) found: 249.1486 ($C_{15}H_{21}O_3$ 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_4Cl) 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%).



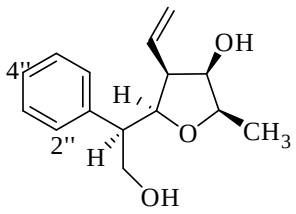
ν_{max} (ATR) : 3452-3430 (broad ***OH***), 2962, 1603, 1493, 1390, 1162, 1080, 948, 868, 756, 699, 592 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.43 (2H, d, *J* 7.6, 2'-***H***), 7.34 (2H, t, *J* 7.6, 3'-***H***), 7.25 (1H, t, *J* 7.6, 4'-***H***), 4.28-4.26 (2H, m, 3-$\boldsymbol{H}_{eq}$, 5-***H***), 4.07 (1H, dd, *J* 9.3, 6.8, 7-***H***), 3.94 (1H, dd, *J* 11.5, 4.6, 3-$\boldsymbol{H}_{ax}$), 2.84-2.82 (1H, m, 4-***H***), 2.41-2.36 (1H, m, 6-***H***), 2.28 (1H, d, *J* 6.8, O***H***), 1.79-1.73 (1H, m, 6-C***H***HCH_3), 1.53-1.49 (1H, m, 6-CH***H***CH_3), 1.52 (3H, s, 1-C$\boldsymbol{H}_3$), 1.05 (3H, t, *J* 7.2, 6-$CH_2C\boldsymbol{H}_3$). δ_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-***C***H_3),

17.2 (6-***C***$H_2$$CH_3$), 13.1 (6-$CH_2$***C***$H_3$). *m/z* ($ES^+$) : 271 ($[M+Na]^+$, 20%), 249 ($[M+H]^+$, 15), 231 ($[M+H-H_2O]^+$, 100). HRMS ($ES^+$) found: 249.1487 ($C_{15}H_{21}O_3$ requires $[M+H]^+$ 249.1485).

(2*RS*,3*RS*,4*SR*,5*SR*,1'*RS*)-4-ethenyl-5-(2'-Hydroxyl-1'-phenylethyl)-2-methyltetrahydrofuran-3-ol (357, 358) :

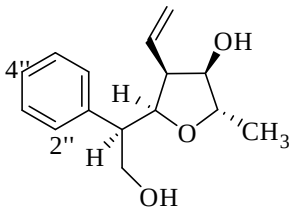
To a solution of bicyclic alcohol **320** (0.03 g, 0.12 mmol) in DCM (5.00 ml) at -78 ^oC was added triethylsilane (80 µl, 0.48 mmol) followed by the dropwise addition of a 1 M solution of titanium tetrachloride (0.15 ml, 0.14 mmol). After stirring at this temperatute for 2 h, the reaction mixture was quenched with an aqueous solution of NaCl and extracted with DCM (3 × 20.0 ml). The combined organic extracts were dried over $MgSO_4$, 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'-Hydroxyl-1'-phenylethyl)-2-methyltetrahydrofuran-3-ol (357) :



ν_{max} (ATR) : 3411 (***OH***), 2875, 1642 (***C*=*C***), 1460, 1388, 1234, 1071, 999, 918, 751, 700, 665 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 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-C***H***=CH_2), 5.32 (1H, dd, *J* 10.1, 1.6, 4-CH=C***H***H), 5.25 (1H, dd, *J* 17.3, 1.6, 4-CH=CH***H***), 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***H), 3.85 (1H, dd, *J* 10.8, 5.7, 2'-H***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, O***H***), 1.18 (3H, d, *J* 6.4, 2-C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 139.2 (***C***-1''), 132.9 (4-***C***H=CH_2), 129.7 (***C***-2''), 128.8 (***C***-3''), 127.5 (***C***-4''), 120.2 (4-CH=***C***H_2), 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-***C***H_3). *m/z* ($ASAP^+$) : 272 ($[M+H+Na]^+$, 10%), 231 ($[M+H-H_2O]^+$, 100), 213 ($[M+H-2 \times H_2O]^+$, 40), 185 ($[M+H-2 \times H_2O-C_2H_4]^+$, 60), 157 (70). HRMS ($ASAP^+$) found: 231.1383 ($C_{15}H_{19}O_2$ requires $[M+H-H_2O]^+$ 231.1385).

4-ethenyl-5-(2'-Hydroxyl-1'-phenylethyl)-2-methyltetrahydrofuran-3-ol (358) :

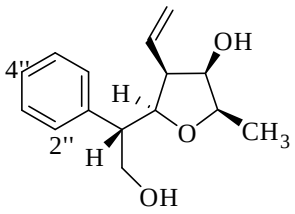


ν_{max} (ATR) : 3380 (***OH***), 2914, 1642 (***C*=*C***), 1460, 1384, 1061, 969, 919, 752, 699, 666 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.35 (2H, t, *J* 7.5, 3''-***H***), 7.31 (2H, d, *J* 7.5, 2''-***H***), 7.27 (1H, t, *J* 7.5, 4''-***H***), 5.93 (1H, dt, *J* 17.1, 10.4, 4-C***H***=CH_2), 5.47 (1H, dd, *J* 10.4, 1.6, 4-CH=C***H***H), 5.37 (1H, dd, *J* 17.1, 1.6, 4-CH=CH***H***), 4.47 (1H, dd, *J* 9.2, 4.4, 5-***H***), 3.98 (1H, dd, *J* 13.0, 6.3, 3-***H***), 3.80 (1H, dd, *J* 11.5, 4.7, 2'-***H***H), 3.78 (1H, dq, *J* 13.0, 6.4, 2-***H***), 3.74 (1H, dd, *J* 11.5, 7.2, 2'-H***H***), 3.05-3.01 (2H, m, 4-***H***, 1'-***H***), 1.43 (1H, s, O***H***), 1.22 (3H, d, *J* 6.4, 2-C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 139.3 (***C***-1''), 131.8 (4-***C***H=CH_2), 128.8 (***C***-2'', ***C***-3''), 127.2 (***C***-4''), 122.1 (4-CH=***C***H_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-***C***H_3). *m/z* ($ASAP^+$) : 231 ($[M+H-H_2O]^+$, 100), 213 ($[M+H^+-2 \times H_2O]^+$, 70), 185 ($[M+H-2 \times H_2O-C_2H_4]^+$, 40), 157 (70). HRMS ($ASAP^+$) found: 231.1386 ($C_{15}H_{19}O_2$ requires $[M+H-H_2O]^+$ 231.1385).

(2*RS*,3*RS*,4*SR*,5*SR*,1'*SR*)-4-ethenyl-5-(2'-Hydroxyl-1'-phenylethyl)-2-methyltetrahydrofuran-3-ol (359, 360) :

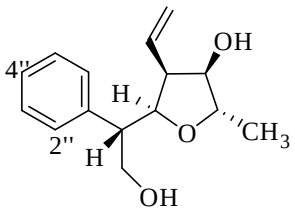
To a solution of bicyclic alcohol **322** (33 mg, 0.13 mmol) in DCM (5.00 ml) at -78 ^oC was added triethylsilane (90 µl, 0.53 mmol) followed by the dropwise addition of a 1 M solution of titanium tetrachloride (0.16 ml, 0.16 mmol). After stirring at this temperature for 2 h, the reaction mixture was 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-ethenyl-5-(2'-Hydroxyl-1'-phenylethyl)-2-methyltetrahydrofuran-3-ol (359) :



ν_{max} (ATR) : 3432-3316 (***OH***), 2932, 2882, 1635 (***C=C***), 1458, 1392, 1158, 1086, 1036, 989, 914, 760, 699 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.29 (2H, t, *J* 7.9, 3''-***H***), 7.21 (1H, t, *J* 7.9, 4''-***H***), 7.15 (2H, d, *J* 7.9, 2''-***H***), 5.87 (1H, dt, *J* 17.4, 10.3, 4-C***H***=CH_2), 5.24 (1H, dd, *J* 10.3, 2.0, 4-CH=C***H***H), 4.92 (1H, dd, *J* 17.4, 2.0, 4-CH=CH***H***), 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'-$\boldsymbol{H}_2$), 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, O***H***), 1.26 (3H, d, *J* 6.4, 2-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 139.1 (***C***-1''), 132.0 (4-***C***H=CH_2), 128.5 (***C***-2''), 128.3 (***C***-3''), 127.0 (***C***-4''), 121.1 (4-CH=***C***H_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-***C***H_3). *m/z* (ES^+) : 312 ($[M+Na+CH_3CN]^+$, 40%), 271 ($[M+Na]^+$, 80), 231 ($[M+H-H_2O]^+$, 100), 213 ($[M+H-2 \times H_2O]^+$, 20). HRMS (ES^+) found: 249.1497 ($C_{15}H_{21}O_3$ requires $[M+H]^+$ 249.1491).

4-ethenyl-5-(2'-Hydroxyl-1'-phenylethyl)-2-methyltetrahydrofuran-3-ol (360) :



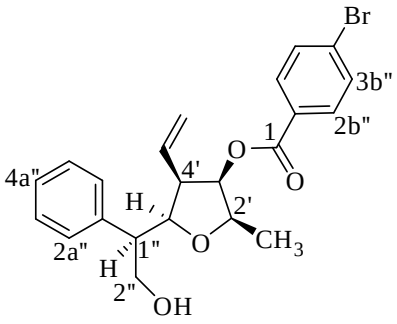
ν_{max} (ATR) : 3460-3290 (***OH***), 2963, 1640 (***C=C***), 1451, 1424, 1377, 1058, 988, 915, 755, 699, 622 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.29 (1H, t, *J* 8.2, 4''-***H***), 7.22 (2H, t, *J* 8.2, 3''-***H***), 7.11 (2H, d, *J* 8.2, 2''-***H***), 5.87 (1H, dt, *J* 17.4, 10.3, 4-C***H***=CH_2), 5.36 (1H, dd, *J* 10.3, 1.7, 4-CH=C***H***H), 4.95 (1H, dd, *J* 17.4, 1.7, 4-CH=CH***H***), 4.46 (1H, dd, *J* 10.6, 3.8, 5-***H***), 4.20 (1H, q, *J* 6.6, 2-***H***), 4.04 (1H, dd, *J* 11.2, 4.0, 2'-***H***H), 4.03 (1H, dd, *J* 11.2, 8.6, 2'-H***H***), 3.71 (1H, bd, *J* 5.3, 3-***H***), 3.08 (1H, ddd, *J* 10.6, 8.6, 4.0, 1'-***H***), 2.56 (1H, ddd, *J* 10.3, 5.3, 3.8, 4-***H***), 1.59 (1H, bs, O***H***), 1.25 (3H, d, *J* 6.6, 2-C$\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 138.4 (***C***-1''), 131.0 (4-***C***H=CH_2),

128.5 (***C***-2''), 128.3 (***C***-3''), 127.1 (***C***-4''), 122.5 (4-CH=***C***H_2), 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-***C***H_3). *m/z* (ES^+) : 271 ($[M+Na]^+$, 90%), 249 ($[M+H]^+$, 100), 231 ($[M+H-H_2O]^+$, 70). HRMS (ES^+) found: 249.1482 ($C_{15}H_{21}O_3$ requires $[M+H]^+$ 249.1491).

(2'*RS*,3'*RS*,4'*RS*,5'*SR*,1''*RS*)-4'-ethenyl-5'-(2''-Hydroxyl-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 ^oC 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%).

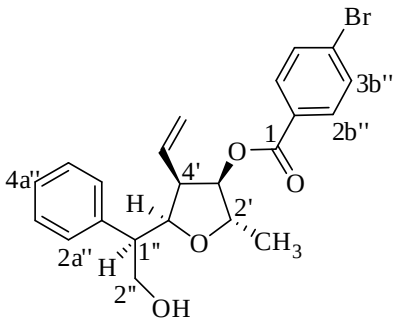
4'-ethenyl-5'-(2''-Hydroxyl-1''-phenylethyl)-2'-methyltetrahydrofuran-3'-yl-4-bromobenzoate (363) :



ν_{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}. δ_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'-C***H***=CH_2), 5.51 (1H, t, *J* 6.6, 3'-***H***), 5.16 (1H, dd, *J* 16.6, 1.7, 4'-CH=C***H***H), 5.15 (1H, dd, *J* 10.5, 1.7, 4'-CH=C***H***H), 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''-***H***H), 3.78 (1H, dd, *J* 10.8, 7.5, 2''-H***H***),

3.37 (1H, ddd, *J* 10.5, 6.6, 5.8, 4'-***H***), 3.06 (1H, ddd, *J* 8.3, 7.5, 5.0, 1''-***H***), 1.24 (3H, d, *J* 6.4, 2'-C***H***$_3$). δ_C (125 MHz; $CDCl_3$) : 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'-***C***H=CH_2), 128.6 (***C***-2a'', ***C***-3a''), 127.0 (***C***-4b'), 119.8 (4'-CH=***C***H_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'-***C***H_3). *m/z* (ES^+) : 885 ($[2M+Na]^+$, 40%), 431 ($[M+H]^+$, 100). HRMS (ES^+) found: 431.0866 ($C_{22}H_{24}O_4{}^{79}Br$ requires $[M+H]^+$ 431.0858).

4'-ethenyl-5'-(2''-Hydroxyl-1''-phenylethyl)-2'-methyltetrahydrofuran-3-yl-4-bromobenzoate (364) :



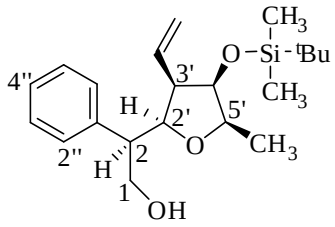
ν_{max} (ATR) : 3482-3388 (***OH***), 2966, 2920, 1724 (***C=O***), 1638 (***C=C***), 1596, 1490, 1397, 1268, 1174, 1093, 1015, 912, 799, 699 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.80 (2H, d, *J* 8.6, 2b''-***H***), 7.57 (2H, d, *J* 8.6, 3b''-***H***), 7.36 (2H, t, *J* 7.3, 3a''-***H***), 7.31 (2H, d, *J* 7.3, 2a''-***H***), 7.27 (1H, t, *J* 7.3, 4a''-***H***), 5.92 (1H, dt, *J* 17.0, 10.4, 4'-C***H***=CH_2), 5.22 (1H, dd, *J* 10.4, 1.6, 4'-CH=C***H***H), 5.18 (1H, dd, *J* 17.0, 1.6, 4'-CH=C***H***H), 5.10 (1H, t, *J* 6.4, 3'-***H***), 4.53 (1H, dd, *J* 9.7, 4.4, 5'-***H***), 4.24 (1H, dq, *J* 6.4, 6.3, 2'-***H***), 3.80 (1H, dd, *J* 10.8, 4.5, 2''-***H***H), 3.72 (1H, dd, *J* 10.8, 7.2, 2''-H***H***), 3.41 (1H, ddd, *J* 10.4, 6.4, 4.4, 4'-***H***), 3.07 (1H, ddd, *J* 9.7, 7.2, 4.5, 1''-***H***), 1.29 (3H, d, *J* 6.3, 2'-C***H***$_3$). δ_C (125 MHz; $CDCl_3$) : 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'-***C***H=CH_2), 128.7 (***C***-2a'', ***C***-3a''), 127.2 (***C***-4b'), 120.1 (4'-CH=***C***H_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'-***C***H_3). *m/z* (ES^+) : 431 ($[M+H]^+$, 100%). HRMS (ES^+) found: 431.0863 ($C_{22}H_{24}O_4{}^{79}Br$ requires $[M+H]^+$ 431.0858).

2-[(2*RS*,2'*SR*,3'*RS*,4'*RS*,5'*RS*)-4'-(*tert*-butyldimethylsilyloxy)-3'-ethenyl-5'-methyltetrahydrofuran-2'-yl]-2-phenylethanol (366, 367) and (3*RS*,4*SR*,5*RS*,6*RS*,7*SR*)-6-(*tert*-butyldimethylsilyloxy)-5-ethenyl-7-methyl-3-phenyloxepan-4-ol (368) :

To a solution of TBDMS protected bicyclic alcohol **362** (68 mg, 0.19 mmol) in DCM (5.00 ml) at -78 ^{o}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 × 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 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.

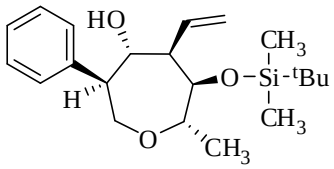
2-[(2*RS*,2'*SR*,3'*RS*,4'*RS*,5'*RS*)-4'-(*tert*-butyldimethylsilyloxy)-3'-ethenyl-5'-methyltetrahydrofuran-2'-yl)]-2-phenylethanol (366) :



ν_{max} (ATR) : 3464-3376 (***OH***), 2942, 2866, 1641 (***C=C***), 1468, 1380, 1256, 1140, 1086, 997, 880, 840, 776, 706, 656 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 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'-C***H***=CH_2), 5.31 (1H, dd, *J* 10.4, 1.9, 3'-CH=C***H***H), 5.19 (1H, dd, *J* 17.1, 1.9, 3'-CH=CH***H***), 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-***H***H), 3.75-3.69 (1H, m, 1-H***H***), 3.07 (1H, ddd, *J* 10.0, 6.7, 4.3, 2-***H***), 2.89 (1H, ddd, *J* 10.4, 6.5, 4.3, 3'-***H***), 1.18 (3H, d, *J* 6.3, 5'-C***H***$_3$), 0.90 (9H, s, SiC(C***H***$_3$)$_3$), 0.08 (3H, s, Si(C***H***$_3$)$_2$), 0.07 (3H, s, Si(C***H***$_3$)$_2$). δ_C (125 MHz; $CDCl_3$) : 139.6 (***C***-1''), 133.6 (3'-***C***H=CH_2), 129.0 (***C***-2''), 128.6 (***C***-3''), 126.9 (***C***-4''), 119.1 (3'-CH=***C***H_2), 80.7 (***C***-4'), 78.1 (***C***-5'), 77.9 (***C***-2'), 64.2 (***C***-1), 52.8 (***C***-3'), 49.6 (***C***-2),

25.7 (SiC(***C***H_3)$_3$), 19.4 (5'-***C***H_3), 18.1 (Si***C***(CH_3)$_3$), -4.5 (Si(***C***H_3)$_2$), -4.9 (Si(***C***H_3)$_2$). *m/z* (ES^+) : 363 ($[M+H]^+$, 100%). HRMS (ES^+) found: 363.2361 ($C_{21}H_{35}O_3Si$ requires $[M+H]^+$ 363.2355).

(3*RS*,4*SR*,5*RS*,6*RS*,7*SR*)-6-(*tert*-butyldimethylsilyloxy)-5-ethenyl-7-methyl-3-phenyloxepan-4-ol (368) :



ν_{max} (ATR) : 3434 (***OH***), 2936, 2860, 1642 (***C*=*C***), 1502, 1461, 1374, 1256, 1098, 1028, 998, 911, 835, 771, 700, 623 cm^{-1}. δ_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-C***H***=CH_2), 5.24 (1H, dd, *J* 9.7, 1.6, 5-CH=C***H***H), 5.22 (1H, dd, *J* 17.4, 1.6, 5-CH=CH***H***), 4.22 (1H, t, *J* 9.7, 4-***H***), 4.19 (1H, dd, *J* 12.4, 9.7, 2-H***H***), 3.98-3.93 (2H, m, 6-***H***, 7-***H***), 3.58 (1H, dd, *J* 12.4, 3.7, 2-H***H***), 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-C***H***$_3$), 1.05 (9H, s, SiC(C***H***$_3$)$_3$), 0.18 (3H, s, Si(C***H***$_3$)$_2$), 0.15 (3H, s, Si(C***H***$_3$)$_2$). δ_C (125 MHz; $CDCl_3$) : 140.0 (***C***-1'), 134.6 (5-***C***H=CH_2), 128.7 (***C***-3'), 128.0 (***C***-2'), 126.9 (***C***-4'), 117.3 (5-CH=***C***H_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(***C***H_3)$_3$), 18.6 (7-***C***H_3), 17.9 (Si***C***(CH_3)$_3$), -3.4 (Si(***C***H_3)$_2$), -4.2(Si(***C***H_3)$_2$). *m/z* (ES^+) : 363 ($[M+H]^+$, 100), 345 ($[M+H-H_2O]^+$, 40). HRMS (ES^+) found: 363.2363 ($C_{20}H_{35}O_3Si$ requires $[M+H]^+$ 363.2360).

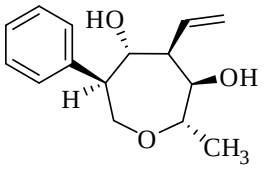
(2*RS*,3*RS*,4*SR*,5*SR*,1'*RS*)-4-ethenyl-5-(2'-Hydroxyl-1'-phenylethyl)-2-methyltetrahydrofuran-3-ol (357, 358) and (2*SR*,3*RS*,4*RS*,5*SR*,6*RS*)-4-ethenyl-2-methyl-6-phenyloxepane-3,5-diol (369) :

To a solution of the TBDMS product **362** (37 mg, 0.10 mmol) in DCM (2.00 ml) at -78 ^oC 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 × 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 $NaHCO_3$, 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.

(2*SR*,3*RS*,4*RS*,5*SR*,6*RS*)-4-ethenyl-2-methyl-6-phenyloxepane-3,5-diol (369) :



ν_{max} (ATR) : 3385 (***OH***), 2969, 2888, 1641 (***C*=*C***), 1598, 1493, 1379, 1253, 1109, 1016, 973, 910, 726, 694, 656 cm^{-1}. δ_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-C***H***=CH_2), 5.28 (1H, dd, *J* 10.4, 1.8, 4-CH=C***H***H), 5.25 (1H, dd, *J* 17.2, 1.8, 4-CH=CH***H***), 4.16 (1H, t, *J* 10.4, 5-***H***), 3.95-3.92 (2H, m, 2-***H***, 7-***H***H), 3.88 (1H, dd, *J* 12.5, 6.2, 7-H***H***), 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, d, *J* 8.2, 3-O***H***), 1.59 (1H, t, *J* 10.4, 5-O***H***), 1.29 (3H, d, *J* 6.5, 2-C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 140.5 (***C***-1'), 138.6 (4-***C***H=CH_2), 128.8 (***C***-3'), 128.5 (***C***-2'), 127.1 (***C***-4'), 118.3 (4-CH=***C***H_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-***C***H_3). *m/z* (ES^+) : 271 ($[M+Na]^+$, 40%), 249 ($[M+H]^+$, 10), 231 ($[M+H-H_2O]^+$, 100). HRMS (ES^+) found: 231.1389 ($C_{15}H_{19}O_2$ requires $[M+H-H_2O]^+$ 231.1385).

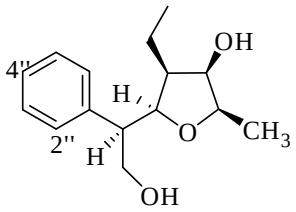
(2*RS*,3*RS*,4*SR*,5*SR*,1'*RS*)-4-ethyl-5-(2'-Hydroxyl-1'-phenylethyl)-2-methyltetrahydrofuran-3-ol (371, 372) :

To a solution of bicyclic alcohol **370** (14 mg, 0.06 mmol) in DCM (2.00 ml) at -78 ^oC 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

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) :

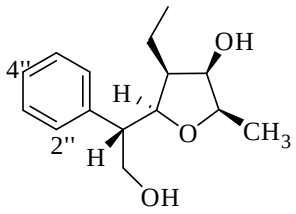


ν_{max} (ATR) : 3540-3294 (***OH***), 2972, 2878, 1490, 1456, 1386, 1250, 1161, 1064, 987, 893, 852, 765, 706, 654 cm^{-1}. δ_H (500 MHz; $CDCl_3$) : 7.51 (2H, d, *J* 7.6, 2''-***H***), 7.37 (2H, t, *J* 7.6, 3''-***H***), 7.31 (1H, t, *J* 7.6, 4''-***H***), 4.51 (1H, dd, *J* 10.3, 1.5, 5-***H***), 3.96-3.90 (2H, m, 2'-$\boldsymbol{H}_2$), 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, O***H***), 1.48-1.41 (1H, m, 4-C***H***HCH_3), 1.22 (3H, d, *J* 6.2, 2-C$\boldsymbol{H}_3$), 0.81-0.90 (1H, m, 4-CH***H***CH_3), 0.91 (3H, t, *J* 7.3, 4-$CH_2C\boldsymbol{H}_3$). δ_C (125 MHz; $CDCl_3$) : 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-$\boldsymbol{C}H_2CH_3$), 14.0 (2-$\boldsymbol{C}H_3$), 13.4 (4-$CH_2\boldsymbol{C}H_3$). *m/z* (ES^+) : 314 ($[M+Na+CH_3CN]^+$, 20%), 273 ($[M+Na]^+$, 40), 251 ($[M+H]^+$, 100).

(2*RS*,3*RS*,4*SR*,5*SR*,1'*SR*)-4-ethyl-5-(2'-Hydroxyl-1'-phenylethyl)-2-methyltetrahydrofuran-3-ol (374, 375) :

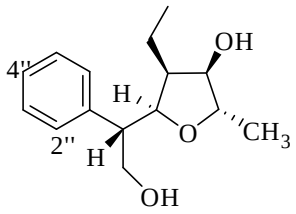
To a solution of bicyclic alcohol **373** (21 mg, 0.08 mmol) in DCM (2.00 ml) at -78 ^oC was added triethylsilane (0.05 ml, 0.33 mmol) followed by the dropwise addition of a 1 M solution of titanium tetrachloride (0.10 ml, 0.10 mmol). After stirring at this temperature for 2 h, the reaction mixture was quenched with an aqueous solution of NaCl and extracted with DCM (3 × 20.0 ml). The combined organic extracts were dried over $MgSO_4$, 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) :



ν_{max} (ATR) : 3386-3278 (***OH***), 2938, 2882, 1458, 1392, 1312, 1158, 1086, 1046, 994, 914, 872, 704, 628 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 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'-***H***H, 3-***H***), 3.96 (1H, qd, *J* 6.4, 2.8, 2-***H***), 3.60 (1H, dd, *J* 11.2, 2.7, 2'-H***H***), 3.21 (1H, td, *J* 8.2, 2.7, 1'-***H***), 2.28-2.24 (1H, m, 4-***H***), 2.12 (1H, bs, O***H***), 1.66 (1H, s, O***H***), 1.61-1.55 (1H, m, 4-C***H***HCH_3), 1.37 (3H, d, *J* 6.4, 2-C***H***$_3$), 1.06-1.01 (1H, m, 4-CH***H***CH_3), 0.82 (3H, t, *J* 7.5, 4-CH_2C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 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-***C***H_2CH_3), 14.4 (2-***C***H_3), 13.2 (4-CH_2***C***H_3). *m/z* (ES^+) : 523 ($[2M+Na]^+$, 20%), 314 ($[M+Na+CH_3CN]^+$, 40), 273 ($[M+Na]^+$, 90), 251 ($[M+H]^+$, 100). HRMS (ES^+) found: 251.1652 ($C_{15}H_{23}O_3$ requires $[M+H]^+$ 251.1647).

4-ethyl-5-(2'-Hydroxyl-1'-phenylethyl)-2-methyltetrahydrofuran-3-ol (375) :



ν_{max} (ATR) : 3466-3218 (***OH***), 2962, 2874, 1454, 1381, 1310, 1148, 1054, 1044, 990, 868, 831, 757, 625 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 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'-***H***H, 3-***H***), 3.65 (1H, dd, *J* 11.1, 4.1, 2'-H***H***), 3.33 (1H, td, *J* 8.9, 4.1, 1'-***H***), 2.15-2.11 (1H, m, 4-***H***), 2.10 (1H, bs, O***H***), 1.46-1.39 (1H, m, 4-C***H***HCH_3), 1.25 (3H, d, *J* 6.6, 2-C***H***$_3$), 1.08-1.05 (1H, m, 4-CH***H***CH_3), 0.75 (3H, t, *J* 7.4, 4-CH_2C***H***$_3$). δ_C (175 MHz; $CDCl_3$) : 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-***C***H_2CH_3), 17.1 (2-***C***H_3), 13.3 (4-CH_2***C***H_3). *m/z*

(ES^+) : 273 ($[M+Na]^+$, 50%), 251 ($[M+H]^+$, 100), 233 ($[M+H-H_2O]^+$, 80). HRMS (ES^+) found: 251.1638 ($C_{15}H_{23}O_3$ requires $[M+H]^+$ 251.1647).

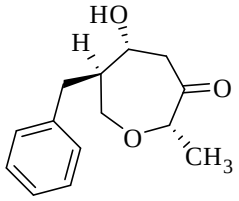
General method for the preparation of samarium (II) iodide (SmI_2) solution (A9):

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 continous 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]

(2*SR*,5*RS*,6*RS*)-6-benzyl-5-hydroxy-2-methyloxepan-3-one (432, 433) :

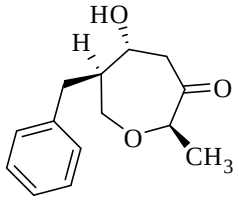
To a stirred solution of freshly prepared 0.1 M solution of samarium (II) iodide (8.00 ml, 0.80 mmol) was added distilled hexamethylphosphoramide (HMPA) (0.15 ml, 0.80 mmol) to give a purple colour. After stirring for 15 min, the resulting mixture was added quite slowly (over ~10 mins) into a stirring 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® and Et_2O 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** :



ν_{max} (ATR) : 3458 (***OH***), 2932, 1753 (***C*=*O***), 1495, 1453, 1368, 1240, 1179, 1030, 745, 700 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.30 (2H, t, *J* 7.5, 3'-***H***), 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-$\boldsymbol{H}_2$), 2.83 (1H, dd, *J* 13.8, 5.2, 6-C***H***HPh), 2.71 (1H, dd, *J* 13.8, 9.2, 6-CH***H***Ph), 2.55 (2H, d, *J* 7.7, 4-$\boldsymbol{H}_2$), 2.20-2.16 (1H, m, 6-***H***), 1.94 (1H, s, O***H***), 1.27 (3H, d, *J* 7.3, 2-C$\boldsymbol{H}_3$). δ_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-***C***H_2Ph), 15.9 (2-***C***H_3). *m/z* (GCMS, EI), t_R = 8.22 min : 234 (M^+, 50%), 216 (M^+-H_2O, 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** :



δ_H (700 MHz; $CDCl_3$) : 7.30 (2H, t, *J* 7.5, 3'-***H***), 7.23-7.21 (3H, 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-$\boldsymbol{H}_2$), 2.78 (1H, dd, *J* 13.8, 6.0, 6-C***H***HPh), 2.63 (1H, dd, *J* 13.8, 7.5, 6-CH***H***Ph), 2.50 (1H, dd, *J* 17.9, 6.1, 4-***H***H), 2.45 (1H, dd, *J* 17.9, 10.8, 4-H***H***), 2.31-2.29 (1H, m, 6-***H***), 1.68 (1H, s, O***H***), 1.34 (3H, d, *J* 6.7, 2-C$\boldsymbol{H}_3$). δ_C (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-***C***H_2Ph), 15.8 (2-***C***H_3). *m/z* (GCMS, EI), t_R = 8.13 min : 234 (M^+, 10%), 216 (M^+-H_2O, 20), 129 (30), 91 ($PhCH_2^+$, 100), 77 (Ph^+,40).

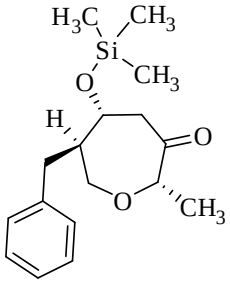
(2*SR*,5*RS*,6*RS*)-6-benzyl-2-methyl-5-(trimethylsilyloxy)oxepan-3-one (434, 435) and (2*SR*,5*RS*,6*RS*)-6-benzyl-5-hydroxy-2-methyloxepan-3-one (432, 433) :

To a stirred solution of freshly prepared 0.1 M solution of samarium (II) iodide (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® and Et_2O 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 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), t_R = 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) :



ν_{max} (ATR) : 2920, 2856 (***CH***-OSi), 1756 (***C*=*O***), 1456, 1254+840 (***Si*-*C***H_3), 1086, 745, 699, 664 cm^{-1}. δ_H (700 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-***H***H), 3.46 (1H, dd, *J* 10.4, 5.4, 7-H***H***), 2.94 (1H, dd, *J* 13.8, 4.5, 6-C***H***HPh), 2.67 (1H, dd, *J* 13.8, 9.2, 6-CH***H***Ph), 2.55 (2H, d, *J* 7.2, 4-$\boldsymbol{H}_2$), 2.05-2.02 (1H, m, 6-***H***), 1.27 (3H, d, *J* 7.2, 2-C$\boldsymbol{H}_3$), 0.05 (9H, s, Si(C$\boldsymbol{H}_3$)$_3$). δ_C (175 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-***C***H_2Ph), 16.1 (2-***C***H_3), -0.7 (Si(***C***H_3)$_3$). *m/z* (GCMS, EI), t_R = 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).

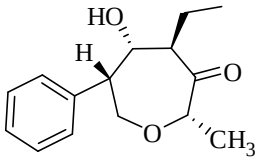
(2*SR*,4*RS*,5*SR*,6*SR*)-4-ethyl-5-hydroxy-2-methyl-6-phenyloxepan-3-one (442, 443) :

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 $NaHCO_3$, an excess of Celite® and Et_2O 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.

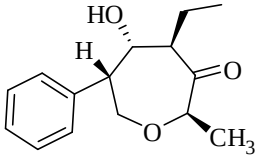
The analytical data for the oxepanone isomers **442** and **443** was obtained on the mixture and is reported below.

Major isomer **442** :



ν_{max} (ATR) : 3552-3396 (***OH***), 2978, 2882, 1749 (***C*=*O***), 1458, 1382, 1228, 1182, 1060, 1014, 988, 752, 701 cm^{-1}. δ_H (700 MHz; $CDCl_3$) : 7.33 (2H, t, *J* 7.6, 3'-***H***), 7.27 (1H, t, *J* 7.6, 4'-***H***), 7.20 (2H, d, *J* 7.6, 2'-***H***), 4.61 (1H, dd, *J* 10.8, 5.0, 5-***H***), 3.93 (1H, q, *J* 6.9, 2-***H***), 3.83-3.79 (2H, m, 7-$\boldsymbol{H}_2$), 3.25-3.22 (1H, m, 6-***H***), 2.79 (1H, bs, O***H***), 2.03 (1H, dt, *J* 10.6, 5.0, 4-***H***), 1.54-1.47 (2H, m, 4-C$\boldsymbol{H}_2CH_3$), 1.36 (3H, d, *J* 6.9, 2-C$\boldsymbol{H}_3$), 0.82 (3H, t, *J* 7.5, 4-$CH_2C\boldsymbol{H}_3$). δ_C (175 MHz; $CDCl_3$) : 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-$\boldsymbol{C}H_2CH_3$), 16.4 (2-$\boldsymbol{C}H_3$), 11.0 (4-$CH_2C\boldsymbol{H}_3$). *m/z* (GCMS, EI), t_R = 7.99 min : 248 (M^+, 10%), 230 (M^+-H_2O, 10), 145 (20), 104 (100), 77 (Ph^+,40). HRMS ($ASAP^+$) found: 247.1332 ($C_{15}H_{19}O_3$ requires 247.1334).

Minor isomer **443** :



δ_H (700 MHz; $CDCl_3$) : 7.33 (2H, t, *J* 7.6, 3'-***H***), 7.27 (1H, t, *J* 7.6, 4'-***H***), 7.20 (2H, d, *J* 7.6, 2'-***H***), 4.61 (1H, dd, *J* 10.5, 5.6, 5-***H***), 3.93 (1H, q, *J* 7.0, 2-***H***), 4.04-3.98 (2H, m, 7-$\boldsymbol{H}_2$), 3.18-3.15 (1H, m, 6-***H***), 2.72 (1H, bs, O***H***), 2.13 (1H, dt, *J* 10.2, 5.6, 4-***H***), 1.67-1.55 (2H, m, 4-

C***H***$_2$CH$_3$), 1.34 (3H, d, *J* 7.0, 2-C***H***$_3$), 0.77 (3H, t, *J* 7.5, 4-CH$_2$C***H***$_3$). δ_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-***C***H$_2$CH$_3$), 16.2 (2-***C***H$_3$), 11.1 (4-CH$_2$***C***H$_3$). *m/z* (GCMS, EI), t_R = 7.86 min : 248 (M^+, 5%), 230 (M^+-H_2O, 10), 145 (90), 104 (100), 77 (Ph^+,20).

9.3 References

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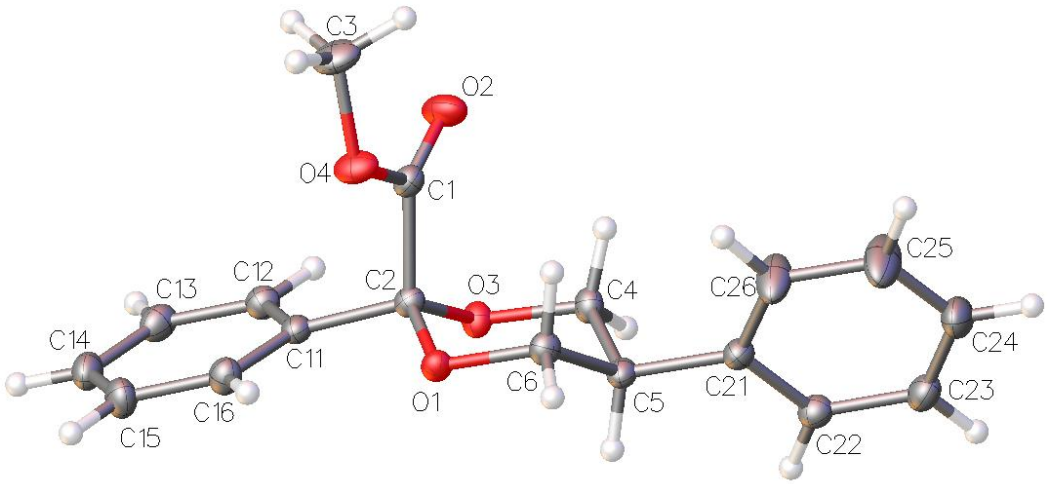
APPENDIX A: Crystal Structure of the ester acetal **151**



2,5-diphenyl-[1,3]-dioxane-2-carboxylic acid methyl ester **151**

Table 1 Crystal data and structure refinement for 07srv147

Identification code	07srv147
Empirical formula	$C_{18}H_{18}O_4$
Formula weight	298.32
Temperature/K	120(2)
Crystal system	Triclinic
Space group	P-1
a/Å, b/Å, c/Å	6.0475(6), 10.7374(11), 12.2817(13)
α/°, β/°, γ/°	105.36(1), 102.09(1), 91.59(1)
Volume/$Å^3$	749.03(13)
Z	2
$\rho_{calc}mg/mm^3$	1.323
m/mm^{-1}	0.093
F(000)	316
Crystal size/mm^3	0.40 × 0.18 × 0.12
Theta range for data collection	1.76 to 29.01°
Index ranges	$-8 \leq h \leq 8, -13 \leq k \leq 14, -16 \leq l \leq 16$
Reflections collected	9006
Independent reflections	3947[R(int) = 0.0412]
Data/restraints/parameters	3947/0/271
Goodness-of-fit on F^2	1.054
Final R indexes [I>2σ (I)]	$R_1 = 0.0430$, $wR_2 = 0.1100$
Final R indexes [all data]	$R_1 = 0.0581$, $wR_2 = 0.1178$
Largest diff. peak/hole / e $Å^{-3}$	0.354/-0.252

Table 2 Atomic Coordinates ($Å \times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 07srv147. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
O1	721.8(13)	4718.9(8)	6292.6(7)	17.11(19)
O2	3498.4(16)	3478.8(10)	8515.3(8)	28.6(2)
O3	4615.8(13)	4900.9(8)	7094.8(7)	17.66(19)
O4	-121.5(15)	3947.2(9)	8113.8(8)	24.4(2)
C1	2045.1(19)	4012.3(11)	8040.8(10)	17.2(2)
C2	2431.8(18)	4960.9(11)	7316.5(9)	15.5(2)
C3	-646(3)	3240.5(16)	8900.1(13)	30.1(3)
C4	4928(2)	3694.1(12)	6307(10)	18.4(2)
C5	3104(2)	3389.4(11)	5183.6(10)	17.3(2)
C6	803(2)	3470.3(12)	5504.6(10)	18.1(2)
C11	2298(2)	6318.6(11)	8065.3(10)	17(2)
C12	4175(2)	6931.9(12)	8933(10)	19.9(2)
C13	4044(2)	8150.2(13)	9658.2(11)	23.3(3)
C14	2056(2)	8760.6(13)	9510.7(11)	24.8(3)
C15	180(2)	8149.2(13)	8645.1(11)	25.2(3)
C16	287(2)	6919.9(13)	7927.8(11)	21.6(3)
C21	3425(2)	2098.6(11)	4385.5(10)	18.6(2)
C22	4973(2)	2071.1(12)	3685.5(10)	20.6(3)
C23	5446(2)	905.8(13)	2989.2(11)	24.4(3)
C24	4358(3)	-246.8(13)	2969.5(12)	30.9(3)
C25	2795(3)	-235.3(15)	3643.4(16)	47(5)
C26	2336(3)	927.4(14)	4351.2(15)	39.8(4)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 07srv147. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka×b×U_{12}]$

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
O1	16.5(4)	19.2(4)	15.1(4)	4.6(3)	2.5(3)	3.3(3)
O2	25.1(5)	37.7(6)	32(5)	21.7(4)	9.4(4)	10.9(4)
O3	13.9(4)	18.2(4)	20.5(4)	2.7(3)	6.5(3)	0.5(3)
O4	17.7(4)	34.2(5)	27.5(5)	16.7(4)	8.3(4)	1(4)
C1	16.7(5)	19.2(6)	15.7(5)	4.2(4)	4.6(4)	1(4)
C2	12.6(5)	18.4(5)	15.8(5)	5.1(4)	3.5(4)	1.3(4)
C3	27.6(7)	40.3(8)	30.2(7)	19.1(6)	12.1(6)	-1.2(6)
C4	16.7(5)	18.5(6)	20.2(5)	3.1(4)	7(4)	2.5(4)
C5	20.2(6)	15.8(5)	17.7(5)	5.1(4)	7.6(4)	0.6(4)
C6	17.1(6)	18.4(6)	17.4(5)	3.1(4)	3.3(4)	0.4(4)
C11	20.2(6)	16.5(5)	16(5)	5.4(4)	6.4(4)	1.4(4)
C12	19(6)	21.4(6)	19.5(5)	5.9(5)	4.5(4)	1.4(5)
C13	25.4(6)	23.5(6)	18.7(6)	2.6(5)	4.6(5)	-3.7(5)
C14	32.9(7)	19(6)	22.8(6)	2.2(5)	11.6(5)	2(5)
C15	26.3(7)	24.3(7)	25.6(6)	4.6(5)	9.1(5)	8.4(5)
C16	20(6)	23.7(6)	20.4(6)	4.3(5)	4.9(5)	3.9(5)
C21	21.4(6)	18.1(6)	17.4(5)	5.2(4)	6.4(4)	2.1(4)
C22	20.6(6)	21.6(6)	20.9(6)	6.7(5)	6.7(5)	0.8(5)
C23	26.3(6)	28.1(7)	20.7(6)	6.4(5)	9.8(5)	5.9(5)
C24	45.6(8)	21.3(7)	26.8(7)	2.4(5)	15.2(6)	5.5(6)
C25	74.6(13)	18.5(7)	54.8(10)	1(7)	42.6(10)	-6.4(7)
C26	57.6(10)	21.3(7)	48(9)	2.8(6)	38.2(8)	-5(6)

Table 4 Bond Lengths for 07srv147.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C2	1.4091(13)	C11	C12	1.3922(17)
O1	C6	1.4398(14)	C11	C16	1.3927(17)
O2	C1	1.1960(15)	C12	C13	1.3889(17)
O3	C2	1.4031(13)	C13	C14	1.3871(19)
O3	C4	1.4411(13)	C14	C15	1.3897(19)
O4	C1	1.3331(14)	C15	C16	1.3911(17)
O4	C3	1.4533(15)	C21	C22	1.3934(16)
C1	C2	1.5612(16)	C21	C26	1.3897(18)
C2	C11	1.5182(16)	C22	C23	1.3908(17)
C4	C5	1.5266(17)	C23	C24	1.378(2)
C5	C6	1.5224(16)	C24	C25	1.379(2)
C5	C21	1.5147(15)	C25	C26	1.392(2)

Table 5 Bond Angles for 07srv147.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	C2	C1	111.05(9)	C13	C12	C11	119.84(11)
O1	C2	C11	108.63(9)	C13	C14	C15	120.12(12)
O1	C6	C5	109.79(9)	C14	C13	C12	120.09(12)
O2	C1	O4	124.83(11)	C14	C15	C16	120.10(12)
O2	C1	C2	125.13(10)	C16	C11	C2	120.53(11)
O3	C2	O1	112.31(8)	C16	C11	C12	120.18(11)
O3	C2	C1	110.47(9)	C21	C5	C4	109.96(10)
O3	C2	C11	107.57(9)	C21	C5	C6	114.74(10)
O3	C4	C5	110.95(9)	C21	C26	C25	120.78(13)
O4	C1	C2	109.92(10)	C22	C21	C5	118.44(10)
C1	O4	C3	115.48(10)	C23	C22	C21	121.07(12)
C2	O1	C6	112.20(8)	C23	C24	C25	119.50(12)
C2	O3	C4	113.70(9)	C24	C23	C22	120.18(12)
C6	C5	C4	107.71(9)	C24	C25	C26	120.49(14)
C11	C2	C1	106.57(9)	C26	C21	C5	123.52(10)
C11	C16	C15	119.64(12)	C26	C21	C22	117.97(11)
C12	C11	C2	119.20(10)				

Table 6 Torsion Angles for 07srv147.

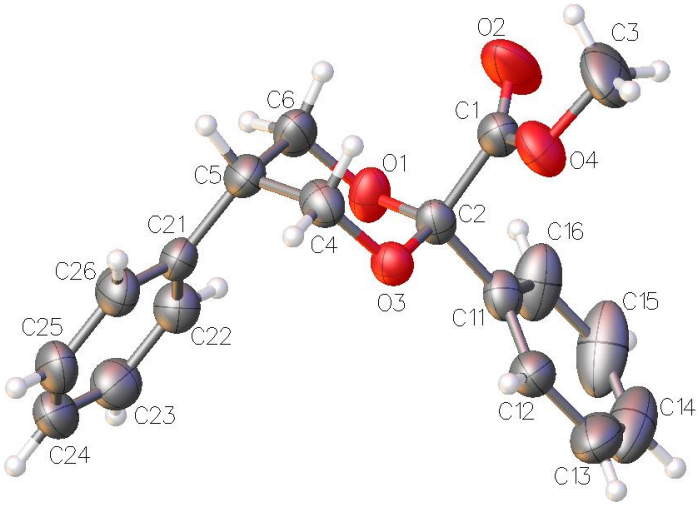
A	B	C	D	Angle/°
O1	C2	C11	C12	-160.53(10)
O1	C2	C11	C16	22.74(14)
O2	C1	C2	O1	137.46(12)
O2	C1	C2	O3	12.17(16)
O2	C1	C2	C11	-104.40(13)
O3	C2	C11	C12	-38.74(13)
O3	C2	C11	C16	144.54(11)
O3	C4	C5	C6	-52.59(12)
O3	C4	C5	C21	-178.28(9)
O4	C1	C2	O1	-46.43(12)
O4	C1	C2	O3	-171.73(9)
O4	C1	C2	C11	71.71(12)
C1	C2	C11	C12	79.75(12)
C1	C2	C11	C16	-96.97(12)
C2	O1	C6	C5	-59.00(12)
C2	O3	C4	C5	53.64(12)
C2	C11	C12	C13	-177.14(10)

C2	C11	C16	C15	178.15(11)
C3	O4	C1	O2	4.44(18)
C3	O4	C1	C2	-171.68(10)
C4	O3	C2	O1	-55.51(12)
C4	O3	C2	C1	69.06(11)
C4	O3	C2	C11	-174.99(9)
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)

Table 7 Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 07srv147.

Atom	***x***	***y***	***z***	**U(eq)**
H31	230(3)	3668(16)	9699(15)	38(5)
H32	-2240(3)	3313(17)	8865(16)	43(5)
H33	-270(3)	2334(18)	8661(16)	40(5)
H41	4890(2)	2967(14)	6672(12)	17(3)
H42	6430(3)	3828(15)	6164(13)	28(4)
H5	3260(2)	4078(14)	4793(12)	19(3)
H61	-440(2)	3444(14)	4851(13)	21(4)
H62	510(2)	2784(13)	5886(12)	16(3)
H12	5550(3)	6485(14)	9028(13)	25(4)
H13	5330(3)	8556(15)	10256(14)	31(4)
H14	1970(3)	9578(16)	10001(14)	32(4)
H15	-1210(3)	8598(15)	8538(13)	25(4)
H16	-1050(3)	6483(16)	7344(14)	32(4)
H22	5750(3)	2918(16)	3688(14)	30(4)
H23	6500(3)	885(16)	2513(15)	34(4)
H24	4670(3)	-1042(17)	2484(15)	40(5)
H25	1990(4)	-1040(2)	3634(18)	60(6)
H26	1280(3)	912(19)	4835(17)	53(5)

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

Identification code	07srv163
Empirical formula	$C_{18}H_{18}O_4$
Formula weight	298.32
Temperature/K	293(2)
Crystal system	Monoclinic
Space group	I2/a
a/Å, b/Å, c/Å	16.050(3), 6.1030(11), 31.212(5)
α/°, β/°, γ/°	90.00, 96.51(3), 90.00
Volume/$Å^3$	3037.5(9)
Z	8
$\rho_{calc}mg/mm^3$	1.305
m/mm^{-1}	0.092
F(000)	1264
Crystal size/mm^3	0.56 × 0.28 × 0.24
Theta range for data collection	2.55 to 27.48°
Index ranges	$-17 \leq h \leq 20, -7 \leq k \leq 7, -38 \leq l \leq 40$
Reflections collected	9477
Independent reflections	3464[R(int) = 0.0386]
Data/restraints/parameters	3464/0/202
Goodness-of-fit on F^2	1.023
Final R indexes [I>2σ (I)]	$R_1 = 0.0468$, $wR_2 = 0.1146$
Final R indexes [all data]	$R_1 = 0.0688$, $wR_2 = 0.1263$
Largest diff. peak/hole / e $Å^{-3}$	0.185/-0.207

Table 2 Atomic Coordinates ($Å \times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 07srv163. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
O1	6065.9(7)	3456.7(18)	1368.9(3)	49.4(3)
O2	6451.3(10)	2430(3)	554.1(5)	94.1(6)
O3	5517.8(6)	-59.9(17)	1393.2(3)	39.6(3)
O4	5767.5(9)	-722(2)	573.4(4)	62(4)
C1	6015.5(10)	1220(3)	725.6(5)	49.7(4)
C2	5606.1(9)	1797(2)	1140.3(5)	39.5(3)
C3	6059.1(16)	-1392(5)	169.7(7)	93.1(9)
C4	6301.9(10)	-954(3)	1575.8(5)	47.2(4)
C5	6808.7(9)	751(3)	1849.9(5)	47.6(4)
C6	6875.1(10)	2755(3)	1567.6(5)	54.4(5)
C11	4737.2(10)	2686(3)	993.1(5)	43.7(4)
C12	4036.4(10)	1392(3)	1007.5(5)	55.1(5)
C13	3253.4(13)	2176(5)	855.5(7)	79.5(7)
C14	3157.9(18)	4217(5)	690.6(8)	97.1(10)
C15	3835(2)	5514(4)	678.1(8)	102.2(10)
C16	4642.7(16)	4763(3)	829.8(7)	74.7(6)
C21	6450.3(9)	1156(3)	2272.9(5)	42.5(4)
C22	6049.4(11)	3068(3)	2367.4(6)	51.9(4)
C23	5722(11)	3329(3)	2755.8(6)	59.9(5)
C24	5785.2(11)	1687(4)	3056(6)	61.5(5)
C25	6179.7(12)	-234(4)	2968.4(6)	60.1(5)
C26	6508.5(10)	-496(3)	2580.2(5)	52.2(4)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 07srv163. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka×b×U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	56.8(7)	44.9(7)	43.5(6)	2.1(5)	-7.4(5)	-15.6(5)
O2	95.5(11)	134.8(15)	56.5(8)	0.5(9)	28.3(8)	-57.7(11)
O3	42.8(6)	38.8(6)	37.5(5)	3.1(4)	4.9(4)	-3.8(4)
O4	80.4(9)	67.1(9)	40.3(6)	-11.5(6)	15(6)	-0.4(7)
C1	43.9(8)	67.2(12)	37.7(8)	4.5(8)	2.9(7)	-7.4(8)
C2	44.9(8)	38.4(8)	34.8(7)	1.5(6)	2.8(6)	-9.5(7)
C3	99.4(17)	136(2)	44.9(11)	-28.1(13)	11.7(11)	25.2(16)
C4	52.4(9)	49.3(10)	40.3(8)	2.6(7)	7(7)	9.3(7)
C5	35.5(8)	65.8(11)	40.8(8)	2.4(8)	0.8(6)	4.7(7)
C6	45.1(9)	73.1(12)	43.9(9)	1.7(8)	-0.4(7)	-18.4(8)
C11	53.1(9)	42.5(9)	34(7)	-7.4(7)	-1.3(6)	3.2(7)
C12	46.1(9)	74(13)	45.1(9)	-2.7(9)	5.4(7)	-0.4(9)
C13	49(11)	126(2)	63.3(12)	-14.1(14)	3.8(9)	14.7(12)
C14	84.8(17)	116(2)	81.9(16)	-46.1(16)	-27.4(13)	47.7(17)
C15	143(3)	56(14)	92.7(18)	-19(13)	-50.7(17)	41.1(16)
C16	97.8(16)	45.5(11)	72.4(13)	-2.6(10)	-26.7(11)	0.2(10)
C21	33.4(7)	55.9(10)	36.8(7)	-0.6(7)	-2.9(6)	-1.8(7)
C22	53.6(10)	52.8(10)	48.4(9)	0.6(8)	1.5(7)	0.4(8)
C23	56.7(10)	65.8(12)	57.2(11)	-13.9(10)	6.9(8)	2.3(9)
C24	54.7(10)	89(15)	41.2(9)	-12.3(10)	7.4(7)	-6.2(10)
C25	60(11)	79.4(14)	39.4(9)	10(9)	-1.5(8)	-3.2(10)
C26	50.4(9)	60.7(11)	44.2(9)	3.7(8)	-0.8(7)	8.2(8)

Table 4 Bond Lengths for 07srv163.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C2	1.4003(18)	C11	C12	1.379(2)
O1	C6	1.439(2)	C11	C16	1.368(3)
O2	C1	1.186(2)	C12	C13	1.378(3)
O3	C2	1.3973(17)	C13	C14	1.350(4)
O3	C4	1.4296(18)	C14	C15	1.348(4)
O4	C1	1.321(2)	C15	C16	1.406(4)
O4	C3	1.452(2)	C21	C22	1.381(2)
C1	C2	1.557(2)	C21	C26	1.387(2)
C2	C11	1.518(2)	C22	C23	1.384(3)
C4	C5	1.523(2)	C23	C24	1.368(3)
C5	C6	1.518(2)	C24	C25	1.375(3)
C5	C21	1.519(2)	C25	C26	1.385(2)

Table 5 Bond Angles for 07srv163.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	C2	C1	109.85(12)	C12	C11	C2	120.68(15)
O1	C2	C11	107.97(13)	C13	C12	C11	120.4(2)
O1	C6	C5	111.74(13)	C14	C13	C12	120.8(2)
O2	C1	O4	124.42(17)	C14	C15	C16	120.9(2)
O2	C1	C2	124.10(18)	C15	C14	C13	119.7(2)
O3	C2	O1	112.34(11)	C16	C11	C2	120.21(17)

O3	C2	C1	111.45(13)	C16	C11	C12	119.08(18)
O3	C2	C11	108.20(12)	C21	C5	C4	111.63(13)
O3	C4	C5	110.67(13)	C21	C22	C23	121.10(17)
O4	C1	C2	111.32(13)	C22	C21	C5	123.67(15)
C1	O4	C3	116.82(17)	C22	C21	C26	117.60(15)
C2	O1	C6	113.69(13)	C23	C24	C25	119.26(17)
C2	O3	C4	113.19(11)	C24	C23	C22	120.64(18)
C6	C5	C4	107.02(13)	C24	C25	C26	120.16(18)
C6	C5	C21	115.60(15)	C25	C26	C21	121.24(17)
C11	C2	C1	106.81(12)	C26	C21	C5	118.71(15)
C11	C16	C15	119.1(2)				

Table 6 Torsion Angles for 07srv163.

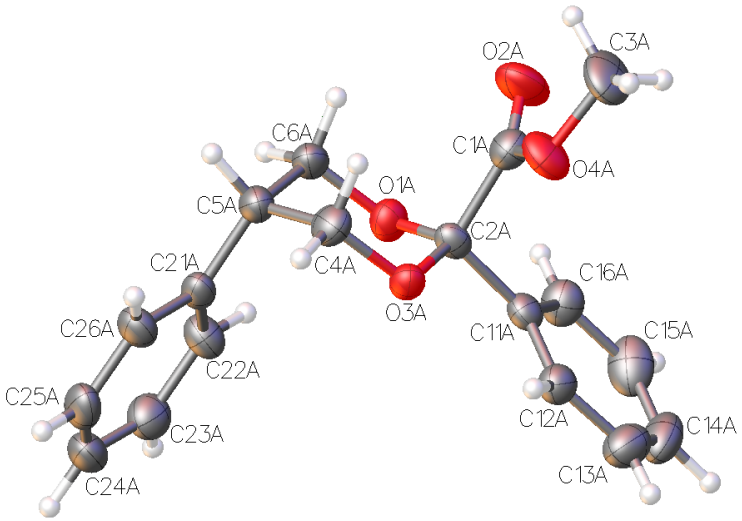
A	**B**	**C**	**D**	**Angle/°**
O1	C2	C11	C12	-139.79(14)
O1	C2	C11	C16	42.53(19)
O2	C1	C2	O1	-23.4(2)
O2	C1	C2	O3	-148.60(18)
O2	C1	C2	C11	93.4(2)
O3	C2	C11	C12	-17.97(19)
O3	C2	C11	C16	164.35(15)
O3	C4	C5	C6	-54.02(16)
O3	C4	C5	C21	73.39(16)
O4	C1	C2	O1	161.03(13)

O4	C1	C2	O3	35.86(18)
O4	C1	C2	C11	-82.12(16)
C1	C2	C11	C12	102.12(17)
C1	C2	C11	C16	-75.56(19)
C2	O1	C6	C5	-53.70(18)
C2	O3	C4	C5	57.85(15)
C2	C11	C12	C13	-177.07(16)
C2	C11	C16	C15	177.22(18)
C3	O4	C1	O2	0.4(3)
C3	O4	C1	C2	175.87(15)
C4	O3	C2	O1	-56.79(16)
C4	O3	C2	C1	66.98(15)
C4	O3	C2	C11	-175.88(11)
C4	C5	C6	O1	52.12(18)
C4	C5	C21	C22	-109.73(18)
C4	C5	C21	C26	68.74(18)
C5	C21	C22	C23	178.85(16)
C5	C21	C26	C25	-178.84(15)
C6	O1	C2	O3	54.40(16)
C6	O1	C2	C1	-70.26(16)
C6	O1	C2	C11	173.62(12)
C6	C5	C21	C22	12.9(2)
C6	C5	C21	C26	-168.64(14)
C21	C5	C6	O1	-72.92(17)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 07srv147.

Atom	***x***	***y***	***z***	**U(eq)**
H31	230(3)	3668(16)	9699(15)	38(5)
H32	-2240(3)	3313(17)	8865(16)	43(5)
H33	-270(3)	2334(18)	8661(16)	40(5)
H41	4890(2)	2967(14)	6672(12)	17(3)
H42	6430(3)	3828(15)	6164(13)	28(4)
H5	3260(2)	4078(14)	4793(12)	19(3)
H61	-440(2)	3444(14)	4851(13)	21(4)
H62	510(2)	2784(13)	5886(12)	16(3)
H12	5550(3)	6485(14)	9028(13)	25(4)
H13	5330(3)	8556(15)	10256(14)	31(4)
H14	1970(3)	9578(16)	10001(14)	32(4)
H15	-1210(3)	8598(15)	8538(13)	25(4)
H16	-1050(3)	6483(16)	7344(14)	32(4)
H22	5750(3)	2918(16)	3688(14)	30(4)
H23	6500(3)	885(16)	2513(15)	34(4)
H24	4670(3)	-1042(17)	2484(15)	40(5)
H25	1990(4)	-1040(2)	3634(18)	60(6)
H26	1280(3)	912(19)	4835(17)	53(5)

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

Identification code	07srv164
Empirical formula	$C_{18}H_{18}O_4$
Formula weight	298.32
Temperature/K	240(2)
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å, b/Å, c/Å	15.959(2), 12.1803(17), 31.154(4)
α/°, β/°, γ/°	90.00, 96.53(2), 90.00
Volume/$Å^3$	6016.6(15)
Z	16
$\rho_{calc}mg/mm^3$	1.317
m/mm^{-1}	0.093
F(000)	2528
Crystal size/mm^3	0.56 × 0.28 × 0.24
Theta range for data collection	1.28 to 26.66°
Index ranges	$-19 \leq h \leq 17, -14 \leq k \leq 15, -39 \leq l \leq 35$
Reflections collected	28962
Independent reflections	11135[R(int) = 0.0553]
Data/restraints/parameters	11135/0/802
Goodness-of-fit on F^2	1.000
Final R indexes [I>2σ (I)]	$R_1 = 0.0523$, $wR_2 = 0.1240$
Final R indexes [all data]	$R_1 = 0.1439$, $wR_2 = 0.1616$
Largest diff. peak/hole / e $Å^{-3}$	0.187/-0.156

Table 2 Atomic Coordinates ($Å \times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 07srv164. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
O1A	3504.3(13)	8016.7(17)	3891.6(6)	37.1(5)
O2A	3878(15)	7648(2)	3058.7(6)	61.8(7)
O3A	3014.3(11)	6213.7(16)	3892(5)	31.6(5)
O4A	3284.7(14)	5995.3(19)	3062.9(6)	49.2(6)
C1A	3479(2)	6978(3)	3225.7(9)	39(8)
C2A	3066.3(18)	7176(2)	3648.8(8)	28.7(7)
C3A	3575(2)	5765(3)	2647.1(9)	67.8(11)
C4A	3816.5(18)	5802(3)	4072.4(9)	39.6(8)
C5A	4308.6(19)	6661(3)	4357.6(8)	36(8)
C6A	4336.1(18)	7694(3)	4079.4(9)	38.3(8)
C11A	2175.8(19)	7584(3)	3513.9(8)	31.5(7)
C12A	1502.3(19)	6863(3)	3510.9(9)	38.7(8)
C13A	698(2)	7212(3)	3365.4(10)	52.3(9)
C14A	549(2)	8261(3)	3234.8(10)	55.4(10)
C15A	1215(2)	8984(3)	3236.4(10)	55.9(10)
C16A	2025.1(18)	8637(3)	3373.6(9)	42.6(8)
C21A	3942.5(18)	6842(3)	4776.6(8)	34.3(8)
C22A	3544(2)	7803(3)	4874.9(9)	39.7(8)
C23A	3214(2)	7900(3)	5266.6(9)	47.4(9)
C24A	3275(2)	7049(3)	5565.2(9)	50.3(10)

C25A	3670(2)	6097(3)	5464(9)	48.1(9)
C26A	3997.3(19)	5980(3)	5074.3(8)	40.7(8)
O1B	3639.6(13)	2929.7(18)	3852.1(6)	44.1(6)
O2B	4056.8(15)	2269(2)	3048.3(7)	73.5(8)
O3B	3009.3(11)	1217.6(16)	3889.6(5)	32.4(5)
O4B	3251.8(14)	793(19)	3074.2(6)	49.1(6)
C1B	3563(2)	1740(3)	3218.5(9)	42.8(8)
C2B	3146(19)	2115(2)	3622.9(8)	31.5(7)
C3B	3549(2)	374(3)	2683(9)	66.5(11)
C4B	3778.6(18)	728(3)	4080.9(9)	40.4(9)
C5B	4323.4(19)	1557(3)	4354.5(8)	38.1(8)
C6B	4428(2)	2548(3)	4066.3(9)	46.2(9)
C11B	2307(2)	2634(3)	3464.6(9)	38.8(8)
C12B	1562(2)	2084(3)	3496.5(9)	45.6(9)
C13B	803(2)	2547(4)	3329.5(11)	68.2(12)
C14B	788(3)	3544(4)	3135.2(12)	82.2(15)
C15B	1529(3)	4096(3)	3097.7(11)	80(13)
C16B	2281(2)	3633(3)	3263(10)	61.3(10)
C21B	3960.2(19)	1798(3)	4770.4(8)	35.5(8)
C22B	3568(2)	2778(3)	4853.5(9)	41.8(8)
C23B	3234(2)	2908(3)	5242.1(10)	48.3(9)
C24B	3283(2)	2089(3)	5552.9(10)	52.3(10)

C25B	3677(2)	1124(3)	5468.2(9)	49.1(9)
C26B	4008.8(19)	971(3)	5079.9(8)	41.5(9)
O1C	1506.3(13)	5517.9(16)	6107.9(6)	36.6(5)
O2C	1116.7(14)	5159(2)	6927.7(6)	62.5(7)
O3C	1987.6(12)	3713.9(16)	6105.9(6)	34.5(5)
O4C	1709.9(14)	3498.4(19)	6934.8(6)	49.5(6)
C1C	1514.6(19)	4472(3)	6765.8(8)	34.6(8)
C2C	1932.3(19)	4682(3)	6343.7(8)	32.8(8)
C3C	1423(2)	3279(3)	7353.2(9)	75.2(13)
C4C	1180(18)	3297(3)	5929.7(8)	35.1(8)
C5C	701.5(19)	4171(3)	5649.8(9)	39.8(8)
C6C	666(19)	5191(3)	5921.4(9)	44.8(8)
C11C	2829(2)	5063(2)	6490.6(8)	32.6(7)
C12C	3507.1(19)	4349(3)	6493.9(9)	37.6(8)
C13C	4309(2)	4698(3)	6639.8(10)	47.9(9)
C14C	4456(2)	5752(3)	6789.8(10)	57.5(10)
C15C	3792(2)	6458(3)	6785.3(10)	57(10)
C16C	2964(2)	6133(3)	6634.9(9)	45.2(8)
C21C	1053.8(18)	4309(3)	5216.2(9)	37.3(8)
C22C	1466.5(19)	5256(3)	5097.4(9)	43.3(9)
C23C	1786(2)	5370(3)	4704.6(10)	51.4(10)
C24C	1702(2)	4506(3)	4420.4(10)	52(10)
C25C	1309(2)	3552(3)	4522.7(9)	51.4(10)
C26C	986.9(19)	3467(3)	4916.8(9)	45.5(9)

O1D	1345.8(13)	10414.8(17)	6158.5(6)	38.2(5)
O2D	950.8(15)	9752(2)	6956.2(7)	75.5(8)
O3D	1981.4(12)	8701.4(16)	6113(6)	35.3(5)
O4D	1745.4(14)	8268.8(18)	6929.7(6)	48.1(6)
C1D	1439.4(19)	9226(3)	6783.6(9)	35.6(8)
C2D	1841.2(19)	9598(3)	6376.5(9)	35.6(8)
C3D	1460(2)	7852(3)	7324.1(9)	68.2(11)
C4D	1213.7(19)	8200(3)	5927.4(9)	37.9(8)
C5D	678.5(19)	9042(3)	5659.9(9)	42.2(8)
C6D	547.5(19)	10012(3)	5949.1(9)	45.7(9)
C11D	2688(2)	10104(3)	6536.9(9)	38.1(8)
C12D	3437(2)	9548(3)	6503.9(10)	51.5(10)
C13D	4198(2)	10019(4)	6660.5(11)	75.4(14)
C14D	4224(3)	11030(4)	6859.2(12)	85.1(16)
C15D	3479(3)	11575(3)	6893.7(12)	89.1(15)
C16D	2705(2)	11130(3)	6727.3(10)	60.6(10)
C21D	1036.3(18)	9290(3)	5234.5(9)	38.1(8)
C22D	1438.2(19)	10267(3)	5156(10)	45.7(9)
C23D	1778(2)	10471(3)	4771(10)	47.8(9)
C24D	1729(2)	9661(3)	4462.8(9)	45(9)
C25D	1346(2)	8670(3)	4530.4(9)	45.5(9)
C26D	1003.4(19)	8502(3)	4913.8(9)	43.4(9)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 07srv164. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka×b×U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1A	37.1(12)	39.6(13)	33.6(11)	-1.2(9)	-1(9)	-8.4(9)
O2A	65.6(15)	78.9(17)	44.5(12)	4(11)	22.4(12)	-26.8(13)
O3A	27.8(12)	36.6(14)	30.1(10)	6(10)	1.6(9)	-5.7(10)
O4A	67.1(16)	51.6(15)	30.9(11)	-9.9(11)	14.6(11)	0.1(12)
C1A	31.6(18)	47(2)	37.9(17)	0.1(15)	0.7(15)	0.8(15)
C2A	34.1(18)	27.2(17)	25.4(15)	0.5(13)	6(14)	-8.4(14)
C3A	71(3)	96(3)	36.2(18)	-24.6(18)	8(18)	13(2)
C4A	32.2(19)	45(2)	40.5(18)	3.6(16)	1.3(15)	6.5(15)
C5A	29.8(18)	50(2)	28.3(15)	4.5(15)	2.3(14)	-1.3(16)
C6A	30.2(18)	55(2)	29.5(15)	2.3(15)	3.3(14)	-8.8(15)
C11A	35.2(18)	36.4(19)	23.3(14)	-2.4(13)	5.2(13)	-0.2(14)
C12A	35.3(19)	47.7(19)	32.7(16)	-3.5(14)	2.8(15)	-2.1(15)
C13A	38(2)	66(2)	53(2)	-10.4(17)	4.9(16)	-2.1(17)
C14A	40.4(19)	75(3)	48(2)	-14(18)	-6.6(16)	17.1(18)
C15A	69(3)	44(2)	52(2)	-6.3(16)	-5.5(19)	18.3(19)
C16A	44.5(19)	38.4(18)	43.8(17)	1.1(14)	1(15)	-0.7(14)
C21A	30.5(19)	45(2)	26.9(15)	7.5(15)	0.7(14)	-9.6(15)
C22A	50(2)	40(2)	29.8(16)	-0.2(15)	6.7(16)	-1.2(17)
C23A	45(2)	55(2)	41.7(18)	-9.6(17)	3.3(17)	0.6(18)
C24A	42(2)	79(3)	30.2(17)	3.9(18)	6(16)	-9(2)

C25A	44(2)	65(3)	33.2(18)	16.9(18)	-3.3(16)	-8(2)
C26A	43(2)	50(2)	29.6(16)	5.9(16)	6.3(15)	-7.1(17)
O1B	47.1(14)	42.2(13)	39.6(12)	3.7(10)	-9.7(10)	-14.3(10)
O2B	78.3(18)	101(2)	45.9(13)	-4.8(13)	26.9(13)	-44.9(15)
O3B	29.5(12)	37.5(14)	29.8(10)	6.8(10)	1.5(9)	-6.6(10)
O4B	69.7(16)	48.3(14)	31.7(11)	-6.5(10)	16(11)	-5.1(12)
C1B	39(2)	51(2)	36.8(17)	5.8(16)	-2(15)	-8.1(16)
C2B	36.6(19)	27.7(17)	29.4(15)	1.2(13)	0(14)	-13(14)
C3B	81(3)	88(3)	31.1(17)	-10.1(17)	10.1(18)	18(2)
C4B	37(2)	45(2)	39.7(17)	6.1(16)	4.1(16)	5(16)
C5B	32.4(19)	52(2)	29.4(16)	6.7(16)	-0.1(14)	-1.2(16)
C6B	39(2)	64(2)	34.4(16)	7.2(16)	-1.8(15)	-18.5(16)
C11B	45(2)	37(2)	32.9(16)	-5.2(15)	-2.1(15)	-3(15)
C12B	41(2)	62(2)	33.3(17)	-6.4(15)	0(16)	-2.8(18)
C13B	43(2)	110(4)	50(2)	-9(2)	3(18)	14(2)
C14B	65(3)	104(4)	70(3)	-36(3)	-22(2)	45(3)
C15B	114(3)	46(2)	69(3)	-9.6(19)	-38(3)	25(2)
C16B	80(3)	39(2)	58(2)	1.3(17)	-21.1(19)	0.3(18)
C21B	33(2)	48(2)	24(15)	6.1(15)	-2.5(14)	-10.4(16)
C22B	52(2)	38(2)	35.3(17)	-2.3(15)	5.6(16)	-3.6(17)
C23B	47(2)	50(2)	48(2)	-14.2(18)	2.6(18)	-4.7(17)
C24B	42(2)	81(3)	34.3(18)	-7(19)	6.2(17)	-11(2)

C25B	45(2)	69(3)	32.6(18)	12.8(18)	-3.1(16)	-7(2)
C26B	43(2)	51(2)	31(16)	2.6(16)	5.3(16)	-5(17)
O1C	39.7(12)	34.1(12)	34.1(11)	2.6(9)	-4(9)	6.8(9)
O2C	62.2(15)	79.4(17)	49.3(13)	-3.1(12)	21.3(12)	22.7(13)
O3C	41.3(13)	29.8(13)	32.9(11)	0.1(10)	6.8(10)	-1(11)
O4C	61.1(16)	54.3(15)	34(11)	9.8(11)	9(11)	1.1(12)
C1C	31.6(18)	46(2)	25.4(15)	-3.4(14)	0.9(13)	3.2(14)
C2C	36.7(19)	31.3(19)	30.2(16)	0.1(14)	2.8(14)	3.2(15)
C3C	80(3)	107(3)	39.3(19)	28(2)	12.6(19)	-15(2)
C4C	44(2)	36(2)	26(15)	-2(14)	7.3(15)	-9.3(15)
C5C	26.2(18)	54(2)	39.3(17)	-0.2(17)	3.2(15)	-7.8(16)
C6C	36(2)	56(2)	40.4(17)	2.1(16)	-3.3(15)	10(16)
C11C	39.3(19)	35.3(19)	22.8(14)	6.1(13)	2.2(13)	0.8(14)
C12C	34.6(19)	42.8(18)	36.2(16)	-1.8(14)	7.6(15)	0.6(14)
C13C	37(2)	65(2)	43(17)	3.6(16)	7.3(15)	3.6(16)
C14C	45(2)	70(3)	56(2)	20.1(19)	-2.7(17)	-13.5(19)
C15C	71(3)	44(2)	52(2)	0.6(16)	-10.2(19)	-19.3(19)
C16C	59(2)	36(18)	38.8(16)	4.6(14)	-3.2(15)	0.7(15)
C21C	22.4(18)	50(2)	37.6(17)	11.2(17)	-4.5(14)	-7.4(16)
C22C	33(2)	52(2)	44.3(19)	-2.4(17)	-0.1(16)	-0.5(16)
C23C	45(2)	65(3)	46.4(19)	14.4(19)	13.3(18)	-3.4(19)
C24C	50(2)	72(3)	35.2(18)	19.9(19)	8.8(17)	7(2)
C25C	58(2)	65(3)	31.1(18)	-1.1(18)	3.7(17)	-2(2)
C26C	38(2)	54(2)	41(18)	0.4(18)	-10.1(16)	-20.5(17)

O1D	46.2(13)	35.6(12)	30.9(10)	-0.9(9)	-3.3(10)	11.2(10)
O2D	81.4(18)	101(2)	47.8(13)	7.5(13)	24.7(13)	46.2(15)
O3D	44(14)	30.7(13)	32.2(11)	1.4(10)	8.3(10)	1.4(11)
O4D	66.7(16)	42.7(13)	36.4(11)	8(10)	12.3(11)	4.3(11)
C1D	37.9(19)	41.6(19)	27.3(15)	-4.8(14)	3.6(14)	4(15)
C2D	37.5(19)	35.9(19)	33.2(16)	0(15)	2.6(15)	4.5(15)
C3D	91(3)	77(3)	38.8(18)	18.6(17)	16(19)	-14(2)
C4D	51(2)	37(2)	27(16)	-2.4(14)	10.5(16)	-10.6(16)
C5D	30.3(19)	58(2)	38.2(17)	0.7(17)	2.1(15)	-9.4(17)
C6D	36(2)	61(2)	40.3(17)	3(17)	3.2(15)	9.5(16)
C11D	48(2)	37(2)	26.9(15)	11.1(14)	-3.9(14)	-4.2(15)
C12D	41(2)	77(3)	38.1(18)	1.9(17)	8.8(17)	-2(19)
C13D	40(2)	141(4)	44(2)	14(2)	2.9(18)	-25(2)
C14D	84(3)	112(4)	53(2)	29(3)	-15(2)	-54(3)
C15D	128(4)	51(2)	77(3)	17(2)	-42(3)	-41(3)
C16D	70(2)	39(2)	65(2)	2.6(17)	-22.6(19)	-2.2(17)
C21D	24(18)	51(2)	37.2(17)	9.3(17)	-5.5(15)	-5.7(16)
C22D	39(2)	49(2)	47.5(19)	-5.2(17)	-3(17)	-0.5(17)
C23D	47(2)	49(2)	48(2)	5.6(18)	3.9(18)	-7.7(17)
C24D	41(2)	60(2)	34.2(17)	12.3(17)	4.2(16)	0.1(18)
C25D	46(2)	58(2)	32.7(17)	1.6(17)	2.4(16)	-2.3(19)
C26D	37(2)	49(2)	41.1(18)	-1.2(17)	-9.9(16)	-17.5(17)

Table 4 Bond Lengths for 07srv164.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1A	C2A	1.410(3)	O1C	C2C	1.388(3)
O1A	C6A	1.443(3)	O1C	C6C	1.455(4)
O2A	C1A	1.190(3)	O2C	C1C	1.195(3)
O3A	C2A	1.404(3)	O3C	C2C	1.400(3)
O3A	C4A	1.429(3)	O3C	C4C	1.435(3)
O4A	C1A	1.323(4)	O4C	C1C	1.321(3)
O4A	C3A	1.452(3)	O4C	C3C	1.454(3)
C1A	C2A	1.558(4)	C1C	C2C	1.561(4)
C2A	C11A	1.519(4)	C2C	C11C	1.524(4)
C4A	C5A	1.530(4)	C4C	C5C	1.525(4)
C5A	C6A	1.531(4)	C5C	C6C	1.508(4)
C5A	C21A	1.506(4)	C5C	C21C	1.530(4)
C11A	C12A	1.387(4)	C11C	C12C	1.388(4)
C11A	C16A	1.368(4)	C11C	C16C	1.388(4)
C12A	C13A	1.379(4)	C12C	C13C	1.376(4)
C13A	C14A	1.353(5)	C13C	C14C	1.377(5)
C14A	C15A	1.379(4)	C14C	C15C	1.363(5)
C15A	C16A	1.382(4)	C15C	C16C	1.407(4)
C21A	C22A	1.383(4)	C21C	C22C	1.399(4)
C21A	C26A	1.397(4)	C21C	C26C	1.382(4)
C22A	C23A	1.388(4)	C22C	C23C	1.385(4)
C23A	C24A	1.389(5)	C23C	C24C	1.372(5)
C24A	C25A	1.374(5)	C24C	C25C	1.375(5)

C25A	C26A	1.382(4)	C25C	C26C	1.388(4)
O1B	C2B	1.410(3)	O1D	C2D	1.398(3)
O1B	C6B	1.432(4)	O1D	C6D	1.449(4)
O2B	C1B	1.188(3)	O2D	C1D	1.184(3)
O3B	C2B	1.405(3)	O3D	C2D	1.399(3)
O3B	C4B	1.432(3)	O3D	C4D	1.431(3)
O4B	C1B	1.315(4)	O4D	C1D	1.325(3)
O4B	C3B	1.450(3)	O4D	C3D	1.450(3)
C1B	C2B	1.559(4)	C1D	C2D	1.552(4)
C2B	C11B	1.512(4)	C2D	C11D	1.518(4)
C4B	C5B	1.527(4)	C4D	C5D	1.521(4)
C5B	C6B	1.525(4)	C5D	C6D	1.515(4)
C5B	C21B	1.508(4)	C5D	C21D	1.532(4)
C11B	C12B	1.378(4)	C11D	C12D	1.389(4)
C11B	C16B	1.368(4)	C11D	C16D	1.382(4)
C12B	C13B	1.382(5)	C12D	C13D	1.380(5)
C13B	C14B	1.356(5)	C13D	C14D	1.377(6)
C14B	C15B	1.377(5)	C14D	C15D	1.376(6)
C15B	C16B	1.372(5)	C15D	C16D	1.394(5)
C21B	C22B	1.386(4)	C21D	C22D	1.386(4)
C21B	C26B	1.391(4)	C21D	C26D	1.382(4)
C22B	C23B	1.386(4)	C22D	C23D	1.394(4)
C23B	C24B	1.386(5)	C23D	C24D	1.373(4)
C24B	C25B	1.373(5)	C24D	C25D	1.380(4)
C25B	C26B	1.388(4)	C25D	C26D	1.384(4)

Table 5 Bond Angles for 07srv164.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1A	C2A	C1A	109.5(2)	O1C	C2C	O3C	113.2(2)
O1A	C2A	C11A	107.6(2)	O1C	C2C	C1C	109.6(2)
O1A	C6A	C5A	111.6(2)	O1C	C2C	C11C	108.8(2)
O2A	C1A	O4A	124.5(3)	O1C	C6C	C5C	111.0(2)
O2A	C1A	C2A	124.2(3)	O2C	C1C	O4C	124.9(3)
O3A	C2A	O1A	111.9(2)	O2C	C1C	C2C	122.6(3)
O3A	C2A	C1A	112.6(2)	O3C	C2C	C1C	111.5(2)
O3A	C2A	C11A	108.2(2)	O3C	C2C	C11C	107.6(2)
O3A	C4A	C5A	111.5(3)	O3C	C4C	C5C	110.0(2)
O4A	C1A	C2A	111.1(3)	O4C	C1C	C2C	112.2(3)
C1A	O4A	C3A	115.6(3)	C1C	O4C	C3C	116.0(3)
C2A	O1A	C6A	113.4(2)	C2C	O1C	C6C	112.6(2)
C2A	O3A	C4A	113.6(2)	C2C	O3C	C4C	113.1(2)
C4A	C5A	C6A	106.2(2)	C4C	C5C	C21C	111.8(2)
C11A	C2A	C1A	106.8(2)	C6C	C5C	C4C	107.6(2)
C11A	C16A	C15A	120.7(3)	C6C	C5C	C21C	116.5(3)
C12A	C11A	C2A	119.6(3)	C11C	C2C	C1C	105.8(2)
C13A	C12A	C11A	119.9(3)	C11C	C16C	C15C	118.5(3)
C13A	C14A	C15A	119.6(3)	C12C	C11C	C2C	121.1(3)
C14A	C13A	C12A	121.0(3)	C12C	C13C	C14C	121.0(3)

C14A	C15A	C16A	119.9(3)	C13C	C12C	C11C	120.3(3)
C16A	C11A	C2A	121.3(3)	C14C	C15C	C16C	121.7(3)
C16A	C11A	C12A	118.9(3)	C15C	C14C	C13C	118.9(3)
C21A	C5A	C4A	112.3(2)	C16C	C11C	C2C	119.3(3)
C21A	C5A	C6A	114.2(3)	C16C	C11C	C12C	119.6(3)
C21A	C22A	C23A	119.8(3)	C21C	C26C	C25C	122.2(3)
C22A	C21A	C5A	123.3(3)	C22C	C21C	C5C	123.7(3)
C22A	C21A	C26A	119.0(3)	C23C	C22C	C21C	123.2(3)
C24A	C23A	C22A	121.4(3)	C23C	C24C	C25C	120.8(3)
C24A	C25A	C26A	121.2(3)	C24C	C23C	C22C	118.4(3)
C25A	C24A	C23A	118.4(3)	C24C	C25C	C26C	119.5(3)
C25A	C26A	C21A	120.3(3)	C26C	C21C	C5C	120.4(3)
C26A	C21A	C5A	117.7(3)	C26C	C21C	C22C	115.8(3)
O1B	C2B	C1B	110.5(2)	O1D	C2D	O3D	112.9(2)
O1B	C2B	C11B	107.1(3)	O1D	C2D	C1D	109.9(2)
O1B	C6B	C5B	112.5(2)	O1D	C2D	C11D	107.7(3)
O2B	C1B	O4B	124.5(3)	O1D	C6D	C5D	111.0(2)
O2B	C1B	C2B	124.6(3)	O2D	C1D	O4D	123.7(3)
O3B	C2B	O1B	111.3(2)	O2D	C1D	C2D	124.6(3)
O3B	C2B	C1B	111.1(2)	O3D	C2D	C1D	111.1(2)
O3B	C2B	C11B	109.1(2)	O3D	C2D	C11D	108.3(2)
O3B	C4B	C5B	111.3(3)	O3D	C4D	C5D	109.6(2)
O4B	C1B	C2B	110.7(3)	O4D	C1D	C2D	111.5(3)
C1B	O4B	C3B	116.7(3)	C1D	O4D	C3D	117.4(3)

C2B	O1B	C6B	114.7(2)	C2D	O1D	C6D	113.4(2)
C2B	O3B	C4B	112.7(2)	C2D	O3D	C4D	112.5(2)
C4B	C5B	C6B	106.8(2)	C4D	C5D	C21D	111.5(3)
C11B	C2B	C1B	107.6(2)	C6D	C5D	C4D	107.9(2)
C11B	C12B	C13B	120.0(3)	C6D	C5D	C21D	116.8(3)
C11B	C16B	C15B	121.1(4)	C11D	C2D	C1D	106.5(2)
C12B	C11B	C2B	120.8(3)	C11D	C16D	C15D	119.0(4)
C13B	C14B	C15B	120.2(4)	C12D	C11D	C2D	121.3(3)
C14B	C13B	C12B	120.3(4)	C13D	C12D	C11D	120.1(4)
C16B	C11B	C2B	120.1(3)	C14D	C13D	C12D	120.7(4)
C16B	C11B	C12B	119.0(3)	C14D	C15D	C16D	121.3(4)
C16B	C15B	C14B	119.4(4)	C15D	C14D	C13D	119.0(4)
C21B	C5B	C4B	111.0(2)	C16D	C11D	C2D	118.8(3)
C21B	C5B	C6B	115.4(3)	C16D	C11D	C12D	119.9(3)
C21B	C22B	C23B	119.2(3)	C21D	C22D	C23D	122.5(3)
C22B	C21B	C5B	123.7(3)	C21D	C26D	C25D	122.4(3)
C22B	C21B	C26B	119.0(3)	C22D	C21D	C5D	123.2(3)
C24B	C23B	C22B	122.1(3)	C23D	C24D	C25D	120.8(3)
C24B	C25B	C26B	120.8(3)	C24D	C23D	C22D	118.5(3)
C25B	C24B	C23B	118.2(3)	C24D	C25D	C26D	119.1(3)
C25B	C26B	C21B	120.7(3)	C26D	C21D	C5D	120.1(3)
C26B	C21B	C5B	117.2(3)	C26D	C21D	C22D	116.7(3)

Table 6 Torsion Angles for 07srv164.

A	B	C	D	Angle/°
O1A	C2A	C11A	C12A	-141.7(2)
O1A	C2A	C11A	C16A	41.7(3)
O2A	C1A	C2A	O1A	-24.6(4)
O2A	C1A	C2A	O3A	-149.8(3)
O2A	C1A	C2A	C11A	91.6(4)
O3A	C2A	C11A	C12A	-20.6(3)
O3A	C2A	C11A	C16A	162.7(2)
O3A	C4A	C5A	C6A	-53.6(3)
O3A	C4A	C5A	C21A	71.9(3)
O4A	C1A	C2A	O1A	159.3(2)
O4A	C1A	C2A	O3A	34.1(4)
O4A	C1A	C2A	C11A	-84.5(3)
C1A	C2A	C11A	C12A	100.8(3)
C1A	C2A	C11A	C16A	-75.9(3)
C2A	O1A	C6A	C5A	-55.5(3)
C2A	O3A	C4A	C5A	57.2(3)
C2A	C11A	C12A	C13A	-176.3(3)
C2A	C11A	C16A	C15A	177.5(3)
C3A	O4A	C1A	O2A	-1.4(5)
C3A	O4A	C1A	C2A	174.7(2)
C4A	O3A	C2A	O1A	-56.2(3)
C4A	O3A	C2A	C1A	67.7(3)

C4A	O3A	C2A	C11A	-174.5(2)
C4A	C5A	C6A	O1A	52.8(3)
C4A	C5A	C21A	C22A	-111.3(3)
C4A	C5A	C21A	C26A	67.4(4)
C5A	C21A	C22A	C23A	179.2(3)
C5A	C21A	C26A	C25A	-179.8(3)
C6A	O1A	C2A	O3A	55.2(3)
C6A	O1A	C2A	C1A	-70.4(3)
C6A	O1A	C2A	C11A	173.9(2)
C6A	C5A	C21A	C22A	9.7(4)
C6A	C5A	C21A	C26A	-171.7(3)
C11A	C12A	C13A	C14A	-1.7(5)
C12A	C11A	C16A	C15A	0.9(4)
C12A	C13A	C14A	C15A	1.7(5)
C13A	C14A	C15A	C16A	-0.4(5)
C14A	C15A	C16A	C11A	-0.9(5)
C16A	C11A	C12A	C13A	0.4(4)
C21A	C5A	C6A	O1A	-71.5(3)
C21A	C22A	C23A	C24A	0.1(5)
C22A	C21A	C26A	C25A	-1.1(5)
C22A	C23A	C24A	C25A	-0.2(5)
C23A	C24A	C25A	C26A	-0.3(5)
C24A	C25A	C26A	C21A	1.0(5)
C26A	C21A	C22A	C23A	0.6(5)

O1B	C2B	C11B	C12B	-136.2(3)
O1B	C2B	C11B	C16B	47.9(3)
O2B	C1B	C2B	O1B	-22.0(4)
O2B	C1B	C2B	O3B	-146.0(3)
O2B	C1B	C2B	C11B	94.6(4)
O3B	C2B	C11B	C12B	-15.6(4)
O3B	C2B	C11B	C16B	168.5(3)
O3B	C4B	C5B	C6B	-53.2(3)
O3B	C4B	C5B	C21B	73.4(3)
O4B	C1B	C2B	O1B	162.3(3)
O4B	C1B	C2B	O3B	38.2(4)
O4B	C1B	C2B	C11B	-81.1(3)
C1B	C2B	C11B	C12B	105.0(3)
C1B	C2B	C11B	C16B	-71.0(4)
C2B	O1B	C6B	C5B	-52.5(3)
C2B	O3B	C4B	C5B	59.1(3)
C2B	C11B	C12B	C13B	-176.6(3)
C2B	C11B	C16B	C15B	176.8(3)
C3B	O4B	C1B	O2B	0.9(5)
C3B	O4B	C1B	C2B	176.6(2)
C4B	O3B	C2B	O1B	-57.5(3)
C4B	O3B	C2B	C1B	66.1(3)
C4B	O3B	C2B	C11B	-175.5(2)
C4B	C5B	C6B	O1B	49.9(3)

C4B C5B C21B C22B -107.5(3)

C4B C5B C21B C26B 70.8(4)

C5B C21B C22B C23B 178.2(3)

C5B C21B C26B C25B -179.0(3)

C6B O1B C2B O3B 54.4(3)

C6B O1B C2B C1B -69.5(3)

C6B O1B C2B C11B 173.5(2)

C6B C5B C21B C22B 14.1(4)

C6B C5B C21B C26B -167.6(3)

C11B C12B C13B C14B -0.2(5)

C12B C11B C16B C15B 0.7(5)

C12B C13B C14B C15B 0.9(6)

C13B C14B C15B C16B -0.7(6)

C14B C15B C16B C11B -0.1(5)

C16B C11B C12B C13B -0.6(5)

C21B C5B C6B O1B -74.0(3)

C21B C22B C23B C24B 0.3(5)

C22B C21B C26B C25B -0.6(5)

C22B C23B C24B C25B 0.0(5)

C23B C24B C25B C26B -0.6(5)

C24B C25B C26B C21B 0.9(5)

C26B C21B C22B C23B 0.0(5)

O1C C2C C11C C12C -141.3(3)

O1C C2C C11C C16C 40.6(3)

O2C	C1C	C2C	O1C	-24.4(4)
O2C	C1C	C2C	O3C	-150.6(3)
O2C	C1C	C2C	C11C	92.7(4)
O3C	C2C	C11C	C12C	-18.3(3)
O3C	C2C	C11C	C16C	163.6(2)
O3C	C4C	C5C	C6C	-54.5(3)
O3C	C4C	C5C	C21C	74.6(3)
O4C	C1C	C2C	O1C	160.6(2)
O4C	C1C	C2C	O3C	34.4(4)
O4C	C1C	C2C	C11C	-82.3(3)
C1C	C2C	C11C	C12C	101.1(3)
C1C	C2C	C11C	C16C	-77.1(3)
C2C	O1C	C6C	C5C	-55.1(3)
C2C	O3C	C4C	C5C	56.6(3)
C2C	C11C	C12C	C13C	-178.0(3)
C2C	C11C	C16C	C15C	177.5(3)
C3C	O4C	C1C	O2C	-1.2(5)
C3C	O4C	C1C	C2C	173.6(2)
C4C	O3C	C2C	O1C	-56.8(3)
C4C	O3C	C2C	C1C	67.3(3)
C4C	O3C	C2C	C11C	-177.1(2)
C4C	C5C	C6C	O1C	53.9(3)
C4C	C5C	C21C	C22C	-112.9(3)
C4C	C5C	C21C	C26C	66.1(4)

C5C C21C C22C C23C 179.8(3)

C5C C21C C26C C25C -179.0(3)

C6C O1C C2C O3C 55.3(3)

C6C O1C C2C C1C -69.9(3)

C6C O1C C2C C11C 174.9(2)

C6C C5C C21C C22C 11.4(5)

C6C C5C C21C C26C -169.6(3)

C11C C12C C13C C14C 0.8(5)

C12C C11C C16C C15C -0.7(4)

C12C C13C C14C C15C -1.1(5)

C13C C14C C15C C16C 0.5(5)

C14C C15C C16C C11C 0.3(5)

C16C C11C C12C C13C 0.1(4)

C21C C5C C6C O1C -72.5(3)

C21C C22C C23C C24C -0.9(5)

C22C C21C C26C C25C 0.1(5)

C22C C23C C24C C25C 0.2(5)

C23C C24C C25C C26C 0.5(5)

C24C C25C C26C C21C -0.7(5)

C26C C21C C22C C23C 0.7(5)

O1D C2D C11D C12D -137.2(3)

O1D C2D C11D C16D 44.1(3)

O2D C1D C2D O1D -20.8(4)

O2D C1D C2D O3D -146.6(3)

O2D	C1D	C2D	C11D	95.6(4)
O3D	C2D	C11D	C12D	-14.8(4)
O3D	C2D	C11D	C16D	166.6(2)
O3D	C4D	C5D	C6D	-55.6(3)
O3D	C4D	C5D	C21D	73.9(3)
O4D	C1D	C2D	O1D	162.6(2)
O4D	C1D	C2D	O3D	36.8(4)
O4D	C1D	C2D	C11D	-81.0(3)
C1D	C2D	C11D	C12D	104.8(3)
C1D	C2D	C11D	C16D	-73.8(3)
C2D	O1D	C6D	C5D	-52.8(3)
C2D	O3D	C4D	C5D	58.8(3)
C2D	C11D	C12D	C13D	-178.7(3)
C2D	C11D	C16D	C15D	177.0(3)
C3D	O4D	C1D	O2D	-0.1(5)
C3D	O4D	C1D	C2D	176.6(3)
C4D	O3D	C2D	O1D	-57.8(3)
C4D	O3D	C2D	C1D	66.3(3)
C4D	O3D	C2D	C11D	-177.0(2)
C4D	C5D	C6D	O1D	52.7(3)
C4D	C5D	C21D	C22D	-107.4(4)
C4D	C5D	C21D	C26D	69.5(4)
C5D	C21D	C22D	C23D	178.5(3)
C5D	C21D	C26D	C25D	-177.5(3)

C6D	O1D	C2D	O3D	54.4(3)
C6D	O1D	C2D	C1D	-70.3(3)
C6D	O1D	C2D	C11D	174.0(2)
C6D	C5D	C21D	C22D	17.2(5)
C6D	C5D	C21D	C26D	-165.9(3)
C11D	C12D	C13D	C14D	1.5(5)
C12D	C11D	C16D	C15D	-1.7(5)
C12D	C13D	C14D	C15D	-1.0(6)
C13D	C14D	C15D	C16D	-0.8(6)
C14D	C15D	C16D	C11D	2.2(6)
C16D	C11D	C12D	C13D	-0.1(5)
C21D	C5D	C6D	O1D	-73.7(3)
C21D	C22D	C23D	C24D	-1.6(5)
C22D	C21D	C26D	C25D	-0.5(5)
C22D	C23D	C24D	C25D	0.6(5)
C23D	C24D	C25D	C26D	0.4(5)
C24D	C25D	C26D	C21D	-0.5(5)
C26D	C21D	C22D	C23D	1.5(5)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 07srv164.

Atom	***x***	***y***	***z***	**U(eq)**
H3A1	3273	6286	2442	117(8)
H3A2	3451	5008	2548	117(8)
H3A3	4192	5900	2664	117(8)
H4A1	4153	5598	3834	47
H4A2	3739	5131	4246	47
H5A	4911	6399	4427	43
H6A1	4604	8301	4261	46
H6A2	4687	7562	3840	46
H12A	1611	6119	3596	46
H13A	242	6696	3355	63
H14A	-19	8488	3140	67
H15A	1102	9730	3153	67
H16A	2481	9152	3379	51
H22A	3500	8398	4675	48
H23A	2948	8571	5334	57
H24A	3052	7125	5835	60
H25A	3703	5496	5662	58
H26A	4260	5306	5007	49
H3B1	3366	860	2437	137(9)
H3B2	3306	-363	2625	137(9)
H3B3	4174	327	2723	137(9)
H4B1	4093	424	3849	48

H4B2	3625	107	4264	48
H5B	4888	1188	4433	46
H6B1	4726	3140	4245	55
H6B2	4802	2317	3847	55
H12B	1535	1395	3641	55
H13B	265	2225	3364	82
H14B	275	3897	3017	99
H15B	1554	4772	2945	96
H16B	2817	3969	3235	74
H22B	3533	3346	4641	50
H23B	2974	3596	5295	58
H24B	3052	2208	5818	63
H25B	3701	552	5678	59
H26B	4268	282	5029	50
H3C1	1606	3909	7539	165(10)
H3C2	1667	2602	7489	165(10)
H3C3	798	3230	7317	165(10)
H4C1	839	3105	6168	42
H4C2	1253	2621	5759	42
H5C	96	3916	5585	48
H6C1	412	5796	5735	54
H6C2	306	5079	6159	54
H12C	3401	3610	6400	45
H13C	4766	4182	6651	57
H14C	5023	5976	6889	69

H15C	3902	7197	6878	68
H16C	2506	6644	6633	54
H22C	1523	5872	5288	52
H23C	2052	6030	4624	62
H24C	1918	4550	4147	62
H25C	1255	2938	4331	62
H26C	720	2805	4995	55
H3D1	1552	8403	7556	164(10)
H3D2	1784	7183	7411	164(10)
H3D3	850	7673	7271	164(10)
H4D1	900	7888	6158	45
H4D2	1369	7586	5742	45
H5D	116	8670	5577	51
H6D1	242	10603	5774	55
H6D2	178	9766	6168	55
H12D	3463	8853	6364	62
H13D	4735	9694	6626	90
H14D	4739	11384	6975	102
H15D	3457	12261	7040	107
H16D	2170	11471	6755	73
H22D	1458	10824	5372	55
H23D	2040	11162	4729	57
H24D	1970	9802	4201	54
H25D	1324	8118	4312	55
H26D	745	7807	4954	52

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
  Durham Postgraduate Symposium, University of Durham, England.

- **March 2009**: Oral Presentation by the author
  SCI Postgraduate Meeting, University of Durham, England.

- **June 2008**: Oral Presentation by the author
  Durham Postgraduate Symposium, University of Durham, England.

- **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
  C-H Activation: Present and Future, AstraZeneca, Charnwood, Loughborough, England.

- **December 2006**: Research Conference attended by author
  Modern Aspects of Stereochemistry, University of Sheffield, England.

APPENDIX E: Scientific Papers Published