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Stereocontrolled Synthesis
Of
Highly Functionalized
Heterocycles

John G. Mina

(Graduate School)

Thesis submitted for the qualification Master of Science

November 2005



11 OCT 2006

ABSTRACT

Stereocontrolled Synthesis of Highly Functionalized Heterocycles

John G. Mina

MSc., November 2005

Polysubstituted heterocycles appear in various natural compounds that have potential biological activity. Consequently, synthetic routes towards such compounds have become a major interest for organic chemists taking into consideration the importance of the stereochemical control during the course of synthesis.

This report presents a tandem C–H insertion – L. A. promoted acetal cleavage sequence for a stereocontrolled synthesis of 2,3,5-trisubstituted THF derivatives and 2,3,5,6-tetrasubstituted oxepane derivatives *via* the use of an intermediate bicyclic template.

This initial step involves ketalization of substituted 1,3-propanediols with methyl pyruvate to yield the 1,3-dioxane ring. Hydrolysis to the acid acetal and acylation of diazomethane using the mixed anhydride procedure yielded the diazocarbonyl precursor for the insertion reaction.

The decomposition of the diazocarbonyl compound was catalysed by $\text{Rh}_2(\text{OAc})_4$ to yield an acceptor metallocarbene which inserted regioselectively into the C–H bond α to the oxygen atom in the dioxane ring to form a five membered ring yielding the bicyclic ketone template in a moderate yield.

Reduction of the ketone was stereoselective and led to one epimer. Direct treatment of the resultant alcohol or the protected derivative with $\text{Et}_3\text{SiH/L.A.}$ led to the formation of the 2,3,5-trisubstituted THF derivative indicating that the diastereoselectivity was a function of the bulkiness of the alcohol protecting group.

Subsequent inversion of the 7-OH stereochemistry directed the acetal cleavage reaction towards the formation of the oxepane ring which proved the crucial role of the hydroxyl or the alkoxy group at C(7) as a controller of the regioselectivity of the acetal cleavage reaction.

DECLARATION

This work in this thesis was carried out in the Department of Chemistry at the University of Durham between January 2004 and October 2005. It has not been submitted for any other degree and is the author's own work, except where acknowledged by reference.

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Born 6th October 1977

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ACKNOWLEDGEMENT

To my parents,

All my teachers,

And my supervisors,

Prof. Judith A. K. Howard, FRS

&

Dr. Patrick G. Steel

Who taught me from A B to MSc.

Thanks for all CY001 colleagues, Aileen, Amel, Kathryn, Chris, Dave, Jonathan, Lisa, Lisa J., Marie, Pete, Tom and Victoria who always made the environment so joyful and encouraging.

Special thanks to my fiancée Aristeia for all the support she gave me.

ABBREVIATIONS

1D	Unidimensional
2D	Bidimensional
5R-MEPY	Methyl-2-pyrrolidone-5(R)-carboxylate
5S-MEPY	Methyl-2-pyrrolidone-5(S)-carboxylate
5S-MEOX	Methyl-2-oxazolidone-4(S)-carboxylate
Ac	Acetyl
acac	Acetylacetonate
aq.	Aqueous
Ar	Aromatic group
atm	Atmosphere (1 atm = 1.013×10^5 Pascal)
(b)	Broad (in IR spectroscopy)
b.p.	Boiling point
Bn	Benzyl
Bu	Butyl
BuLi	Butyllithium
c.a.	<i>circa</i> , about
conc.	Concentrated
Cosy	H^1-H^1 correlation spectroscopy
Δ	Heat
δ / ppm	Chemical shifts / parts per million
d	Doublet
DCM	Dichloromethane (CH_2Cl_2)
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
DIBAH	Diisobutylaluminium hydride
DMAP	4-(N,N-Dimethylamino)pyridine
DMF	N,N-dimethylformamide
DNA	Deoxyribonucleic acid
e.g.	For example
EDG	Electron donating group
eq.	Equivalents
Et	Ethyl
EWG	Electron withdrawing group
FGI	Functional group interconversion
g.	Gram
GC	Gas chromatography
GC / MS	Gas chromatography / Mass spectroscopy
h.	Hours
HMBC	Heteronuclear shift correlation <i>via</i> multiple bond connectivities
HSQC	Heteronuclear single quantum correlation
i.e.	<i>In extensor</i>
<i>i</i> Pr	Isopropyl
IR	Infrared
<i>J</i> / Hz	Coupling constant / Hertz
L.A.	Lewis acid
LDA	Lithium diisopropylamide

LiHMDS	Lithium bis(trimethylsilyl)amide
Ln	N Ligands
m	Multiplet
m.p.	Melting point
Me	Methyl
mg.	Milligram
min	Minutes
MLn	Metal-Ligands complex
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
nOesy	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
Ph	Phenyl
R	Alkyl group
R.T / r.t	Room temperature
s	Singlet
SM	Starting material
S _N 1	Unimolecular nucleophilic substitution
S _N 2	Bimolecular nucleophilic substitution
t	Triplet
<i>t</i> BDMS	<i>tert</i> -Butyldimethylsilyl
<i>t</i> Bu	<i>tert</i> -Butyl
Tf	Triflate (trifluoromethanesulfonate)
Tfa	Trifluoroacetate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl (<i>p</i> -toluenesulfonyl)

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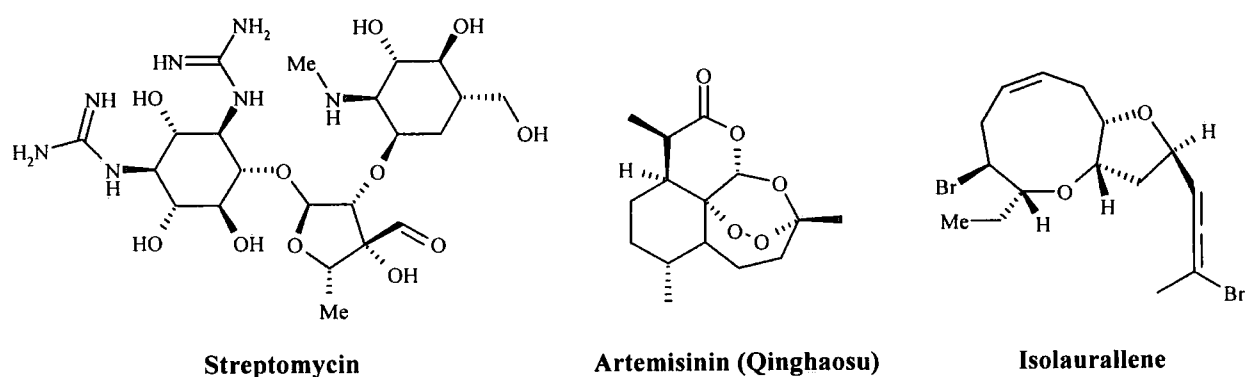
CHAPTER I

INTRODUCTION

1 CHAPTER (I): INTRODUCTION

1.1 General Introduction

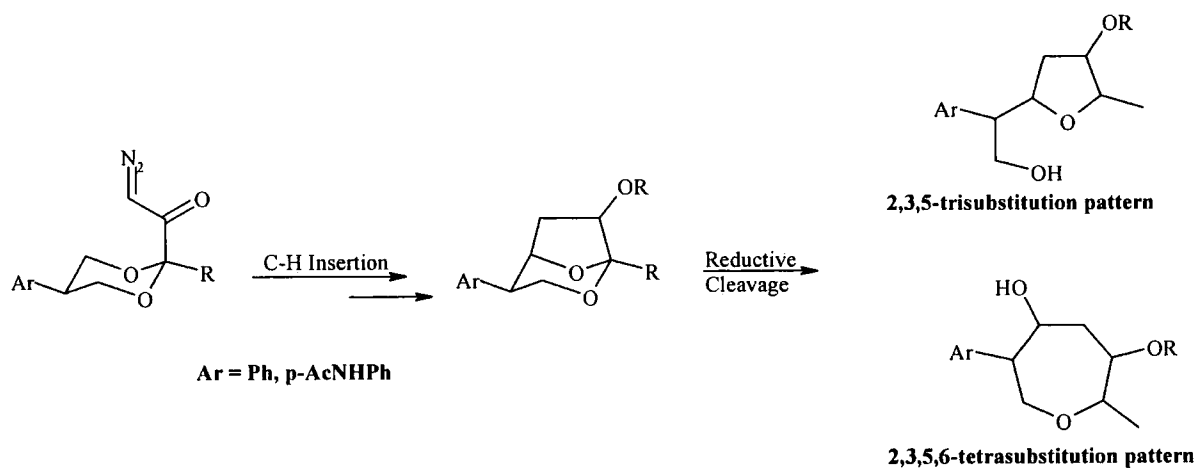
An extensive number of naturally bioactive compounds, market drugs and endogenously created substances contain one or more non-aromatic heterocyclic core structures which strongly influence their biological activity. As a result, the development of new efficient methods for the preparation of such heterocycles with control of stereochemistry and incorporation of a range of substituents and ring sizes represents a major goal for organic synthesis (*Scheme 1*).



***Scheme 1* – Examples of naturally occurring heterocyclic compounds**

This project addresses this topic through the exploration of a sequence deploying Rh(II)-mediated C–H insertion reactions to generate a bicyclic acetal, followed by Lewis-acid-promoted ring cleavage to give the desired heterocycle. More specifically, the work focuses on the use of *O,O*-bicyclic acetals mainly in the formation of 2,3,5-trisubstituted THF derivatives and explores the possibility of the formation of 2,3,5,6-tetrasubstituted oxepane derivatives, investigating the effect of substituents in the bicyclic acetal upon the C–H insertion reaction and acetal cleavage step (*Scheme 2*).





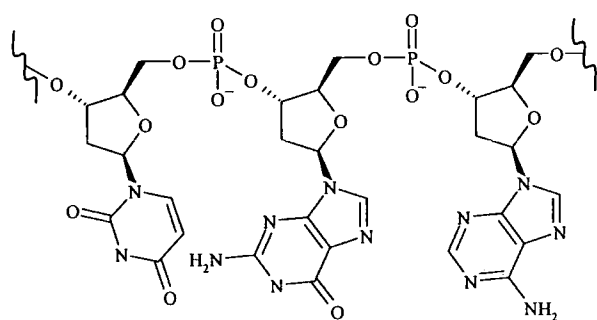
Scheme 2 – Outline of the project strategy

This chapter includes a brief description of some of the contemporary available syntheses of THF derivatives and the background to the synthetic methodology adopted. Chapter II will discuss the results obtained and their analysis. Chapter III will summarise the conclusions and shed light on the future work, whilst fully detailed reaction protocols will be discussed in Chapter IV.

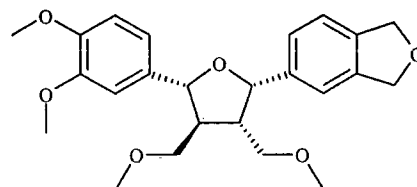
1.2 Tetrahydrofurans

1.2.1 Introduction

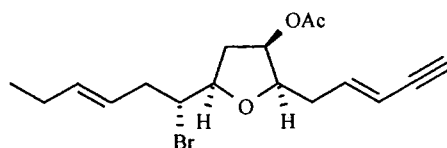
THF derivatives are abundant in nature and constitute an integral part of the chemical structure of various compounds ranging from the sugar-derived backbone of the DNA strands, pheromones, polyether antibiotics, lignans and other natural compounds of biological interest (*Scheme 3*) and consequently a large number of synthetic routes have been developed for their preparation.



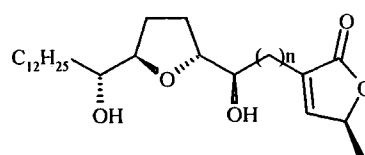
(A) Short chain segment of a single-stranded backbone of DNA.



(B) (-)-Virgatusin, Inhibitor of endogenous DNA polymerase of hepatitis B virus.



(+)-*trans*-kumausyne

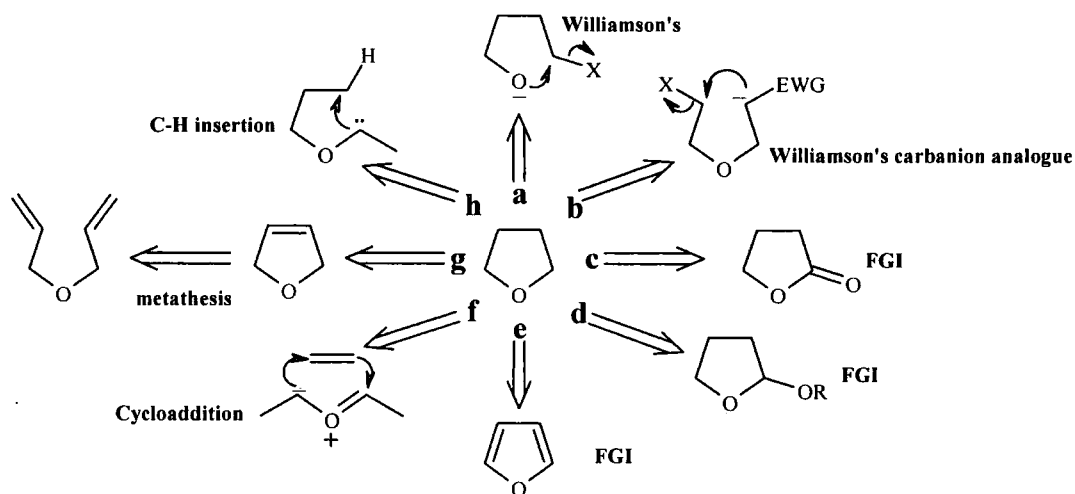


Reticulatacin $n = 14$, Solamine $n = 12$

Scheme 3 – Examples of natural occurring THF derivatives

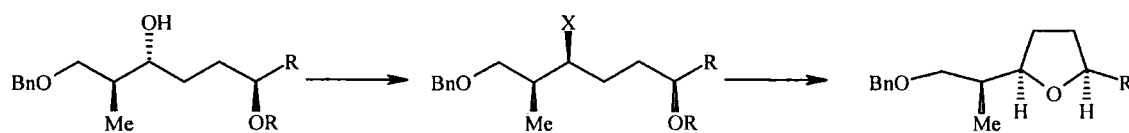
1.2.2 Synthesis

From a retrosynthetic point of view, prominent synthetic methods for THF derivatives can be grouped into three strategies (*Scheme 4*).



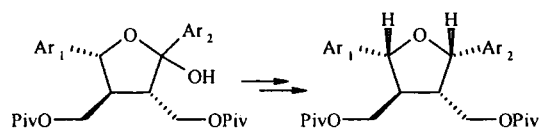
Scheme 4 – Various synthetic routes for THF derivatives

The first strategy (*groups a*) involves C–O bond formation through intramolecular ring closure which mostly occurs *via* an S_N2 -type reaction, e.g. synthesis of 2,5-disubstituted and 2,3,5-trisubstituted THF derivatives reported by Lindsay *et al.*¹ (Scheme 5).



Scheme 5 – THF synthesis *via* C–O bond formation

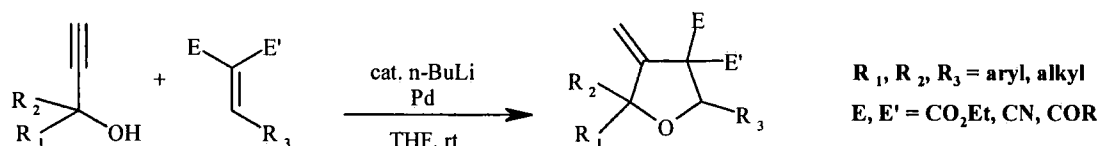
The second one (*groups c,d,e*) involves FGI of a pre-existing ring precursor, e.g. full synthesis of (–) and (+)-virgatusin reported by Yamauchi *et al.*² (Scheme 6).



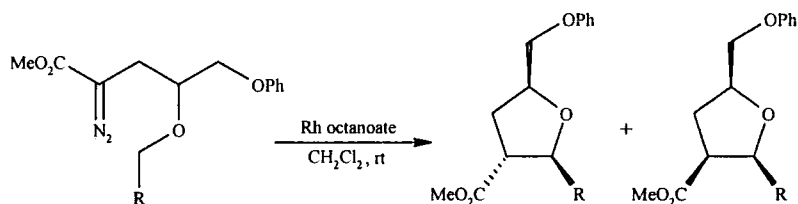
Scheme 6 – THF synthesis *via* FGI

The last strategy (*groups b,f,g,h*) involves C–C bond formation *via* S_N reactions, e.g. the palladium-mediated reaction of propargylic alcohols with activated olefins that was reported by

Balme *et al.*³ in 1997 and later modified in 2002⁴ (Scheme 7), *via* cycloaddition, *via* ring metathesis and *via* C–H insertion reactions, e.g. the reported procedure by Taber *et al.*⁵ deploying a Rh(II)-mediated C–H insertion reaction in the synthesis 2,3,5-trisubstituted THF derivatives (Scheme 8). The latter involves the use of metallocarbenes and will be discussed in detail as it represents a cornerstone of this project.



Scheme 7 – THF synthesis *via* C–C bond formation

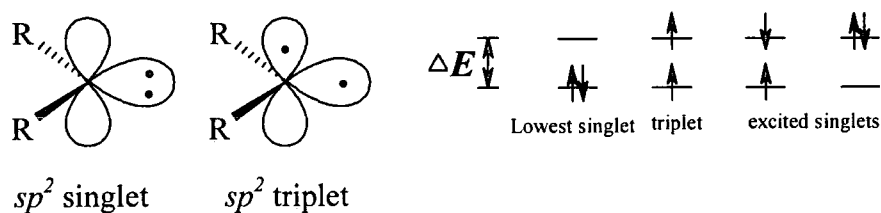


Scheme 8 – THF synthesis *via* C–H insertion reaction

1.3 Carbenes

1.3.1 Introduction

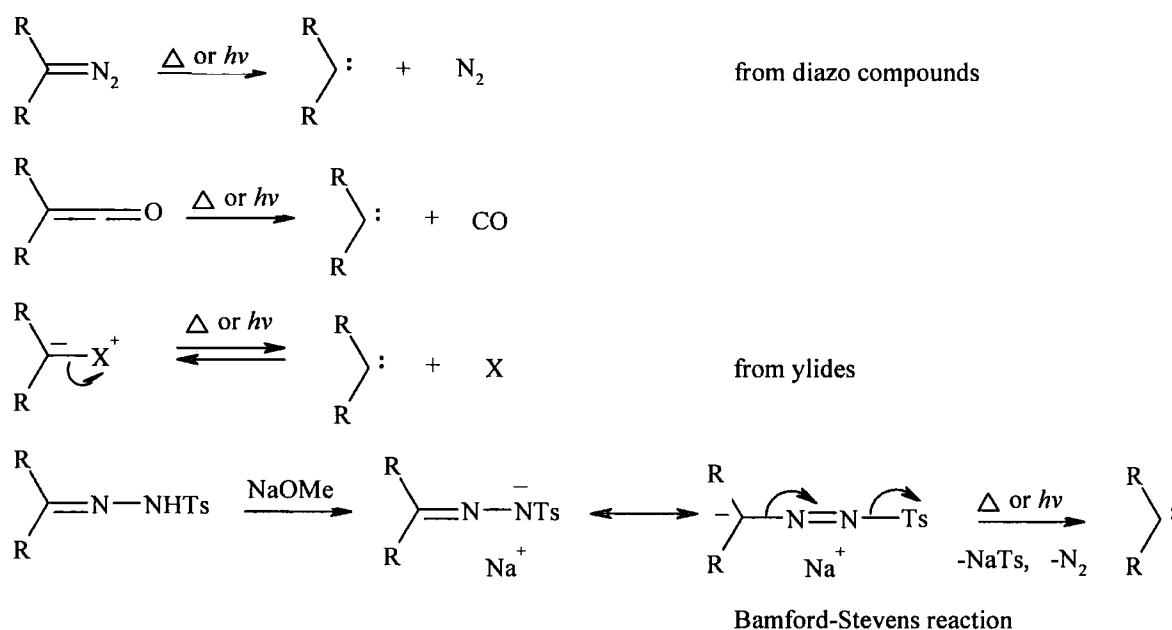
Carbenes are reactive intermediates which have been proven to be useful synthetic tools in modern chemistry. The simplest carbene is $\text{H}_2\text{C}:$, called methylene with divalent carbon having two non-bonded electrons⁶. Carbenes are in either sp^2 singlet or sp^2 triplet states based on the gap between energy levels according to the relative stabilization by substituents (*Scheme 8*).



Scheme 8 – Electronic configuration of carbene

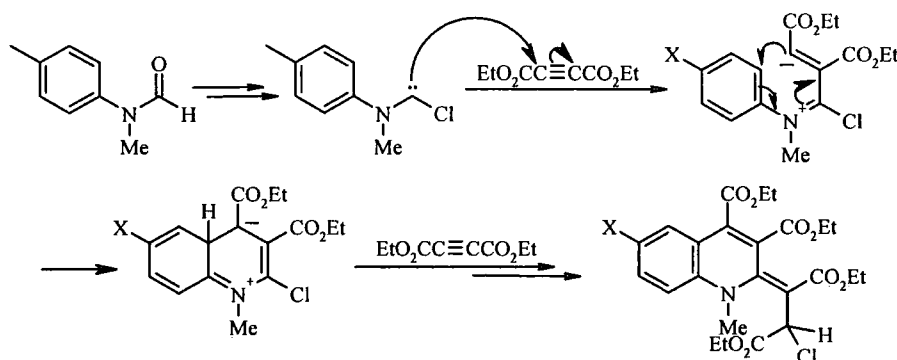
1.3.2 Generation & reactivity

There are numerous methods for the generation of carbenes. The majority of these involve the formation of the carbene together with a highly thermodynamically stable by-product to drive the reaction to completion. Examples of these processes include photolysis and thermolysis of diazo compounds and ketenes resulting in loss of nitrogen and carbon monoxide respectively. Other synthetic routes include photolysis and thermolysis of ylides and strained small rings, thermolysis of strained alkenes and some heterocycles or base hydrolysis of tosylhydrazones. However many of these involve severe conditions and therefore have limited synthetic potential (*Scheme 9*)⁷.



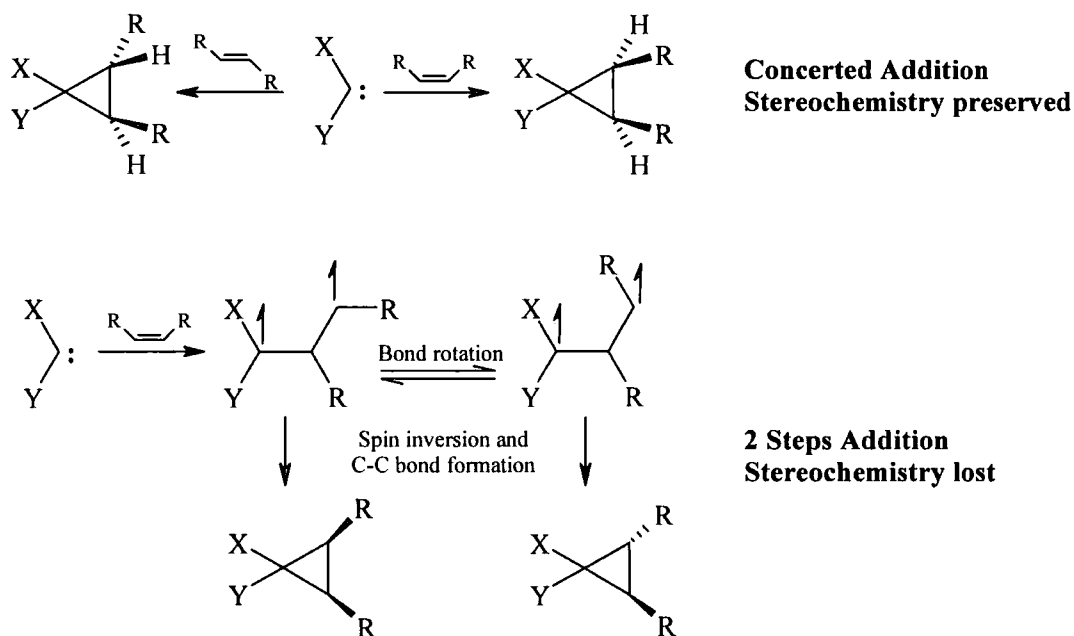
Scheme 9 – Different routes of carbene generation

Carbenes have a divalent carbon with only six electrons in the outermost energy level. Therefore, they are highly electron deficient species and react as strong electrophiles. However, in the presence of strong π -donating substituents, they become nucleophilic⁸ in reactions (Scheme 10).



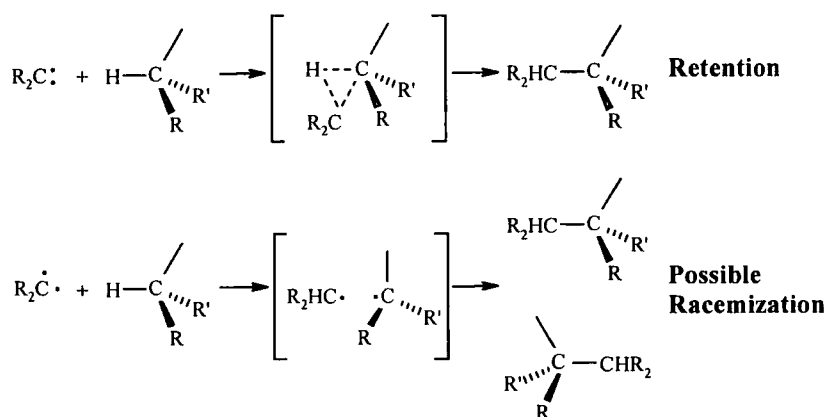
Scheme 10 – Nucleophilic carbene reaction

Carbenes undergo cycloaddition, ylide formation⁹ and C–H insertion reactions. They can react either as singlets or triplets.¹⁰ This is well demonstrated in their cycloaddition reactions. A singlet carbene reacts stereoselectively *via* a concerted mechanism while a triplet carbene reacts non-selectively *via* a diradical mechanism involving two adiabatic bond-making processes, with spin-inversion being a discrete intermediate step (Scheme 11).



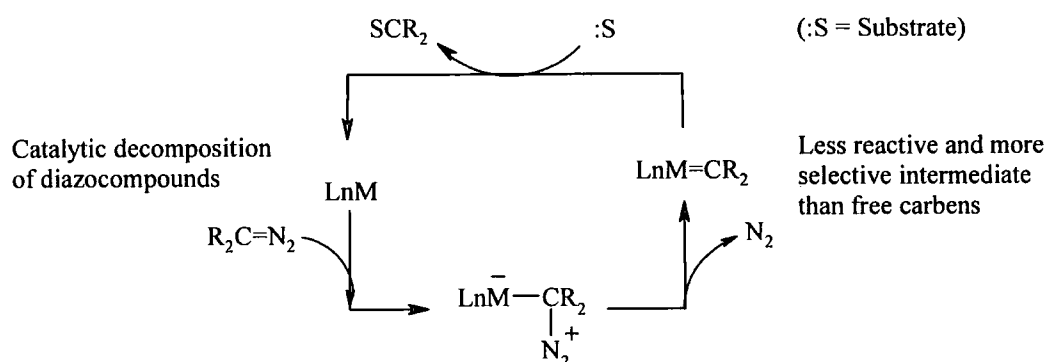
Scheme 11 – Cycloaddition reaction of singlet and triplet carbene

Also in C–H insertion reactions, singlet carbenes insert into C–H bonds with retention of configuration and triplet carbenes can result in racemization⁷ (Scheme 12). C–H insertion reactions of carbenes exhibit preferential insertion into tertiary over secondary over primary C–H bonds in both intermolecular¹¹ and intramolecular¹² reactions with balance between reactivity and selectivity.^{12,13}



Scheme 12 – C–H insertion reaction of singlet and triplet carbenes

Generally, free carbenes exhibit low selectivity due to their high reactivity. On the other hand transition metal metallocarbene intermediates¹⁴ undergo reactions more selectively due to their significant stability, and are therefore a powerful synthetic tool. This approach will be discussed more fully in the next section (*Scheme 13*).



Scheme 13 – Reaction mechanism of metallocarbenes

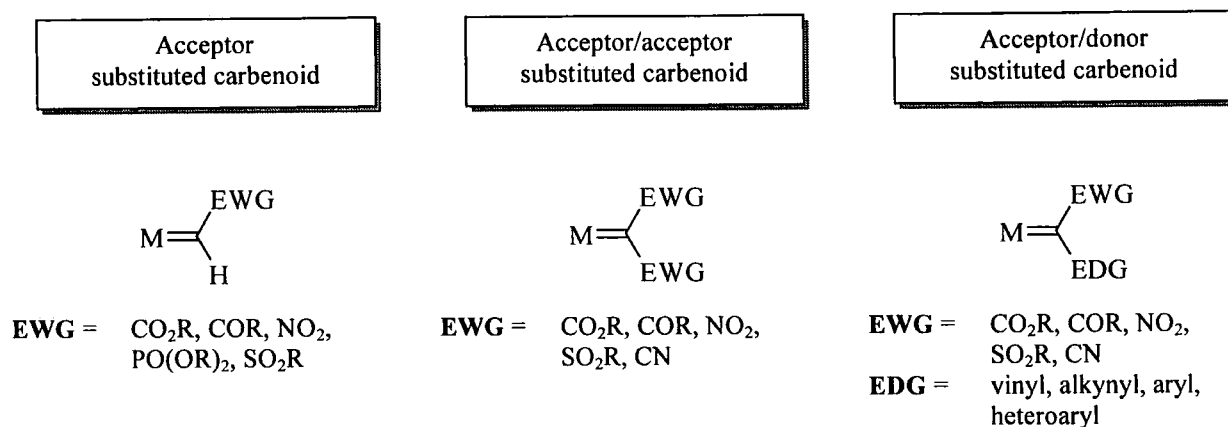
1.3.3 Metallocarbenes in C–H insertion chemistry

1.3.3.1 Introduction

As discussed in the previous section, metallocarbenes offer significant synthetic advantages when compared to free carbenes. This section will highlight the key features of these reagents with particular focus on C–H insertion reactions.

Historically, the first C–H insertion reaction of carbenes was reported by Werner¹⁵ in 1942 but its real renaissance was in the work of Doering in 1951.¹⁶ Then in 1958 an intramolecular C–H insertion reaction was reported by F. Greuter¹⁷ resulting from the catalytic decomposition of an α -diazoketone. Historically, Cu catalysts^{16,18,19} were the first to be used. This was followed by the introduction of Pd(II) acetate²⁰ and Rh(II) acetate²¹ by Teyssie and co-workers in the early 1970s. In spite of the expansive recent development of new transition-metal catalysts, Cu(II), Pd(II) and Rh(II) remain the most commonly used.

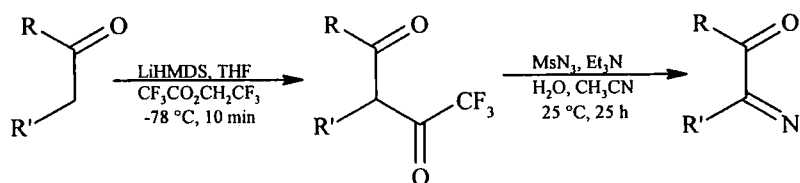
Metallocarbenes can be classified into three categories depending on the substitution pattern which deeply influence their characteristics in reactions in terms of yield, chemoselectivity and enantioselectivity²² (*Scheme 14*).



Scheme 14 – Classification of metallocarbenes

1.3.3.2 Generation

Metallocarbenes are most commonly generated from the corresponding diazoketone precursors to form acceptor-substituted carbenoids. In turn the α -diazoketone precursors are generally prepared *via* two major strategies. First, acylation of diazomethane with acid chloride²³ using an excess (>2 eq.) of an ethereal solution of diazomethane. This strategy represents the major route for acyclic terminal α -diazoketone preparation. Anhydrides²⁴ and mixed anhydrides²⁵, formed from the corresponding carboxylic acids and chloroformate ester, also prove to be effective in diazomethane acylation. The second strategy is the diazo transfer reaction introduced by Regitz²⁶ involving a transfer of a complete diazo group from a donor to an acceptor which is a viable synthetic route for the preparation of both cyclic and acyclic α -diazoketones where acylation fails. This strategy was later modified by Doyle²⁷ to achieve diazo-transfer to a base-sensitive substrate and by Danheiser²⁸ using the corresponding α -trifluoroacetyl derivative (*Scheme 15*).



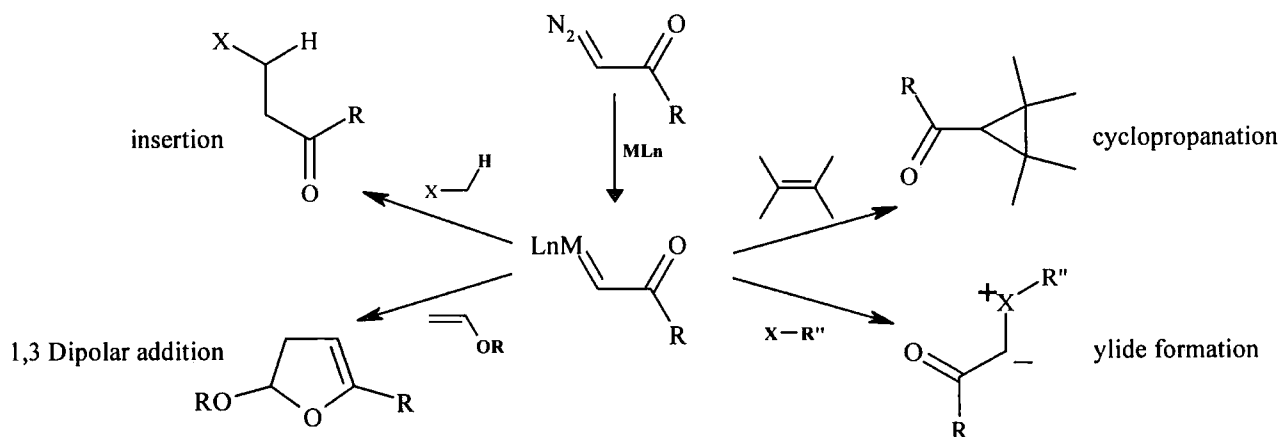
Scheme 15 – Danheiser acyclic α -diazoketone synthesis

Mechanistically, the formation of the metallocarbene can be considered as an electrophilic addition of the transition metal catalysts, ML_n, to the diazocompound with liberation of a

nitrogen molecule and formation of a metal-stabilised carbene, metallocarbene. The reactivity of the metal towards the diazo-decomposition is a function of the Lewis acidity^{29,29} of the metal complex. Although some late transition metals in the 3rd and 4th periods have been shown to catalyse the diazo-decomposition, copper and rhodium are the most frequently used.

1.3.3.3 Reactivity

Although metallocarbenes undergo almost all the same reactions as carbenes, including cyclopropanation, dipolar addition, insertion reactions, and ylide generation (*Scheme 16*)^{30,31} they react more selectively due to the intrinsic stability of the carbenoid complex. Most of those reactions are beyond the scope of this report, which mainly focuses on intramolecular C-H insertion reactions.



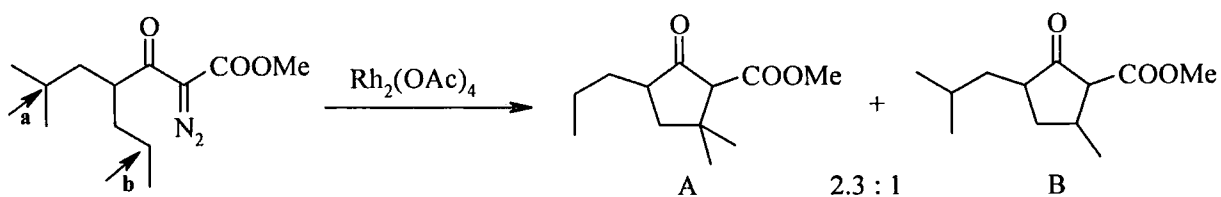
Scheme 16 – Reactions of metallocarbenes

1.3.3.4 Rh(II) in intramolecular C-H insertion reactions

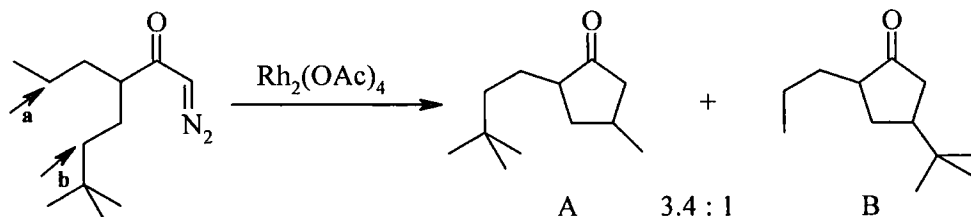
In the past few decades, fantastic advances have been made in catalytic C-H activation. Since Wenkert³² reported the effectiveness of Rh₂(OAc)₄ in intramolecular C-H insertion reactions, many other achiral and chiral Rh(II) catalysts have been extensively investigated. Numerous studies have been carried out to determine and manipulate the factors controlling the selectivity of such transformations.

Intrinsic factors like conformational, steric³³ and electronic³⁴ properties of the substrate deeply influence the outcome of the reaction. Normally, the general rule of the kinetically preferential insertion³⁵ into tertiary over secondary over primary C-H bond applies (*Scheme 17*). However, it

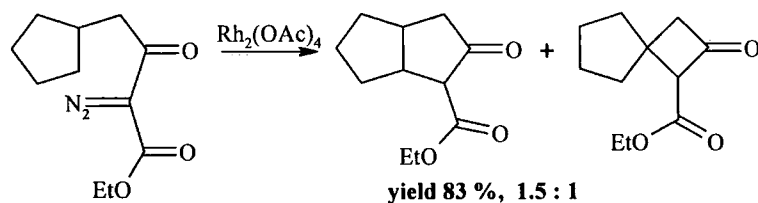
can be overridden by steric factors, especially in intramolecular annulation favouring insertion into secondary over tertiary centres to avoid steric interactions (*Scheme 18*), or to form the unstrained five-membered ring rather than the strained four-membered ring (*Scheme 19*). Also, specific site activation through the inductive effect of substituents or the mesomeric effect of adjacent hetero-atoms can preferentially redirect the C-H insertion into a $-\text{OCHR}_2$ group over $-\text{CH}_2\text{CHR}_2$ (*Scheme 20*).



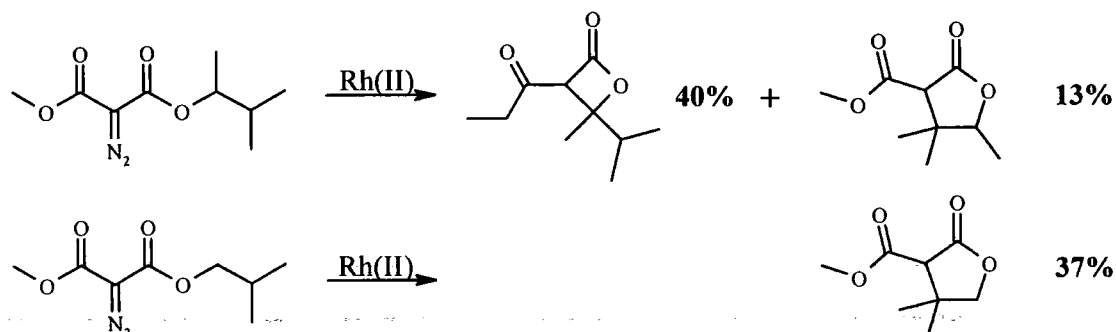
Scheme 17 – Preferential insertion into tertiary C–H bonds



Scheme 18 – Steric effect in C–H insertion reaction

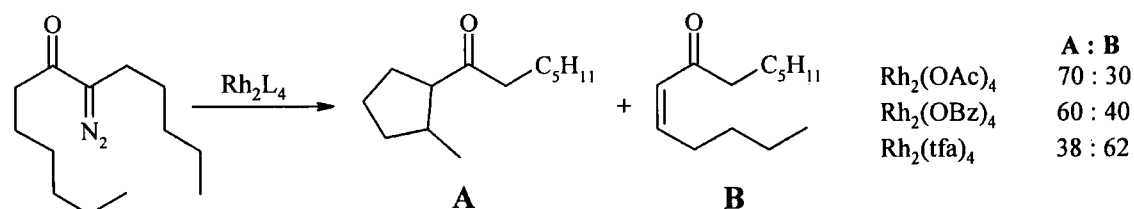


Scheme 19 – Preferential formation of the 5-membered ring



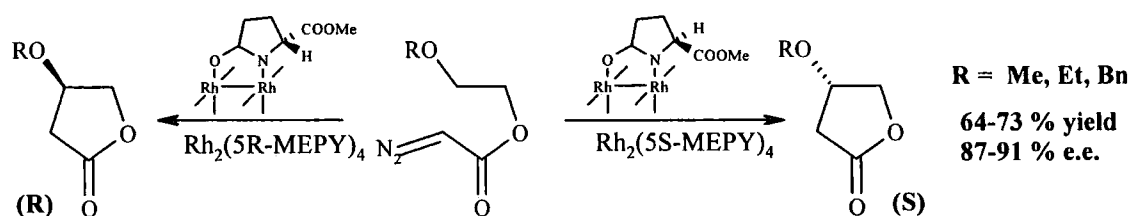
Scheme 20 – Activation by substituents and adjacent heteroatom

On the other hand, the stability-reactivity balance of the carbenoid is fine tuned by the electronegativity^{36,37} of the catalyst ligands. The more strongly electron-withdrawing the ligand, the more electron-deficient the carbenoid is, resulting in lower stability and loss of selectivity, which directs the reaction towards the more entropically favourable pathway of β -hydride elimination (*Scheme 21*).



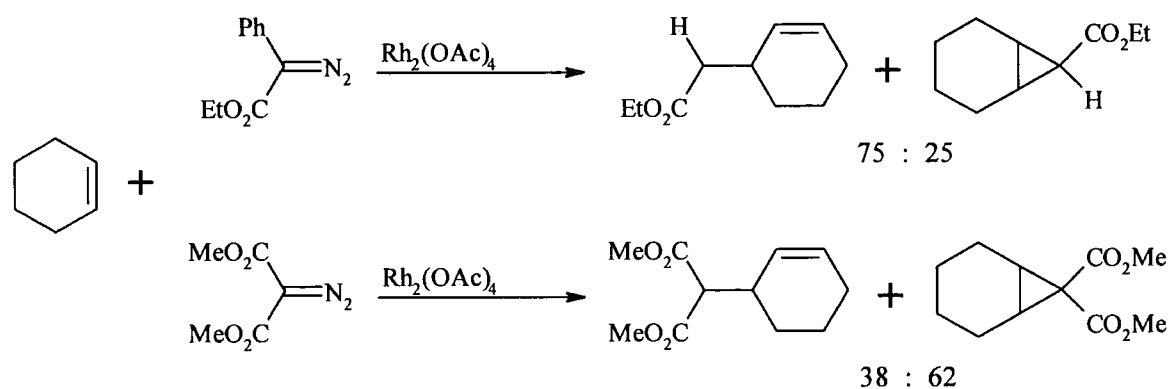
Scheme 21 – β -Hydride elimination pathway

As a consequence of the successful achievements in the chemoselectivity of the reactions of metallocarbenes, recent studies targeted control of enantioselectivity aspects and it was proven that chirality³⁸ of the ligands has a direct effect in the asymmetric induction occurring in the reaction (*Scheme 22*).

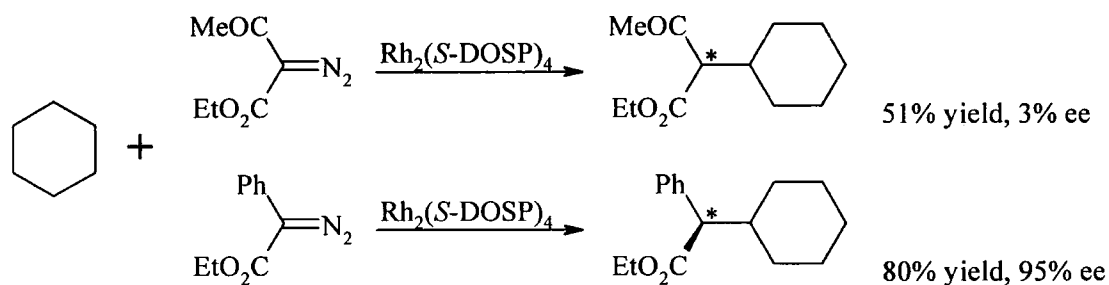


Scheme 22 – Enantioselective C–H insertion reaction

For a long time, intermolecular applications of the knowledge obtained from the catalytic intramolecular asymmetric C–H insertion reactions encountered significant problems because the process displayed very poor chemoselectivity and carbene dimerization was a major competing reaction.³⁹ Recent successes were achieved by using acceptor/donor carbenoids which have been shown to be superior to acceptor and acceptor/acceptor carbenoids in terms of chemoselectivity (*Scheme 23*), yield and enantioselectivity⁴⁰ (*Scheme 24*). Elaborated discussion of this topic is beyond the scope of this report.



Scheme 23 – Acceptor/donor and acceptor/acceptor carbenoids in Chemoselective intermolecular C–H insertion reaction

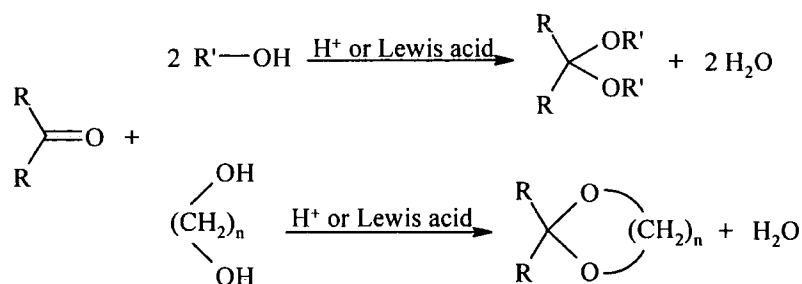


Scheme 24 – Acceptor/acceptor and acceptor/donor carbenoids in Enantioselective intermolecular C–H insertion reaction

1.4 Cyclic acetal cleavage

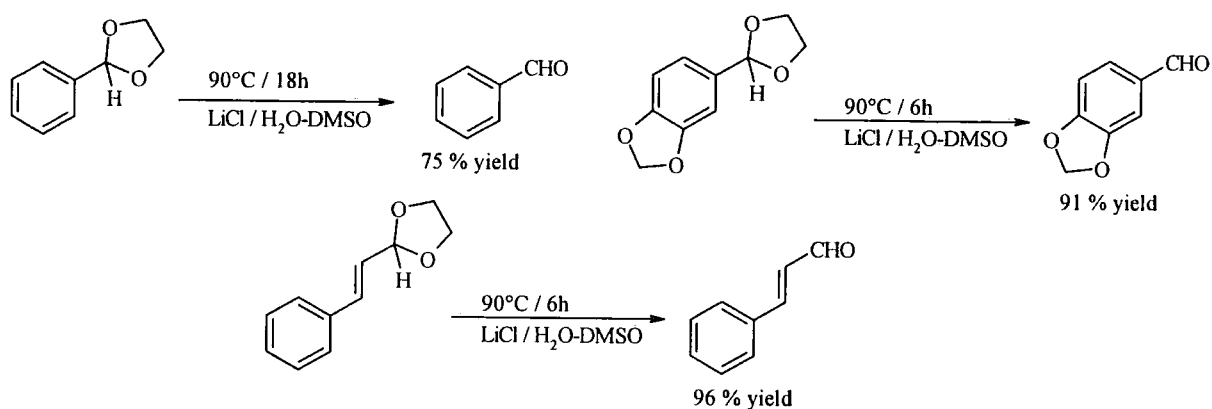
1.4.1 Introduction

Acetals are the class of compounds with two single bonded oxygen atoms attached to the same carbon mostly generated from the corresponding parent carbonyl compound and alcohols under acid catalysis (*Scheme 25*). Generally, acetals are acid labile and base stable with cyclic acetals showing greater stability than acyclic ones. Principally, acetals are used for the protection of the carbonyl functionality due to their high stability against organometallic and strongly basic reagents.



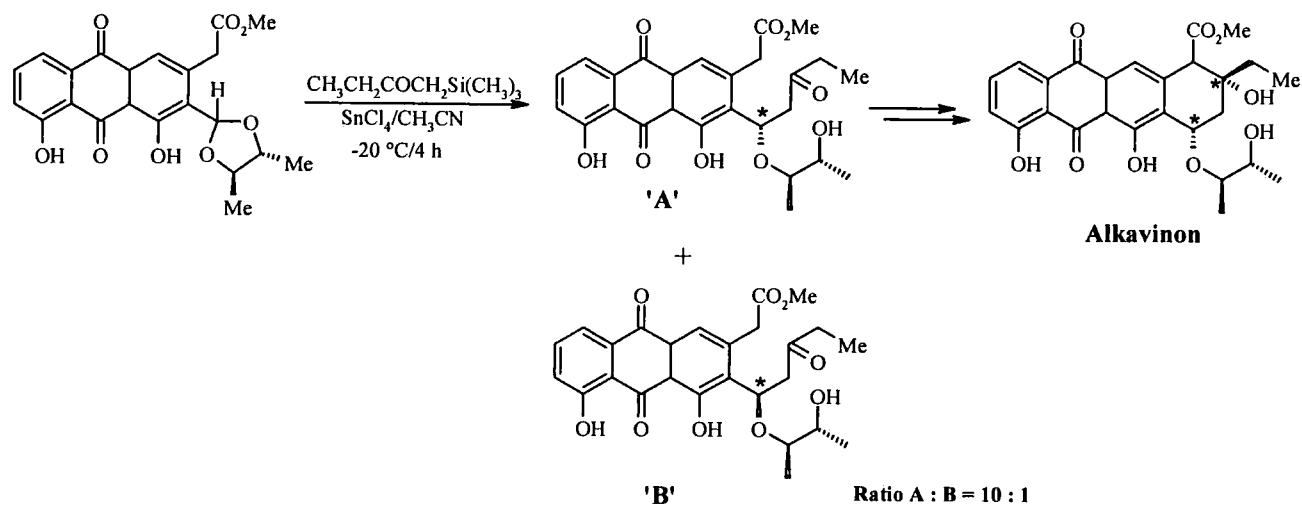
Scheme 25 – Acid catalysed acetal formation

The great significance of selective introduction and removal of protecting groups in organic synthesis is well established. The success of the methodology largely depends on the stability of the protecting groups and how easily they can be installed and removed. Generally, acetals can be hydrolyzed under acid catalysis to regenerate the original carbonyl functionality. However, several methods for the conversion of acetals back into the corresponding carbonyl compounds⁴¹ have been developed to fulfill specific requirements of the substrate as in the case of acid-sensitive moieties. For example, the neutral hydrolysis reported by Roy⁴² using excess LiCl in H₂O-DMSO afforded a mild way to selectively regenerate the corresponding carbonyl compounds from aryl and α,β -unsaturated acetals (*Scheme 26*).



Scheme 26 – Neutral acetal hydrolysis

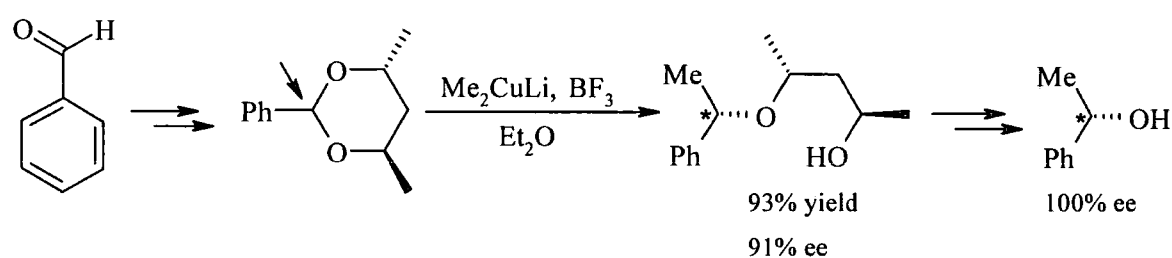
In addition to the use of acetals as protecting groups other applications have been developed, notably the use of acetals in various acetal cleavage sequences. This has been demonstrated in many applications in the synthesis of complex natural molecules and in asymmetric synthesis (Scheme 27).⁴³ This reaction is discussed in detail in the following section.



Scheme 27 – Example of an asymmetric acetal cleavage sequence

1.4.2 Cyclic acetal reductive cleavage

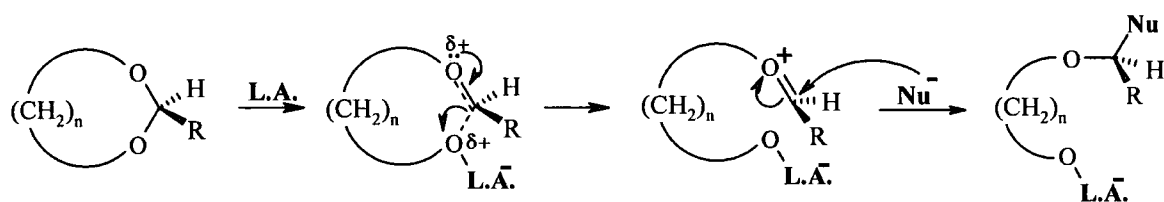
In recent decades, far more advanced uses of acetal cleavage have been explored, especially the use of cyclic chiral acetals as intermediate templates towards the asymmetric synthesis of different compounds *via* a key step involving stereoselective acetal cleavage. An example of this strategy was reported by Alexakis⁴⁴ in the synthesis of chiral secondary alcohols from aldehydes (*Scheme 28*). The core strategy involved a nucleophilic attack on the carbon atom precursor of the chiral centre of the final product.



Scheme 28 – Asymmetric synthesis of a secondary alcohol from an aldehyde

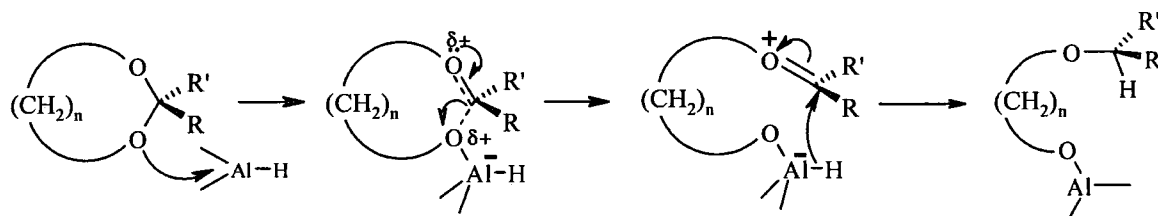
Contemporary to Alexakis, elegant work by Johnson⁴⁵, Kishi⁴² and Yamamoto⁴⁶ showed that different silicon-based nucleophiles ($\text{CH}_2=\text{CHCH}_2\text{SiMe}_3$, $\text{R}-\text{C}\equiv\text{C}-\text{SiMe}_3$, $\text{N}\equiv\text{C}-\text{SiMe}_3$, $\text{CH}_3\text{COCH}_2\text{SiMe}_3$), in the presence of a Lewis acid (TiCl_4 or SnCl_4) were able to cleave cyclic acetals with high asymmetric induction. This led to the investigation of the potential synthetic value of asymmetric reductive cleavage of cyclic chiral acetals.

Mechanistically, the reductive cleavage pathway of acetals involves a Lewis-acid catalysed ring opening-reduction sequence. Co-ordination of the Lewis-acid with one of the oxygen atoms yields an oxocarbenium ion intermediate which then undergoes nucleophilic attack as the reduction step.⁴⁷ Alternatively, organoaluminium hydride reagents can be used to carry out both steps of the mechanism (*Scheme 29*).



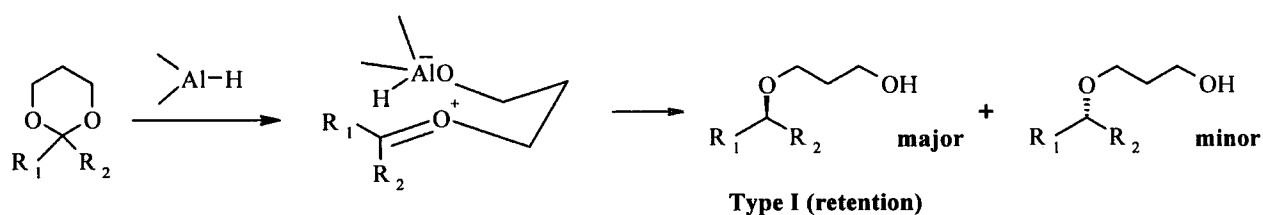
L.A. = TiCl_4 , SnCl_4 , AlCl_3 , ZnCl_2 , BF_3 ,
 $\text{BF}_3 \cdot \text{OEt}_2$, Me_3SiOTf , Me_3SiOMs ,

Nu = NaBH_4 , NaBH_3CN , DIBAL-H ,
 LiAlH_4 , Et_3SiH , Ph_2SiH_2



**Scheme 29 – Reductive cleavage using organometallic reagents vs.
 L.A.-Nucleophile combination**

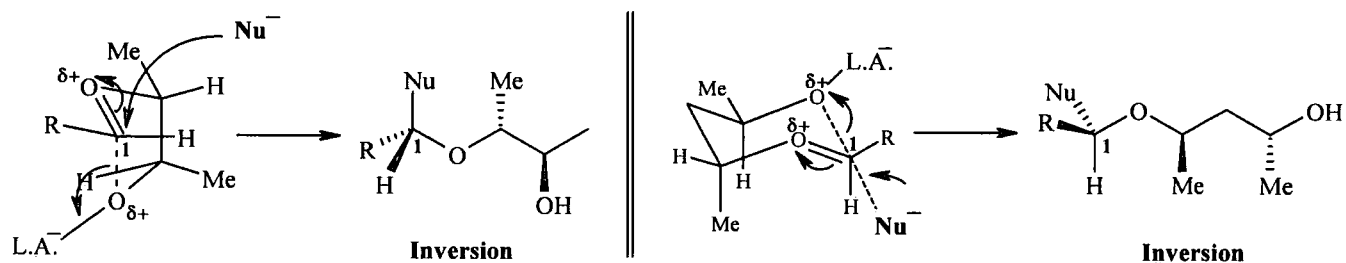
From a stereochemical point of view, reductive cleavage of acetals with organoaluminium hydride reagents afforded a product with retention of configuration. The observed diastereoselectivity was ascribed to the stereospecific co-ordination of the organoaluminium reagent to one of the acetal oxygen atoms followed by the intramolecular hydride attack. This reaction probably proceeds by a tight ion-paired intramolecular $\text{S}_{\text{N}}1$ -type like mechanism⁴⁸ (Scheme 30).



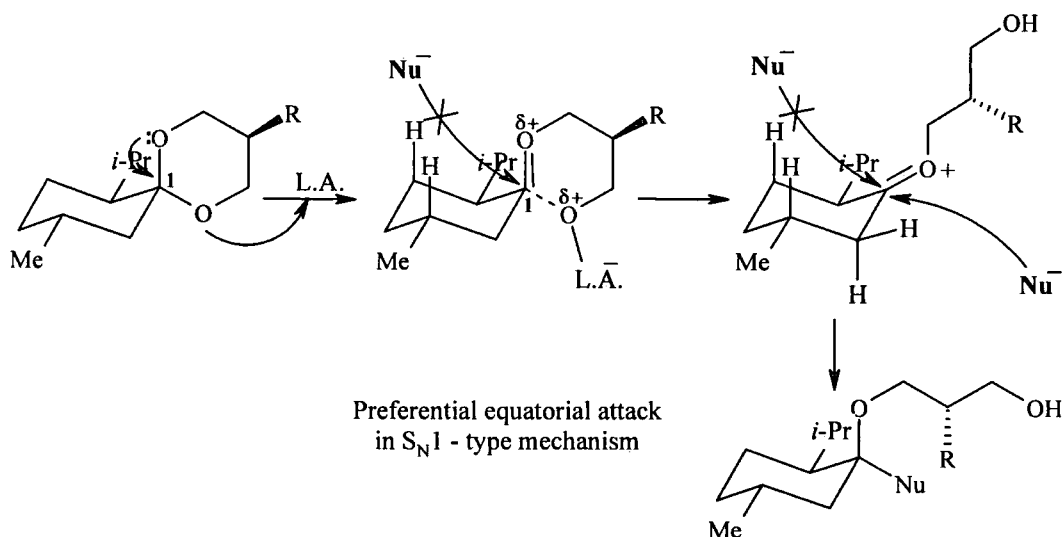
Scheme 30 – Reductive cleavage using organometallic reagents

On the other hand, exposure of the acetal to silane in the presence of Lewis acid gave a product with inversion of configuration as the major outcome of the reaction. This can be explained by a closer examination of the transition state of the nucleophilic attack on the acetal-L.A. complex⁴⁴

(Scheme 31). The overall result is a stereochemical inversion due to the S_N2 -type concerted nucleophilic attack on the developing carbocationic centre. However, this stereochemistry can be overridden by the stereochemical characteristics of the acetal substrate which might hinder the concerted approach of the nucleophile resulting in formation of an explicit oxocarbenium ion intermediate⁴⁹ resulting in a product with retention of configuration as reported by Oku *et al*⁵⁰ (Scheme 32).



Scheme 31 – Reductive cleavage using L.A.-Nucleophile combination

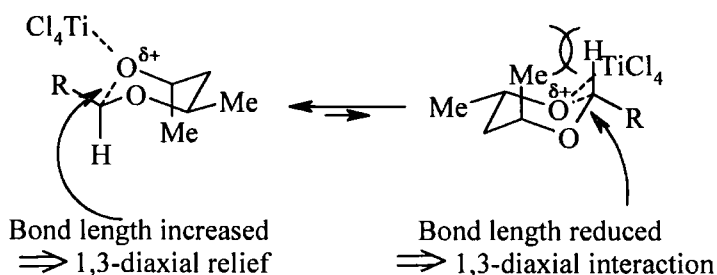


Scheme 32 – Invertive concerted mechanism overridden by steric interaction

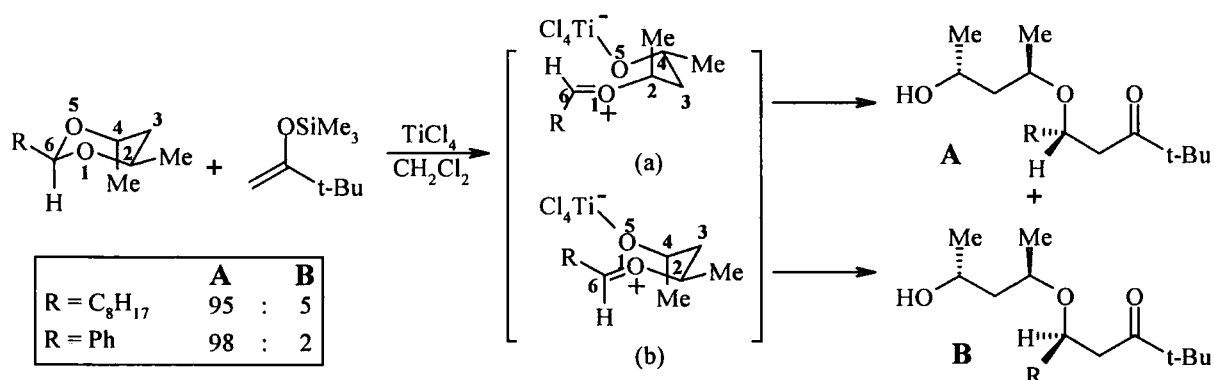
Such observations highlighted the influence of the acetal-L.A. complex, the solvent stabilisation and the relative stability and configuration of the intermediate oxocarbenium ion as the summation of these factors directly influences the stereochemistry of the reaction outcome.

An example of acetal-L.A. interaction was reported by the experimental results obtained from a chiral dioxane system displaying the bias of the Lewis-acid to coordinate with the oxygen next to

the axial methyl group rather than the oxygen next to the equatorial methyl group⁵¹ which is attributed to the difference in the relative stabilities of the two possible transition states, favouring the one with least 1,3-diaxial interaction (*Scheme 33*). Consequently, this interaction determines the stereochemistry of the reaction outcome (*Scheme 34*).

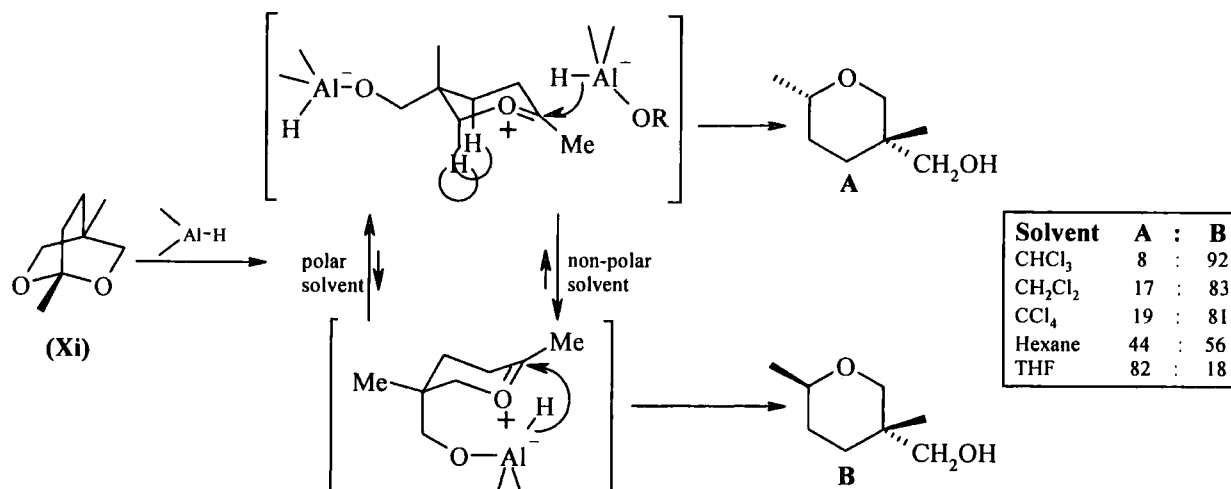


Scheme 33 – Preferential complexation of L.A.



Scheme 34 – Acetal-L.A. complex determines the stereochemistry of the product

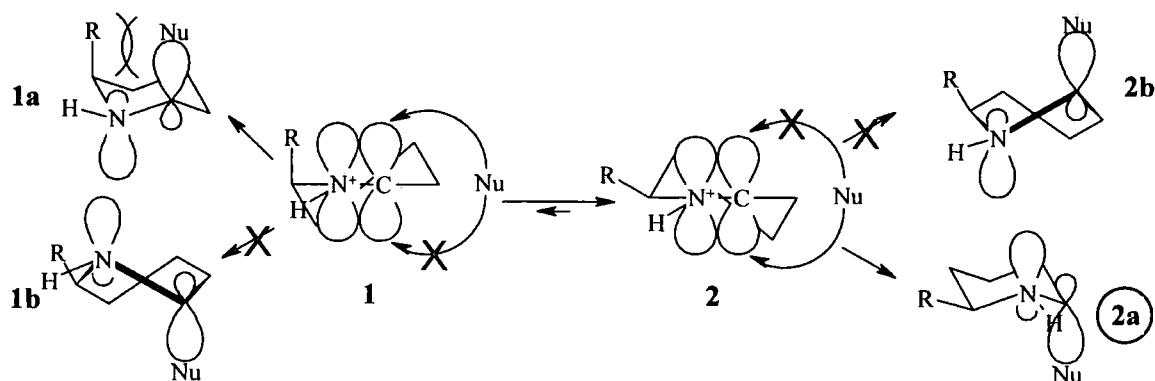
Also, the solvent system can modulate the acetal-L.A. complex through possible solvation effects which might result in a change in the stereochemistry of the reaction outcome. Yamamoto *et al*⁵² used the bicyclic acetal (**Xi**) to investigate the stereoselectivity of the reaction in terms of the solvent system (*Scheme 35*)



Scheme 35 – Solvent effect on the stereochemistry of the product

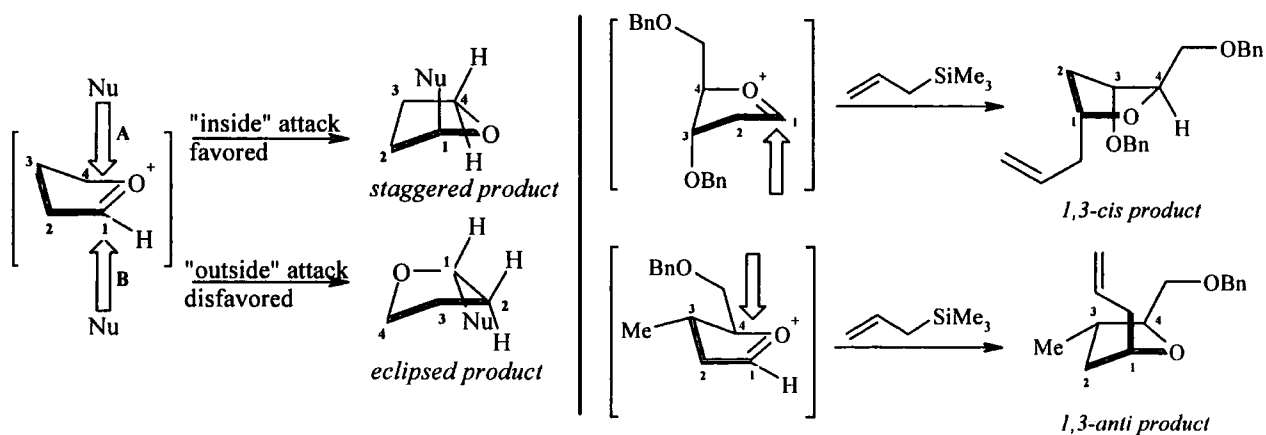
When (Xi) was exposed to organoaluminium compounds, it gave a product with retention of configuration (B). However, changing the reaction solvent could completely redirect the reaction to the opposite stereochemistry. Using a non-polar solvent, such as DCM, hexane or carbon tetrachloride, resulted in retention of configuration, while using polar solvents like THF resulted in inversion of configuration which could be explained by the possible solvation of the charged intermediate complex.

Several studies have investigated the configuration of the intermediate oxocarbenium ion, which is believed to control the stereochemistry of the final product. In the case of the 6-membered ring system, we can refer to the model developed by Stevens and Lee⁵³ elaborating the stereochemistry of nucleophilic attack on a 6-membered iminium ion (analogous to an oxonium ion). There are four possible transition states wherein maximum orbital overlap is maintained with respect to the incoming nucleophile Nu and the developing lone-electron pair on nitrogen. Two of these, **1b** and **2b**, require boat-like transition states and are kinetically disfavored. Of the two possible chair-like transition states (**1a** and **2a**), the former suffers from an unfavorable 1,3-diaxial interaction between R and the incoming nucleophile Nu. Therefore, of the four possibilities wherein maximum orbital overlap is maintained, **2a** is the least objectionable and leads to the observed product (Scheme 36).



Scheme 36 – Nucleophilic attack on the 6-membered ring oxocarbenium ion

As well as the 6-membered-ring, many studies investigated the five-membered-ring-oxocarbenium ions as important reactive intermediates in bioorganic and synthetic organic chemistry and many models were postulated about its stereochemistry in reactions. One of the most advanced models was introduced by Reissig based upon a systematic study of reactions of monomethyl γ -lactols.^{54,55} However, it encountered some limitations which were not satisfactorily explained. In 1999, K. A. Woerpel *et al*⁵⁶, introduced the “inside attack” model to explain the stereoselective reactions of five-membered-ring-oxocarbenium ions. The model highlighted the strong influence of the substituent in position 3 and how the stereoselectivity can be reversed depending whether it is a methyl or an alkoxy group. The former prefers the pseudoequatorial configuration while the latter adopts a pseudoaxial conformation consistent with computational investigations⁵⁷ (Scheme 37).

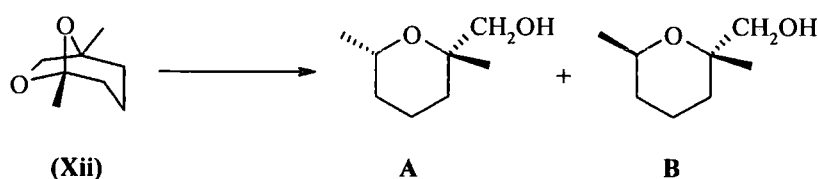


Scheme 37 – Nucleophilic attack on the 5-membered ring oxocarbenium ion

Application of the theories explaining the stereochemistry of the five-membered-ring oxocarbenium ion within this report⁵⁸ will be discussed in detail in Chapter II.

1.4.3 Bicyclic acetal reductive cleavage

To explore the generality and scope of the reductive cleavage in terms of ring size and substitution pattern, some bicyclic ethers were prepared and subjected to the sequences described previously leading to more elucidation of the factors influencing the reaction. For example, the bicyclic acetal (Xii)⁵⁹ was used to investigate the regioselectivity and stereoselectivity of the reaction in terms of the reagents used (*Scheme 38*).

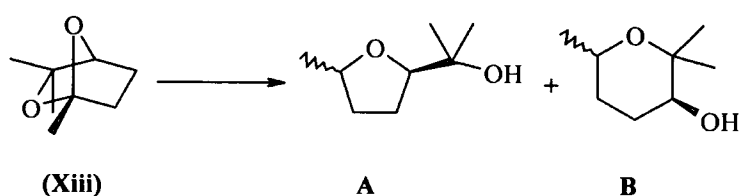


Reaction conditions	Yield %	A	B
DIBAH (6 eq.), CH ₂ Cl ₂ , 0°C	82	3	97
Et ₃ SiH (1.5 eq), TiCl ₄ (1.2 eq) CH ₂ Cl ₂ , -78°C	82	99	1
Ph ₂ SiH ₂ (1.2 eq), TiCl ₄ (1.2 eq) CH ₂ Cl ₂ , -78 to -21°C	76	93	7

Scheme 38 – Bicyclic acetal cleavage

When (Xii) was exposed to organoaluminium compounds, it gave a product with retention of configuration and exposure to a Lewis-acid-silane combination resulted in a product with inversion of configuration consistent with the explanation of the stereoselectivity mentioned previously.

Although the extensive work was carried out, there was still no satisfactory explanation of regioselectivity which was sometimes ambiguous and attributed to the approximate equal accessibility of the two oxygen atoms in some of the compounds studied (*Scheme 39*).

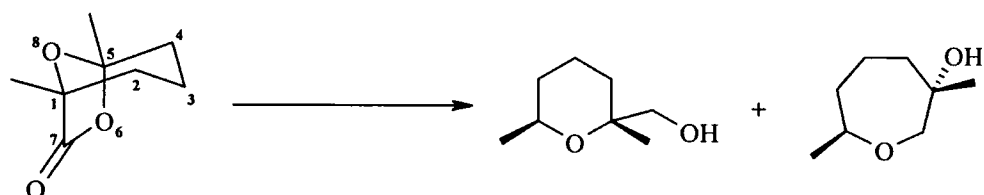


Condition	Yield %	<i>cis</i> A	<i>trans</i> A	<i>cis</i> B	<i>trans</i> B
DIBAH (6 eq.), CH ₂ Cl ₂ , 0°C	61	0.6	55.5	2.1	41.8
Et ₃ SiH (1.5 eq), TiCl ₄ (1.2 eq) CH ₂ Cl ₂ , -78°C	61	42.6	0.8	48.7	7.9

Scheme 39 – Non-regioselectivity resulting from approximate equal accessibility of the two oxygen atoms

In summary, Yamamoto and coworkers' study revealed that reductive cleavage of bicyclic acetals most likely proceeds *via* a dissociative mechanism. However, the reaction is heavily dependent on several factors inherent to the structure of the acetal moiety including the steric effect of the acetal-Lewis-acid complex, relative stabilities and the stereochemical configuration of the intermediate oxocarbenium ion.

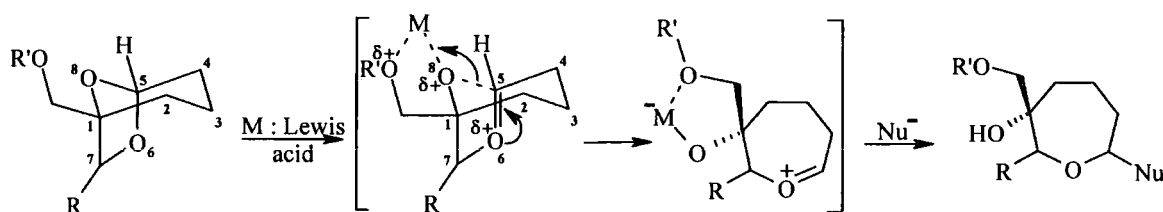
Also, regioselective acetal-Lewis-acid co-ordination was observed in bicyclic acetals. An example was introduced by Jun⁶⁰ in the selective cleavage of 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octan-7-one to selectively generate 6-membered or 7-membered heterocyclic ring systems depending on optimised conditions for the reaction (*Scheme 40*).



Hydride	Lewis-acid	Time	A: 6-membered ring	B: 7-membered ring
NaBH ₄ (4 eq)	BF ₃ .Et ₂ O (30 eq.)	15 h	93	0
NaBH ₄ (6 eq.)	AlCl ₃ (30 eq.)	2.5 h	0	94

Scheme 40 – Regioselective bicyclic acetal cleavage

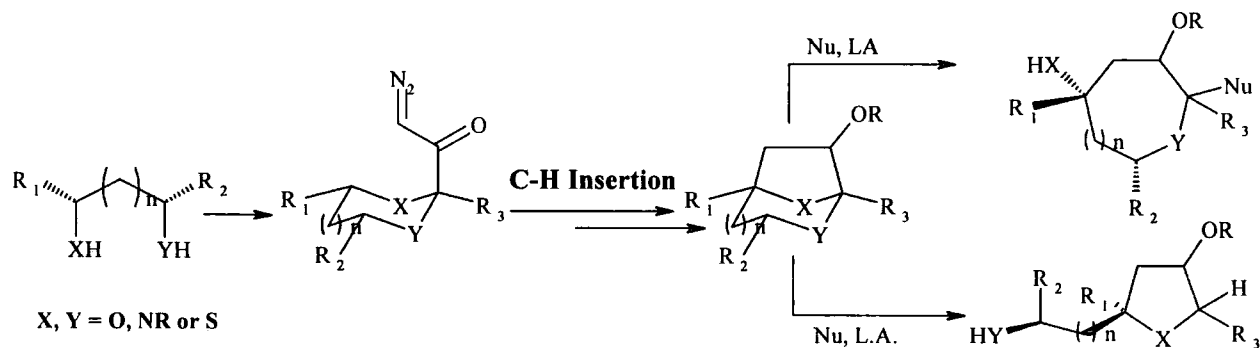
The regioselectivity observed was attributed to the difference in the acidity of the Lewis-acids. The fact that AlCl_3 contains an available d-orbital, whereas $\text{BF}_3 \cdot \text{Et}_2\text{O}$ does not led to the coordination of AlCl_3 to the slightly more electron rich O-8 rather than O-6 which is involved in the resonance effect with the carbonyl group of the lactone. A more recent study by Fujiwara and Murai⁶¹ also showed that TiCl_4 catalysed the reductive cleavage reaction of 6,8-dioxabicyclo[3.2.1]octanes having alkoxymethyl groups at C1 as an internal ligand and led to oxepane formation. Also, the stereochemistry of the methyl substituent at C7 in the bicyclic acetal strongly affected the selectivity proving that regioselectivity can be controlled by manipulation of the substitution pattern of the parent cyclic acetal (*Scheme 41*).



Scheme 41 – Substituents-induced regioselective bicyclic acetal cleavage

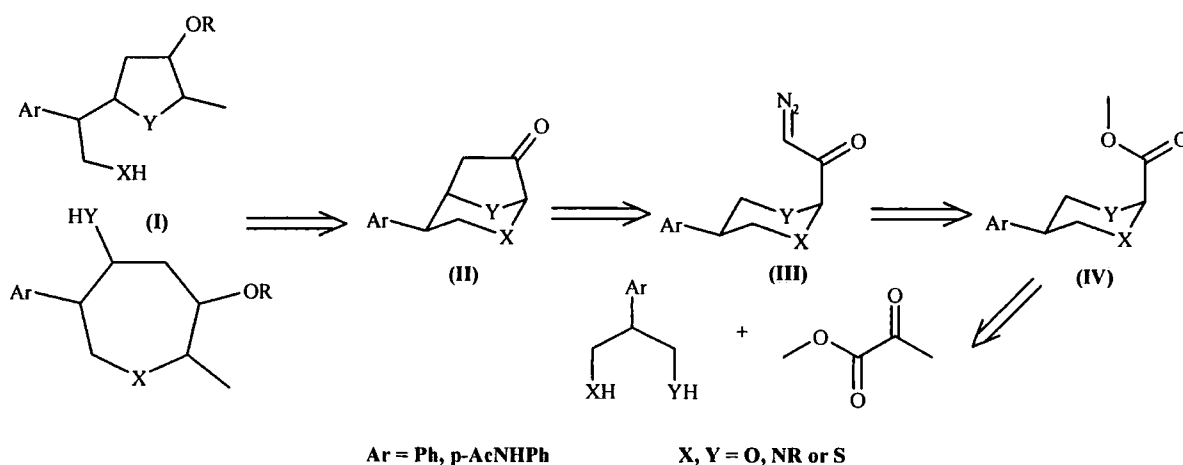
1.5 Aims of the project

The main target of the project is to establish a viable general route towards a stereocontrolled synthesis of highly functionalised heterocycles (ethers, amines and thioethers) *via* the use of a tandem C-H insertion-Lewis-acid-induced ring fragmentation sequence as a general procedure (*Scheme 42*).



Scheme 42 – Project strategy outline

As in previous work done within the group⁵⁸, the same retrosynthetic disconnection approach was adopted. This report discusses the progress achieved in the synthesis of THF derivatives with different substitution patterns (*Scheme 43*).



Scheme 42 – The project retrosynthetic strategy

1.6 References

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- ⁶¹ Fujiwara, K.; Amano, A.; Tokiwano, T.; Murai, A., *Tetrahedron*, **2000**, 56, 1065

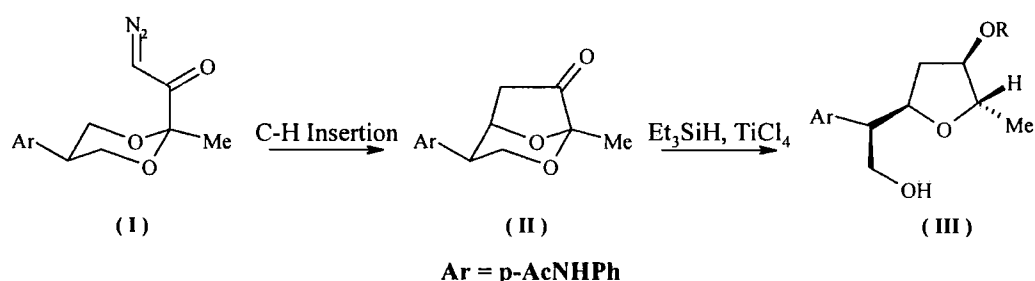
CHAPTER **II**

RESULTS AND **D**ISCUSSION

2 CHAPTER (II): RESULTS AND DISCUSSION

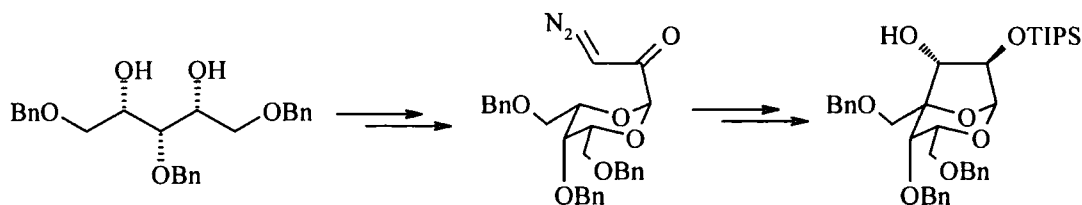
2.1 Introduction

This report focuses on the effect of a different substitution pattern analogous to that from previous work done within the group to confirm the viability of the bicyclic-template-based five-membered ring asymmetric synthesis strategy. The example used was the acetanilido derivative of the cyclic acetal (I) to study the effect of the inserted EDG upon the C-H insertion reaction and the reductive cleavage (*Scheme 43*).



Scheme 43 – The example used to confirm viability of the project strategy

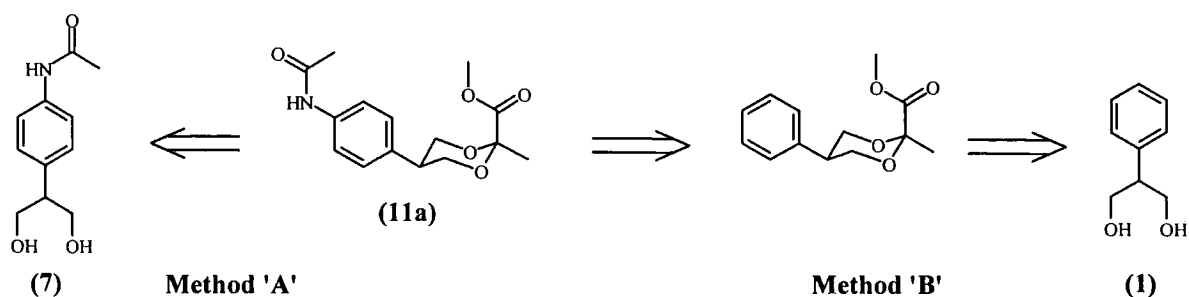
The strategy involves three key steps, ketalization of a 1,3-diol then intramolecular C-H insertion reaction and finally the cleavage of the bicyclic acetal. The first and the second key steps are analogous to the preparation of the core of the zaragozic acids reported by Wardrop *et al*¹ (*Scheme 44*).



Scheme 44 – Wardrop synthesis of the Zaragozic acids core

2.2 Preparation of the target precursor ester acetal (11a)

From the retrosynthetic analysis, there were two available routes. Trials were carried out to determine the efficiency of both in terms of time, yield and ease of purification (*Scheme 45*).



Scheme 45 – The retrosynthetic analyses of compound (11a)

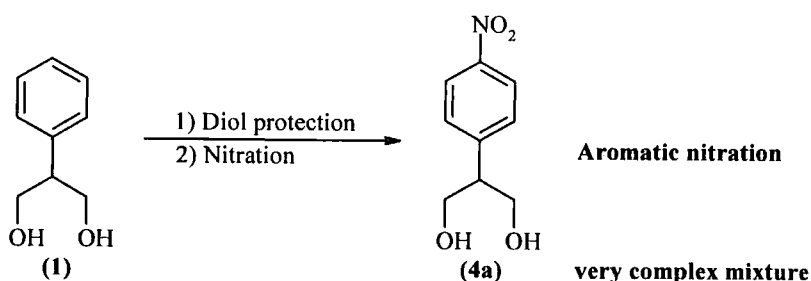
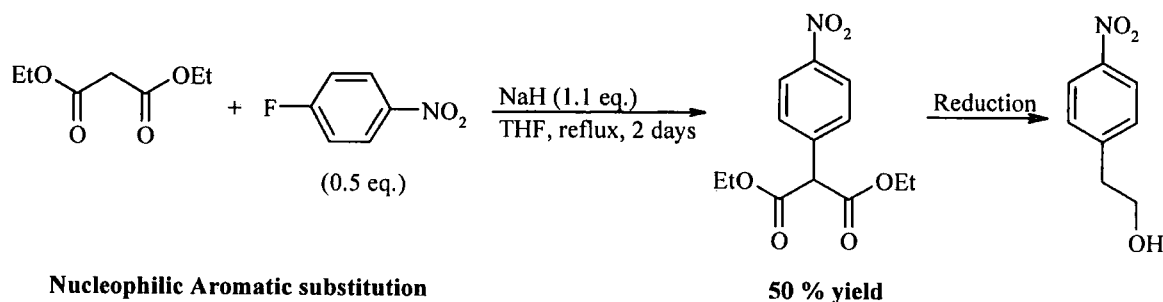
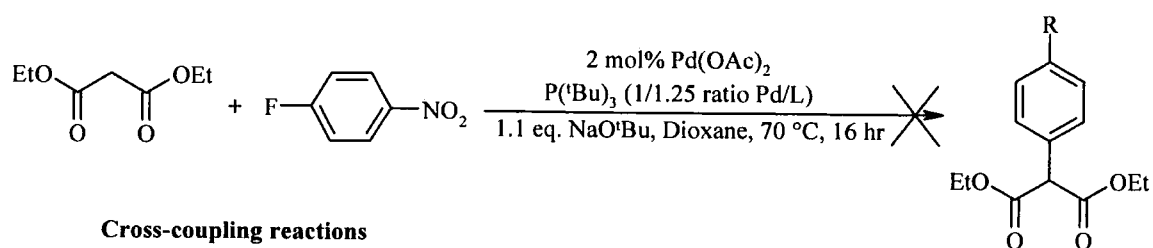
2.2.1 Method 'A'

Method 'A' would adopt the chemistry previously done within the group following the Wardrop strategy. This required preparation of the corresponding diol (7) which is discussed in the next section.

2.2.1.1 Preparation of the *p*-acetamidophenyl diol (7)

2.2.1.1.1 Preparation of the *p*-nitrophenyl diol (4a)

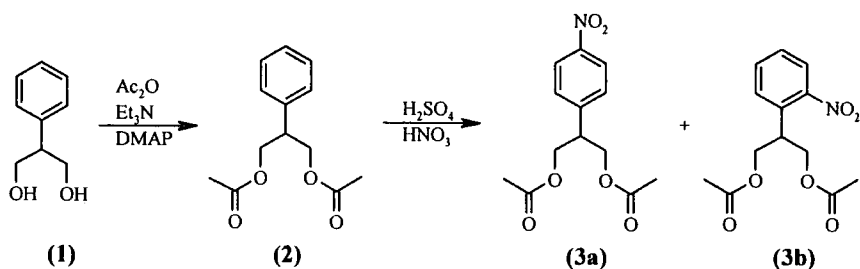
Several strategies to determine the most efficient route towards the synthesis of the 2-arylpropane-1,3-diol have been investigated. These include cross coupling reactions, nucleophilic aromatic substitution and aromatic nitration. The latter proved to be superior in terms of both yield and time (*Scheme 46*).



Scheme 46 – Synthesis of the *p*-nitrophenyl diol (4a)

The initial strategy involved aromatic nitration of the commercially available 2-phenylpropan-1,3-diol (**1**). First attempts were made using the classical aromatic nitration reaction mixture of $\text{H}_2\text{SO}_4/\text{HNO}_3$. However this led to a complex mixture and problems with extraction due to the polarity of the diol. Further attempts to optimise the reaction by controlling the temperature or the sequence of addition of the reagent failed to achieve satisfactory results.

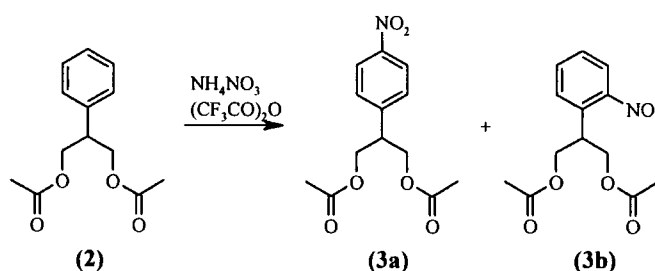
To circumvent these problems, it was decided to protect the diol prior to the nitration step followed by final de-protection to give the target diol (*Scheme 47*).



Scheme 47 – Protection-nitration sequence

Following the procedure reported by Guanti *et al*², the diol was treated with Ac_2O and Et_3N with a catalytic amount of DMAP to yield the diacetate (2) in 89% yield. Evidence for the formation of (2) was observed in the IR spectrum by the absence of the broad hydroxyl peak and appearance of a carbonyl absorption at 1733 cm^{-1} and confirmed by $^1\text{H NMR}$ $2\times\text{MeCO}$ $\delta=2$ ppm, $^{13}\text{C NMR}$ $2\times\text{MeCO}$ $\delta=21.1$ ppm, $2\times\text{COMe}$ $\delta=171.1$ ppm and MS (ES+) 259 (M+Na)^+ .

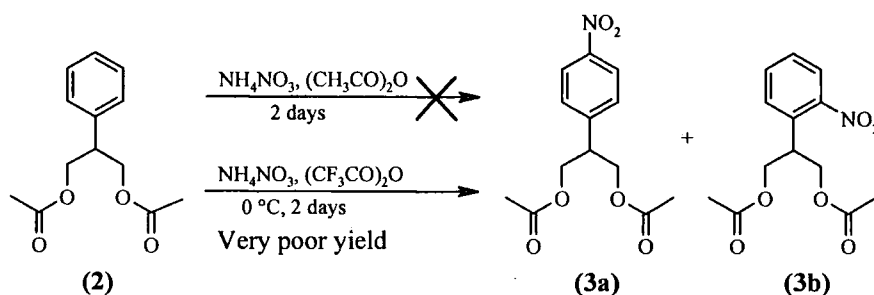
Again, further trials for nitration with $\text{H}_2\text{SO}_4/\text{HNO}_3$ of the diacetate (2) led to a complex mixture. However, a milder protocol for the nitration³ of (2) using trifluoroacetic anhydride and ammonium nitrate in dry chloroform was successful. The reaction resulted in the two isomers (3a) and (3b) with a ratio of 3.8:1 respectively (Scheme 48).



Scheme 48 – The alternative nitration reaction

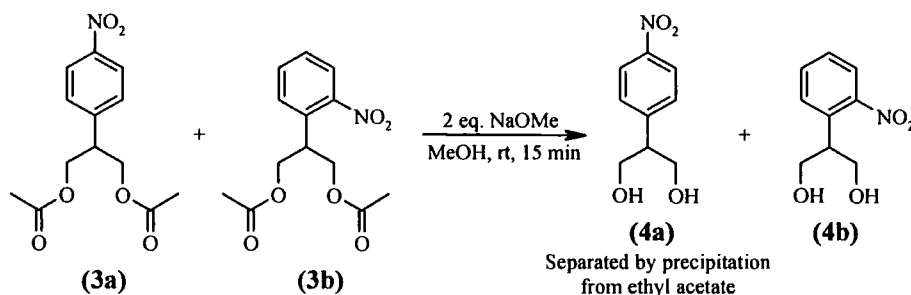
Evidence for the formation of (3a) and (3b) was confirmed by $^1\text{H NMR}$ of the crude reaction mixture by the change in pattern and downfield chemical shift of the aromatic protons to 8.2 (2H, d) and 7.3 (2H, d) for the major isomer with 7.6 (2H, m) and 7.8 (2H, d) corresponding to the minor isomer.

Further trials for optimisation of the reaction conditions to decrease or eliminate the formation of the *ortho*-isomer were then investigated. Using a milder reagent for the generation of the nitrating agent O_2N^+ from the ammonium salt by replacing trifluoroacetic anhydride by acetic anhydride resulted in no reaction (2 days). A second trial to moderate the speed of the reaction by keeping the temperature of the reaction at 0°C resulted in incomplete reaction with very poor yield (2 days) (*Scheme 49*).



Scheme 49 – Optimisation trials of the nitration reaction

Separation of the *ortho*- and *para*-isomers by column chromatography failed. However, removal of the acetyl groups by treatment of (3a) and (3b) with (2 eq.) MeONa in methanol generated diols (4a) and (4b) which could be separated through precipitation of (4a) from concentrated solution in ethyl acetate upon cooling while (4b) remains soluble (*Scheme 50*).



Scheme 50 – Separation sequence of the *para* isomer

Evidence for the purity of (4a) was confirmed from ^1H NMR by the presence of the *para*-substitution pattern as two doublets in the aromatic region 8.2 (2H, d, $J=8.5$ Hz,) and 7.3 (2H, d,

$J=8.5$ Hz) and the complete absence of the aromatic multiplet corresponding to the *ortho*-isomer previously observed in the crude mixture.

2.2.1.1.2 Reduction of the *p*-nitrophenyl precursor

After successfully obtaining the *para* isomer (**4a**) in a pure form, the next step planned was the reduction of the nitro group taking into consideration the highly polar character of the resultant amino diol, its possible solubility in water and difficult purification using column chromatography. Consequently, the pure *para*-isomer (**4a**) was then re-protected as the diacetate to reduce the risk of possible loss of the material in the aqueous phase by the same procedure of diacetylation shown in Scheme 47.

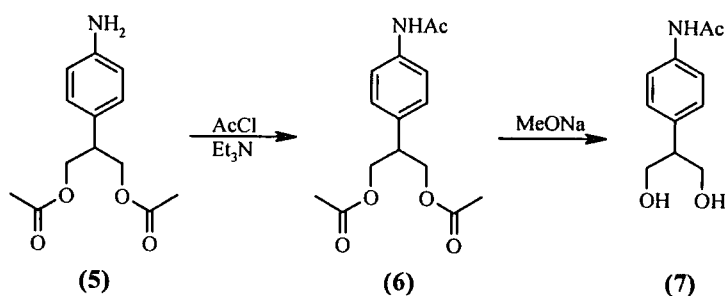
A literature search revealed several routes to reduce an aromatic nitro group to an amino group. Initial attempts using Zn metal / conc. HCl resulted in 100% conversion of the nitro group into the amine group which was confirmed by ^1H NMR with the downfield shift of the aromatic band from 8.2 (2H, d) and 7.3 (2H, d) to 7.0 (2H, d) and 6.6 (2H, d). However, the reaction was accompanied by the loss of the diacetate protection groups yielding a highly polar amino diol compound rendering the isolation and purification of the compound too complicated and time-consuming.

Subsequent approaches exploring reduction *via* catalytic hydrogenation were undertaken. Initial attempts using H_2 with 10% Pd-C in THF resulted in incomplete reaction affording a complex mixture of nitrophenyl SM, product and intermediate compounds. Consequently, the effect of changing the metal catalyst was investigated. Using H_2 /(0.3 eq.) PtO_2 in ethanol⁴ on a small scale provided a very clean reaction product, which did not need any further purification. The metal was separated by simple filtration yielding (**5**) in 90% yield. Due to the high cost of the catalyst, the loading was reduced to (0.03 eq.) and whilst this led to an elongation of the reaction time from 16 hours up to 2 days, no significant change in the yield was encountered.

Evidence for the formation of amine (**5**) was confirmed in the IR spectrum: disappearance of the peaks at 1525, 1345 (NO_2 group) and appearance of the amine absorption at 3230, 3356 (NH_2) cm^{-1} , ^1H NMR by the upfield shift of the *para*-substitution pattern as two doublets in the

aromatic region 7.0 (2H, d, 8.4 Hz), 6.6 (2H, d, 8.4 Hz) and the broad singlet at 3.6 (2H, broad s, NH₂) and m/z (ES⁺): 274 (M+Na)⁺.

Following the reduction, acylation of the amino group took place and final de-protection of the diol functionality with NaOMe yielded the target diol (7) (Scheme 51).



Scheme 51 – Synthesis of diol (7)

Evidence for the formation of diol (7) was confirmed by the IR spectrum: broad peak 3190-3466 (intramolecular H-bonded alcoholic OH); 1635 (amide); 823 (*para*-substitution) cm⁻¹ and absence of the ester carbonyl band. ¹H NMR: 2.1 (3H, s, NHCOCH₃) with loss of the corresponding peak of (OCOCH₃) and ¹³C NMR: 171.3 (NHCOMe); 24.2 (NHCOMe) with absence of the peaks corresponding to the acetyl groups at 170.8 (OCOMe) and (MeCOO) δ=21.1 ppm.

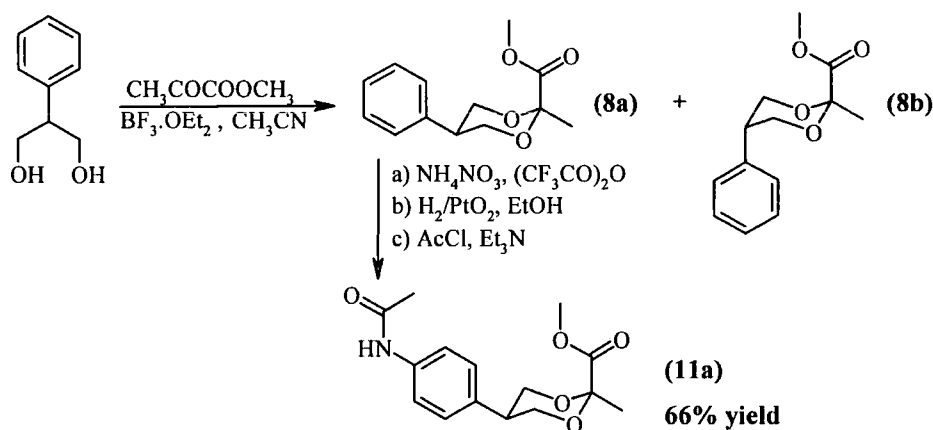
2.2.1.2 Method 'A' : Procedure

Applying the procedure reported by Wardrop *et al*⁵ and used previously within the group for ketalization of 1,3-diols with methyl pyruvate, we encountered two major problems. Firstly the diol (7) was insoluble in the recommended reaction solvent, acetonitrile⁶, and more importantly it was incompatible with the use of BF₃.OEt₂. This was suspected to be due to co-ordination with the more electron-rich oxygen of the acetanilido group which resulted in an extremely poor yield of the target molecule with high decomposition of the starting diol. Consequently this approach

was abandoned and the alternative pathway previously illustrated in Scheme 43 was then explored. This is discussed in the next section.

2.2.2 Method 'B'

Method 'B' involved initial preparation of the phenyl-substituted-cyclic-ester-acetal (**8a**) followed by FGI to the *p*-acetamidophenyl derivative. This method afforded the target ester acetal (**11a**) in 66% overall yield (Scheme 52).



Scheme 52 – Elaboration of method 'B' for the cyclic ester acetal formation

Two major advantages with this method were observed, firstly no acetate protection deprotection steps were required, and secondly, the avoidance of the unwanted interaction between the amide group and the Lewis-acid in the ketalisation step was achieved.

The ketalisation step afforded the two diastereoisomers (**8a**) and (**8b**) in the ratio 4:1. They were easily separated by flash chromatography and the major isomer was used for the rest of the scheme.

Evidence for the formation of (**8a**) was confirmed by the IR spectrum: 1742 (ester carbonyl); 1144 (ether) cm^{-1} with absence of the alcohol peak, ^1H NMR: 4.1 (2H, dd, 4- H_{eq} , 6- H_{eq}); 3.9

(2H, t, 4- H_{ax} , 6- H_{ax}); 3.9 (3H, s, COOCH₃); 3.3 (1H, tt, 5- H), ¹³C NMR: 171.3 (COMe); the quaternary carbon (C-2) at 98.4 ppm and m/z (ES⁺): 259 (M+Na)⁺.

Nitration of (**8a**) yielded no *ortho*-isomer, most probably due to the bulkiness of the acetal ring rendering positions 2' and 6' of the phenyl ring very hindered towards attack by the nitration moiety O₂N⁺.

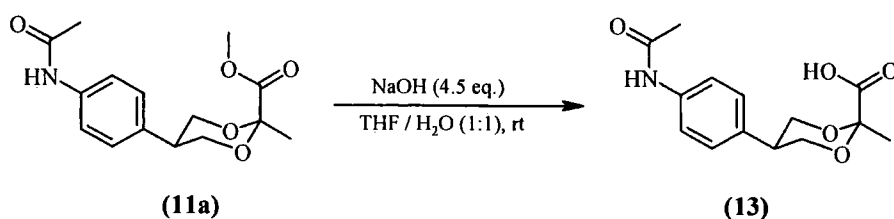
Evidence for the formation of (**9**) was confirmed by the IR spectrum: 1743 (ester carbonyl); 1514, 1350 (NO₂); 1142 (ether) cm⁻¹, ¹H NMR: downfield shift of the aromatic band to 8.2 (2H, d) and 7.3 (2H, d), ¹³C NMR: 147.6 (C-4').

Reduction of (**9**) followed by acetylation yielded the target ester acetal (**11a**). Evidence for the formation of (**11a**) was confirmed by IR spectra: 1742 (carbonyl); 1687 (amide); 1144 (ether) cm⁻¹, ¹H NMR: the upfield shift of the aromatic band to 7.4 (2H, d) and 7.1 (2H, d); 7.2 (1H, bs, MeCONH); 2.2 (3H, s, NHCOCH₃), ¹³C NMR: 168.5 (NHCOMe); 133.8 (C-4'), m/z (ES⁺): 316 (M+Na)⁺; 294 (M+H)⁺

2.3 Preparation of the corresponding acid (**13**)

With the ester acetal (**11a**) in hand, it was treated with NaOH pellets in a THF/H₂O 1:1 mixture. Although the amide group is far more stable than the ester group to base hydrolysis, there was a concern of the possible partial hydrolysis of the amide group as well. Therefore, the reaction was monitored by TLC and investigated against different reaction times. The acid (**13**) was obtained in a very good yield of 93% (*Scheme 53*).

Evidence for the formation of (**13**) was confirmed by the IR spectrum: broad peak 3210-3640 (COOH); 1761 (acid carbonyl monomer); 1710 (acid carbonyl dimer) cm⁻¹, ¹H NMR: absence of the methyl ester peak at 3.9 (3H, s), ¹³C NMR: 173.6 (COOH) and absence of 42.7 (COOMe), m/z (ES⁺): 302 (M+Na)⁺; 280 (M+H)⁺.



Reaction time	Ester hydrolysis	Amide Hydrolysis %
19 hr	Complete	1.65
13 hr	Complete	< 1
2 hr	Complete	Could not be detected

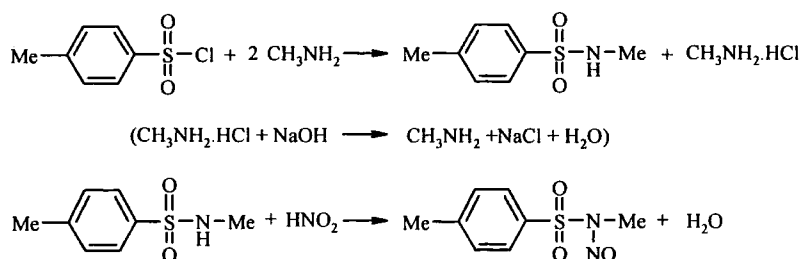
Scheme 53 – Hydrolysis of the methyl ester acetal

2.4 Preparation of the diazoketone (15)

Previous work within the group revealed that acylation of diazomethane was the reaction of choice to prepare the diazoketone from the cyclic acetal acid compound. Previous attempts at the use of a diazo-transfer reaction were not successful and resulted in no reaction, poor yield or a complex mixture.

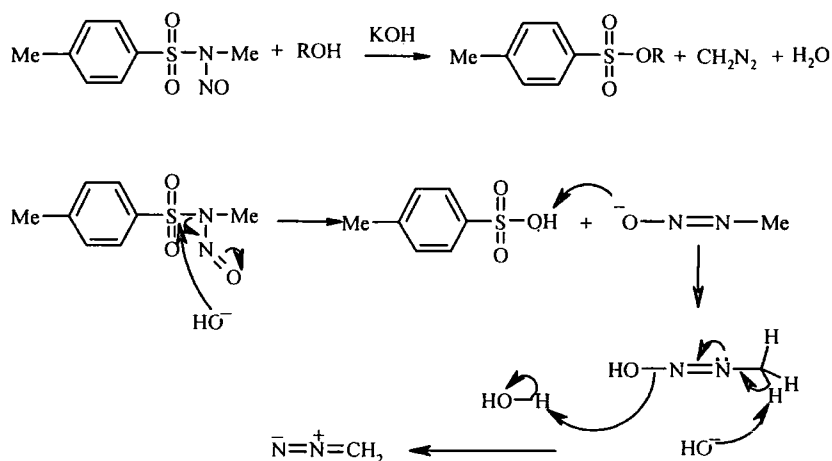
Although diazomethane is explosive and needs extra care in handling, and although the diazomethane precursor, Diazald[®], had ceased to be commercially available which necessitated its preparation, the acylation of diazomethane gave the best results in the preparation of the diazoketone (15).

Initially, Diazald[®] was prepared following the De Boer⁷ procedure from *p*-toluenesulfonyl chloride and methylamine (Scheme 54).



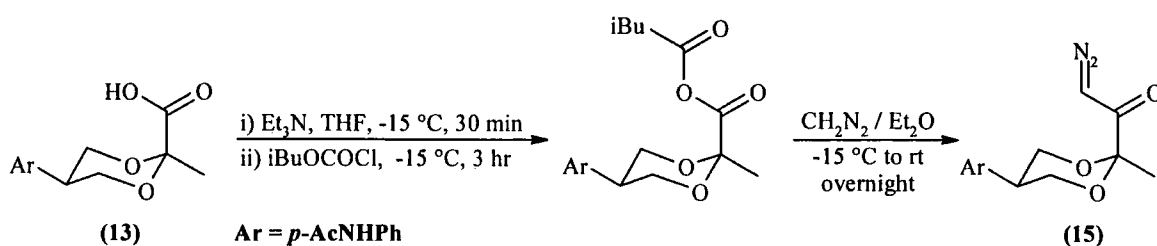
Scheme 54 – Diazald[®] preparation by the De Boer procedure

Once Diazald[®] was prepared, it was used in a non-ethanolic diazomethane preparation⁸ by dissolution in anhydrous ether, which was then slowly dripped into a mixture of KOH and di(ethyleneglycol)methyl ether in a 1:1 mixture of H₂O/ether at 60 °C. The resultant diazomethane was distilled as an ethereal solution (*Scheme 55*).



Scheme 55 – Diazomethane preparation by the De Boer procedure

Concurrently with the preparation of diazomethane, the acid (13) was treated with isobutyl chloroformate in the presence of Et₃N in THF to form the mixed anhydride. The reaction was followed by TLC and upon complete consumption of the acid indicating the formation of the mixed anhydride, the ethereal solution of the freshly prepared diazomethane was added to the reaction mixture. Following workup and flash chromatography, the target diazoketone (15) could be obtained in 79% yield (*Scheme 56*).

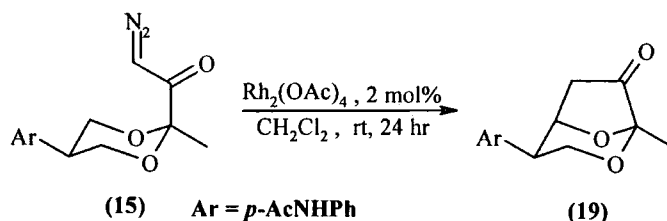


Scheme 56 – Preparation of the diazoketone by diazomethane acylation

Evidence for the formation of **(15)** was confirmed by the IR spectrum: 2116 (CHN_2) cm^{-1} , ^1H NMR: the characteristic peak at 5.8 (1H, s, COCHN_2), ^{13}C NMR: 194.1 (COCHN_2); 44.2 (COCHN_2).

2.5 Preparation of the C-H insertion product (19)

After successful preparation of **(15)**, it was submitted to a Rh(II)-mediated C-H insertion reaction. With reference to the discussion in **Chapter I**, the expected product is that of the insertion into the C-H bond adjacent to an oxygen atom which is favoured by the heteroatom activation and the unstrained five-membered ring formation (*Scheme 57*). The reaction yield was moderate and ranged from 30 to 38%.

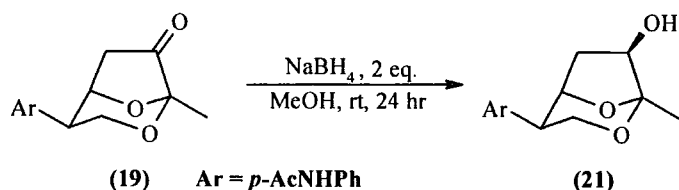


Scheme 57 – the formation of the bicyclic ketone via C-H insertion reaction

Evidence for the formation of **(19)** was confirmed by the IR spectrum: 1764 (carbonyl) cm^{-1} and the disappearance of the (CHN_2) peak at 2116, ^1H NMR: 4.9 (1H, dd, 5-*H*); 2.5 (1H, dd, 6-*H*_α); 2.4 (1H, d, 6-*H*_β) and absence of 5.8 (1H, s, COCHN_2), ^{13}C NMR: 210.5 (*C*-7); 76.2 (*C*-5), *m/z* (ES⁺): 316 ($\text{M}+\text{Na}+\text{H}_2\text{O}$)⁺; 298 ($\text{M}+\text{Na}$)⁺.

2.6 Reduction of the bicyclic ketone (19)

Due to the presence of two carbonyl functionalities, NaBH_4 represented a mild reducing agent which selectively reduces the ketone functional group over the amide functionality. The bicyclic ketone **(19)** was treated with NaBH_4 in methanol and stirred overnight at room temperature. The reaction was complete in 12 h and gave **(21)** in 80% yield (*Scheme 58*).

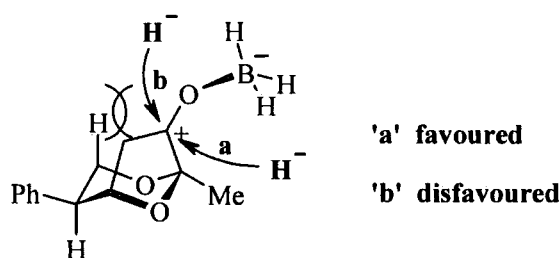


Scheme 58 – Reduction of the bicyclic ketone

Evidence for the formation of **(21)** was confirmed by the IR spectrum: 3200-3500 (broad OH) cm^{-1} , $^1\text{H NMR}$: 4.5 (2H, m, 5-*H*, 7-*H*); 2.5 (1H, ddd, 6-*H α*); 2.1 (1H, d, 7-*OH*); 1.8 (1H, dd, 6-*H β*), $^{13}\text{C NMR}$: absence of the peak at 210.5 (*C-7*) and appearance of the peak 75.8 (*C-7*).

The full assignment of the $^1\text{H NMR}$ and $^{13}\text{C NMR}$ spectra was accomplished by the help of 2D NMR experiments (HSQC, HMBC). The stereochemistry at position 7 was ascertained by nOe experiments and further confirmation was gained by using the *t*-BDMS derivative **(22)** mentioned later in this chapter.

Previous attempts⁹ to obtain the other alcohol epimer had involved screening different reaction conditions and different reducing reagents but with no success. This can be explained as the preferential complexation of the reducing agent from the least hindered side followed by *syn* attack of the hydride to give the alcohol **(21)** (Scheme 59).

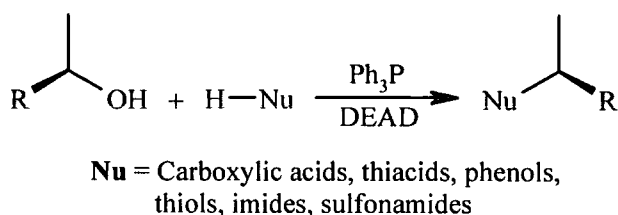


Scheme 59 – The preferential formation of the endo-isomer

2.6.1 Inversion of the 7-OH stereochemistry

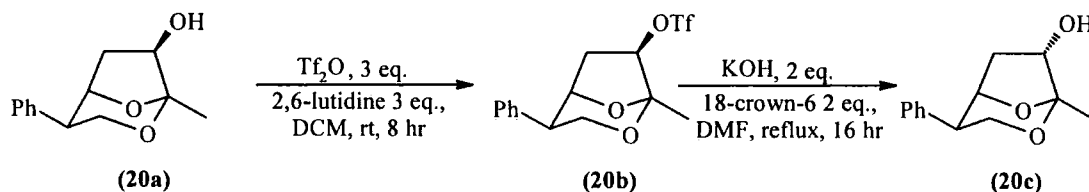
When all the attempts to obtain the other alcohol epimer directly from the reduction step had failed, another route was explored. The idea was to convert the alcohol into a good leaving group followed by S_N2 reaction resulting in inversion of configuration.

Initial attempts⁹ were carried out using the Mitsunobu reaction (*Scheme 60*) with acetic acid. In spite of taking into consideration the observations of Harvey¹⁰ and Dodge¹¹ to avoid the formation of the anhydride (*in the case of carboxylic acid nucleophiles*), this method failed to yield the desired product.



Scheme 60 – Inversion of stereochemistry using Mitsunobu reaction

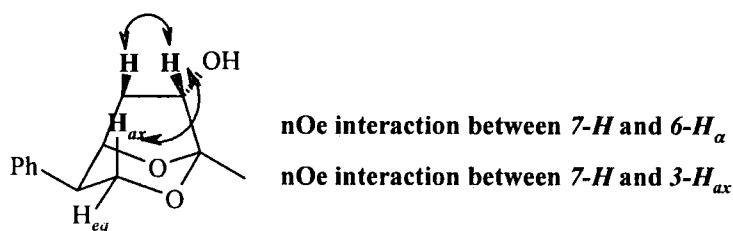
Converting the alcohol into the mesylate derivative followed by treatment with different nucleophilic reagents⁹ (LiOH (2 eq.), H_2O_2 (30 % w/w in H_2O , 6 eq.) or KOAc/18-crown-6) failed to achieve the objective, revealing that the mesylate group was far more stable than anticipated. Finally, treatment of the alcohol (**20a**) with trifluoromethanesulfonic anhydride (3 eq.) and 2,6-lutidine (3 eq.) in DCM yielded the triflate derivative which was subsequently treated with KOH (2 eq.) and 18-crown-6 (2 eq.) in DMF to give the inverted alcohol (**20c**) in 40% yield (*Scheme 61*).



Scheme 61 – Inversion of the 7-OH stereochemistry

Evidence for the formation of **(20b)** was confirmed by the ^{19}F NMR spectrum with the fluorine peak at -74.78 ppm, the quadruplet at 119.0 ppm in the ^{13}C NMR corresponding to the CF_3 group and the disappearance of the broad alcohol peak in the IR spectrum.

Evidence for the formation of **(20c)** was confirmed by the IR spectrum: $3680\text{-}3200$ (broad OH) cm^{-1} and the disappearance of the peaks corresponding to the CF_3 group in both ^{19}F NMR and ^{13}C NMR. The stereochemistry was confirmed by a nOe experiment (*Scheme 62*).

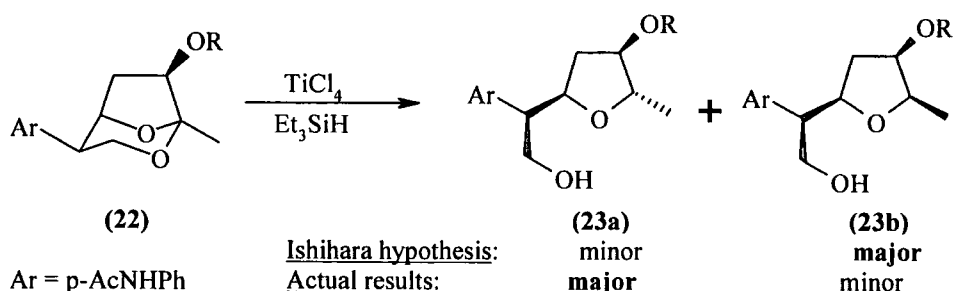


Scheme 62 – nOe evidence of 7-OH stereochemistry inversion

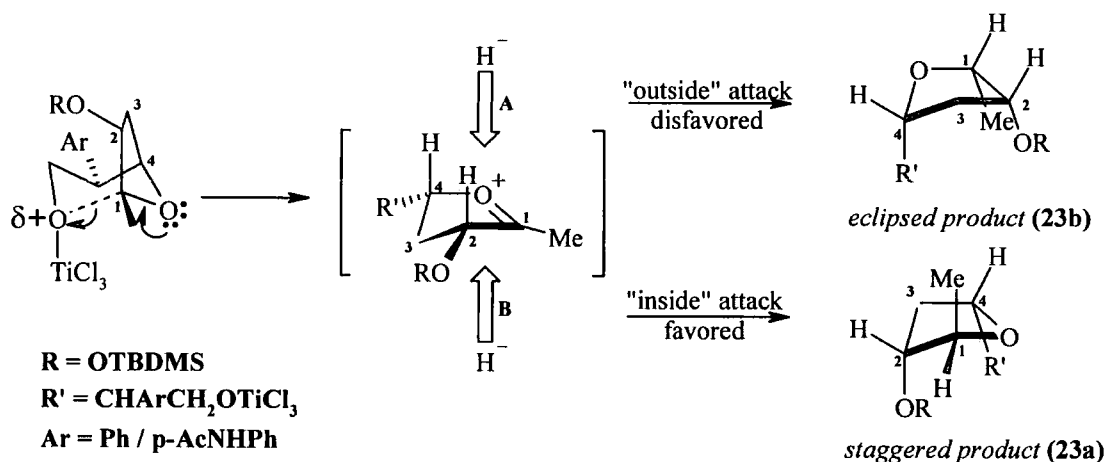
2.7 Cleavage of the protected bicyclic alcohol (**22**)

Following the reductive cleavage procedure reported by Ishihara *et al*¹² (using TiCl_4 as a Lewis acid and Et_3SiH as a reducing agent) compound **(22)** was dissolved in DCM and cooled to -78°C , and Et_3SiH (4 eq.) was added. Later a 1M solution of TiCl_4 in DCM (1.2 eq.) was added dropwise and the reaction mixture was stirred at -78°C overnight.

According to the results reported by Ishihara and his group, the major and minor products of the reaction were expected to be compound **(23b)** and compound **(23a)** respectively (*Scheme 63*). Surprisingly, the opposite results were obtained indicating that the intermediate of the reaction does not follow the hypothesis of invertive $\text{S}_{\text{N}}2$ -type postulated by Ishihara and his group while it is compliant with the “inside attack” model reported by Woerpel¹³ (*Scheme 64*).



Scheme 63 – Ishihara hypothesis vs. actual findings

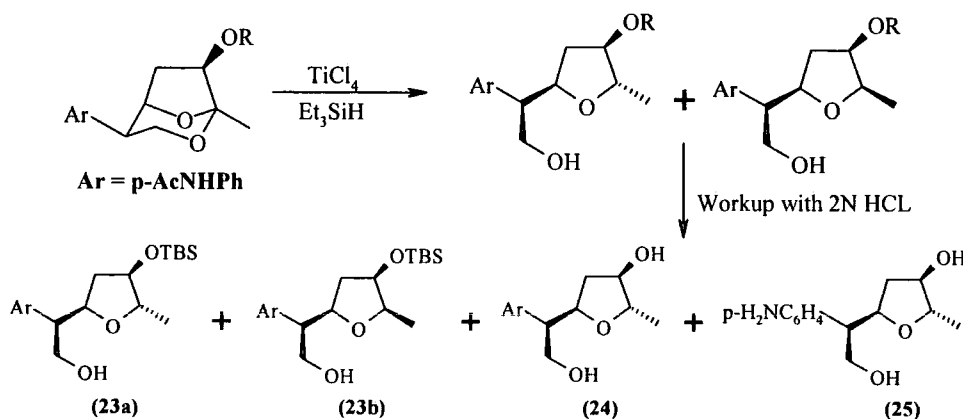


Scheme 64 – Explanation of the product stereochemistry according to the "inside attack" model

Once completed, the reaction mixture was poured into 2N HCl and extracted with EtOAc to yield **(23a)** and **(23b)** in a ratio of 87 : 13 –according to the ^1H NMR spectrum of the crude mixture– with a very poor yield (14%) of the pure major isomer **(23a)** and 16% of a mixture of both. **(23b)** could not be isolated in pure form.

Further investigations into the reasons for the poor yield compared to the average 78% yield obtained in the analogous series (where the nitro-group substituent is in the *para*-position on the phenyl ring) assumed that loss of the *t*-BDMS group and partial hydrolysis of the amide group might have occurred during the work-up. With the aqueous phase in hand, the pH was raised to the basic side (pH 8) and re-extraction with EtOAc (4×10 ml) recovered a solid material (7 mg) with high UV absorbance which was assumed to be due to the chromophoric aromatic

substituent. Further analysis with ^1H NMR spectroscopy confirmed the presence of another two compounds (**24**) and (**25**) in a ratio (1:1.67) respectively which passed to the aqueous phase due to the possible ionisation of (**24**) and the high polarity of (**25**). Inclusion of these findings would raise the yield of the reaction up to *c.a.* 70% (*Scheme 65*). Repeating the reaction and using NaHCO_3 as a quenching agent instead of 2N HCl led to a higher isolated yield (60%).



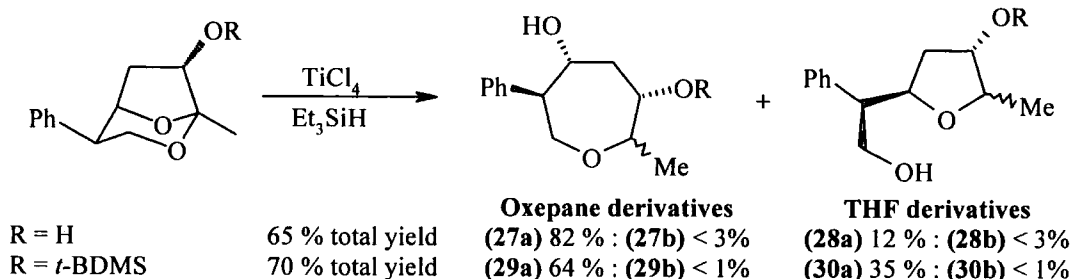
Scheme 65 – Effect of the acidic workup of the reaction

2.8 Cleavage of the bicyclic inverted alcohol series (20c, 20d)

Inversion of the stereochemistry of 7-OH, led to the idea of the possible formation of a bidentate complex with TiCl_4 in the acetal reductive cleavage reaction which may lead to the formation of the oxepane derivative.

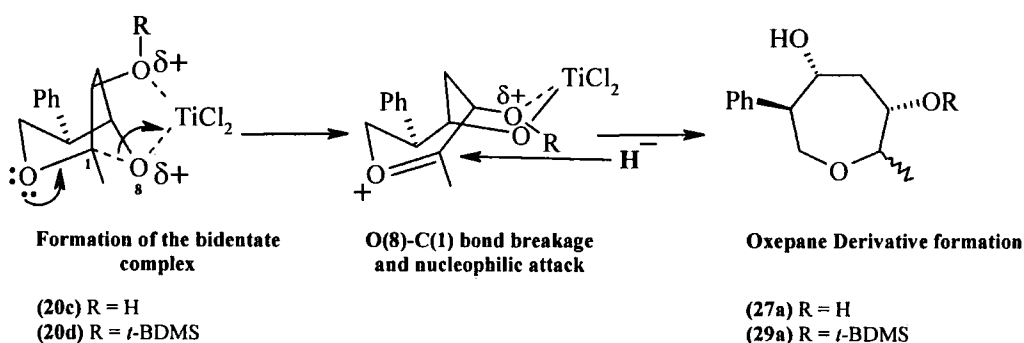
Following the reductive cleavage procedure used previously, compound (**20c**) and (**20d**) were dissolved in DCM, cooled to -78°C , and treated with Et_3SiH followed by dropwise addition of TiCl_4 . The reaction mixture was stirred at -78°C overnight.

Each reaction gave four isomers with good overall yield. Two isomers are presumed to be oxepane derivatives while the other two are THF derivatives. Comparison of the isomers ratios has shown that the regioselectivity of the reaction is dependent on the nature of the group at C-7 of the bicyclic acetal. (*Scheme 66*).



Scheme 66 – Reductive cleavage of the inverted 7-OH alcohol series

Explanation of the regioselectivity of the reaction outcome to give the oxepane derivative rather than the THF derivative can be attributed to the formation of the more favoured bidentate complex of the TiCl_4 with O-8 and 7-OH/7-OR in the bicyclic acetal and subsequent breakage of O(8)–C(1) bond to give the oxepane derivative (*Scheme 67*). This is consistent with the fact that the silyl ether is less co-ordinating than the free alcohol which resulted in lower regioselectivity in the reductive cleavage reaction of the protected alcohol (**20d**).



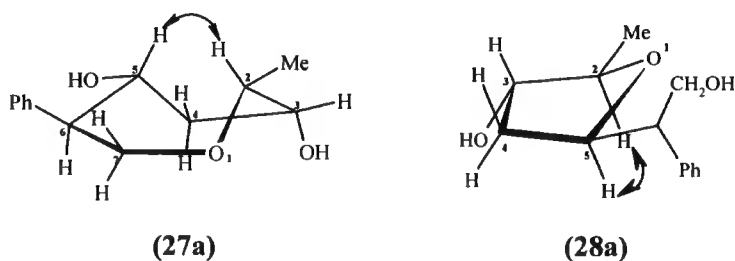
Scheme 67 – New regioselectivity due to the bidentate complex

Unfortunately, all the isomers appeared as one broad spot on the TLC plate and rendering the separation using column chromatography not possible. While the characterisation of the two minor isomers in both reactions was not possible, the two major isomers in each reaction were fully characterised. Assignment of the ^1H NMR and ^{13}C NMR spectra of the products was carried out with the help of 2D NMR experiments (COSY and HSQC). Further analysis of the HMBC spectra and comparison with the data obtained from The Chemical Database Service

(CDS) provided little evidence for the regiochemistry of the reaction. Analysis of the ^1H - ^1H coupling constants of (27a) using the Karplus equation gave a basic idea of the dihedral angles (Table 1) which helped in hypothesising a conformation of the product which is consistent with the results obtained from a nOe experiment (Scheme 68).

Spectrum	Findings	Possible dihedral angle
^1H NMR	2-Me, $J = 6.5$ (2-H)	$\theta = 30^\circ / 150^\circ$
	2-H, $J_1 = 6.5$ (2-Me), $J_2 = 3$ (3-H)	$\theta_1 = 30^\circ / 150^\circ$, $\theta_2 = 55^\circ / 125^\circ$
	3-H, $J_1 = 6.5$ (2-H), $J_2 = 3$ (4-H _a), $J_3 = 3$ (4-H _b)	$\theta_1 = 30^\circ / 150^\circ$, $\theta_2 = 55^\circ / 125^\circ$, $\theta_3 = 55^\circ / 125^\circ$
	4-H, $J_1 = 11$, $J_2 = 9$ (5-H), $J_3 = 3$ (3-H)	$\theta_1 = \text{Geminal}$, $\theta_2 = \text{nearly axial}$, $\theta_3 = 55^\circ / 125^\circ$
	5-H, $J_1 = 9$ (4-H _b), $J_2 = 6$ (4-H _a), $J_3 = 4.5$ (6-H)	$\theta_1 = \text{nearly axial}$, $\theta_2 = 30^\circ / 150^\circ$, $\theta_3 = 45^\circ / 135^\circ$
	6-H, $J_1 = 7$ (7-H), $J_2 = 4.5$ (5-H)	$\theta_1 = 30^\circ / 150^\circ$, $\theta_2 = 45^\circ / 135^\circ$
	7-H, $J_1 = 11$, $J_2 = 7$ (6-H)	$\theta_1 = \text{Geminal}$, $\theta_2 = 30^\circ / 150^\circ$

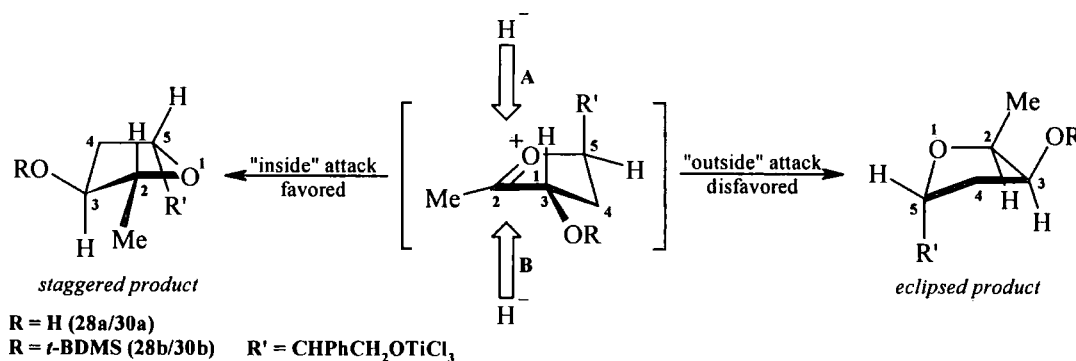
Table 1 - ^1H - ^1H coupling constants of (27a) and dihedral angles assumptions according to Karplus equation



Scheme 68 - The proposed conformations of (27a) and (28a) depending on the analysis of ^1H - ^1H coupling constants and the nOe findings

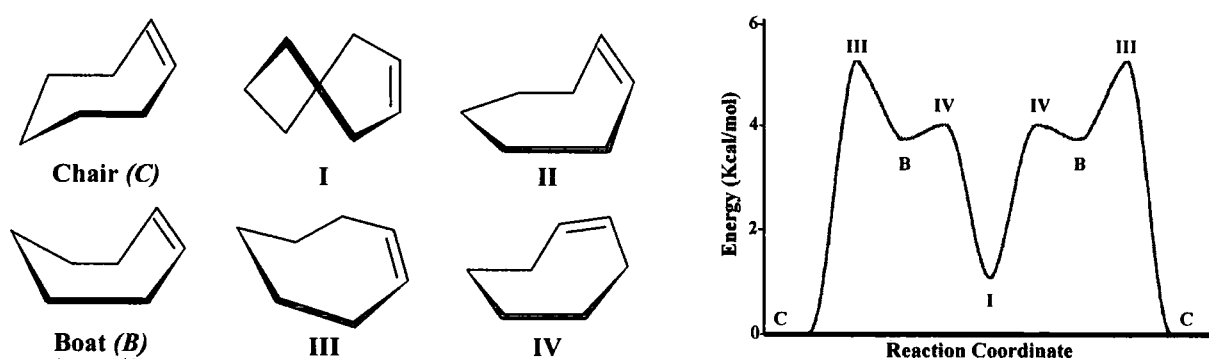
As mentioned earlier in this chapter, the stereochemistry of the THF derivatives resulted from the reductive cleavage of the bicyclic acetal (22) was dependent on the conformation of the five-membered-oxocarbenium ion intermediate. On the same basis, the stereochemistry of the THF

products was consistent with Woerpel's "inside attack" model to give the *staggered* product resulting from the lower-energy conformer of the five-membered-ring oxocarbenium ion (Scheme 69).



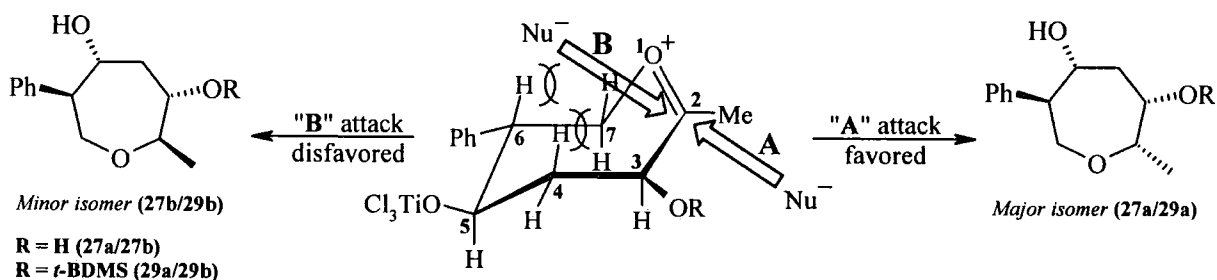
Scheme 69 – Explanation of the product stereochemistry according to the "inside attack" model

The same approach was adopted to elucidate the stereochemistry of the oxepane derivatives. A literature search revealed a study carried out by Boggs *et al*¹⁴ on the conformation of some cycloalkenes. In their study they reported that cycloheptene, as a pseudo six-membered ring, is believed to exist in stable chair (*C*) and boat (*B*) conformers. Also, they reported the existence of one more intermediate (*I*) and another three transition states between the chair and boat conformers. The energy profile of all the possible conformers indicated that the chair conformer is the most stable one depending on recent molecular mechanics calculations (Scheme 70).



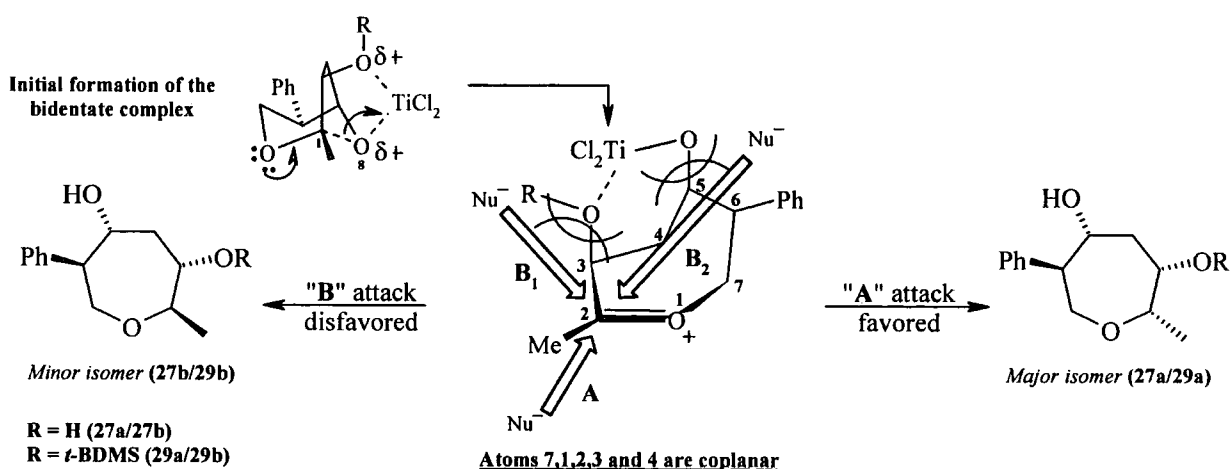
Scheme 70 – Possible conformations of cycloheptene and their energy profile

This model could help to visualise the conformation of the seven-membered-oxocarbenium ion intermediate which by turn controls the stereochemistry of the reaction outcome. According to the energy profile of the possible conformations, the oxocarbenium ion will adopt a chair conformation with the nucleophilic attack occurring preferentially from the less hindered face, pathway 'A' (Scheme 71).



Scheme 71 – The seven-membered-ring oxocarbenium ion

An alternative explanation involves nucleophilic attack occurring on the bidentate complex (Scheme 72). This complex hinders nucleophilic attack from the same face and leaves the other side more accessible to the attacking nucleophile.



Scheme 72 – The hypothesis of the nucleophilic attack on the bidentate complex

In summary, the reductive cleavage of the bicyclic acetals **(20c)** and **(20d)** resulted in two major isomers, one is an oxepane derivative and the other is a THF derivative. However, these results remain as speculations and the reaction needs to be repeated on a larger scale with more focus on the separation of the resultant compounds and further investigations involving X-Ray diffraction methods which will give a clear evidence for the regioselectivity of the reaction outcome.

2.9 References

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CHAPTER III

CONCLUSION AND FUTURE WORK

3 CHAPTER (III): CONCLUSION AND FUTURE WORK

3.1 Conclusion

This research was done analogous to previous work within the group to confirm the validity of the adopted strategy towards the stereoselective synthesis of 2,3,5-trisubstituted THF derivatives. By the end of this work, it was possible to obtain the 2,3,5,6-tetrasubstituted oxepane ring by changing the stereochemistry of the 7-OH in the bicyclic alcohol prior to the acetal cleavage step.

The strategy involved 3 key steps, initial formation of the cyclic ester acetal *via* ketalization of 1,3-diols with methyl pyruvate, Rh(II) mediated C–H insertion of the diazoketone formed by diazomethane acylation using the corresponding acid acetal and finally the reductive cleavage of the bicyclic acetal in a highly stereoselective fashion to yield either the THF derivative or the oxepane derivative.

Initial work within the project was done with simple 1,3-diols which encountered problems of volatility and difficulty in tracking due to lack of a chromophore. Subsequent work was done using the phenyl derivative and the nitrophenyl derivative as an example of mild and strong EWG respectively. The work encountered in this report involved the use of the acetanilido derivative as an EDG to fulfil the study of the effect of such substitution upon the key steps of the strategy, the C–H insertion reaction and the bicyclic acetal reductive cleavage.

This report showed that using the acetanilido derivative of the bicyclic acetal template doesn't have a significant affect upon the C–H insertion or the bicyclic acetal reductive cleavage. However, it proved that the acetanilido derivative of the 1,3-diol was incompatible with the initial ketalization step, however, this could be overcome by the formation of the phenyl derivative of the cyclic ester acetal followed by subsequent FGI to the acetanilido derivative. The overall results were consistent with the previous work done within the group.

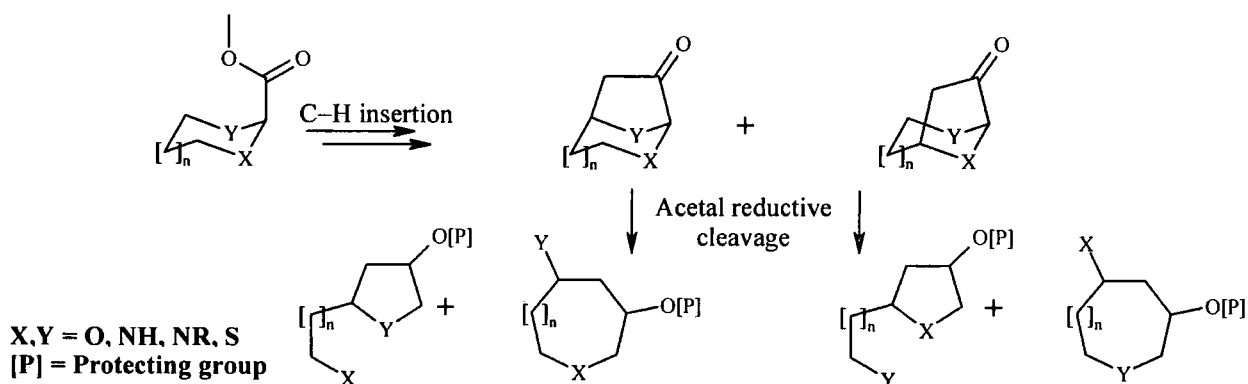
The manipulation of the 7-OH was done using the phenyl series. Subsequent to inversion of stereochemistry, both the free and the protected bicyclic alcohol led to the formation of the

oxepane ring indicating the crucial effect of the configuration of the hydroxyl/alkoxy group in that position upon the acetal cleavage reaction.

3.2 Future work

3.2.1 The cyclic precursor

All the previous work was carried out using the cyclic O,O-ester acetal template. Further attempts towards the synthesis of new templates with different heteroatoms (O, N or S) will be investigated. This will allow further study of the effect of the different heteroatoms upon the diastereoselectivity of C–H insertion reaction and consequently the final bicyclic acetal reductive cleavage reaction (*Scheme 60*).

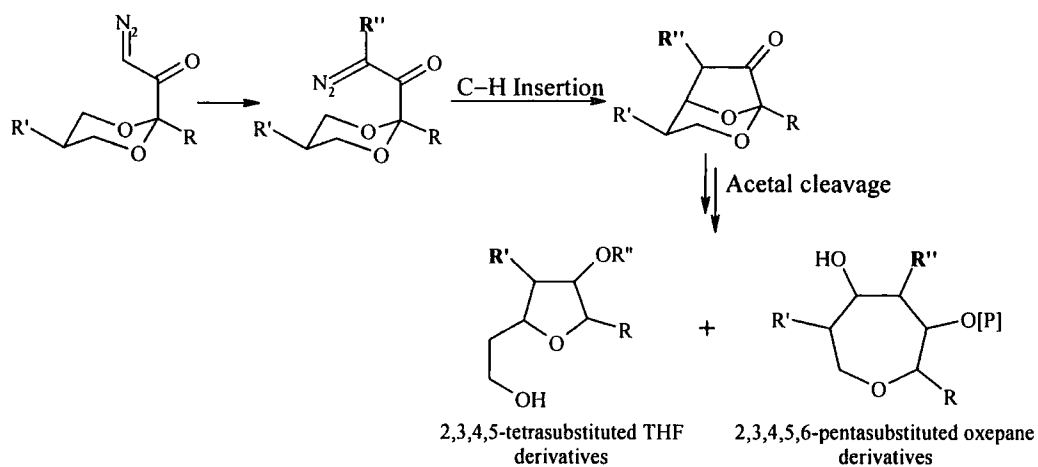


**Scheme 60 – Future work using different heteroatoms
in the bicyclic template**

3.2.2 The diazocarbonyl compound

The strategy adopted within this project and the previous work within the group involved the use of a diazoketone resulting in an acceptor metallocarbene in the C–H insertion sequence. More research will be done exploring the possibility of substituting the active diazocarbon to obtain different diazocompounds to form an acceptor/acceptor or acceptor/donor metallocarbenes which

would enable us to investigate the new region and stereoselectivity in the C–H insertion reaction and subsequently the acetal cleavage step (*Scheme 61*).



Scheme 61 – Route to higher substitution pattern

CHAPTER IV

EXPERIMENTAL

4 CHAPTER (IV): EXPERIMENTAL PROCEDURES

4.1 General procedure

All solvents were dried and distilled by standard procedures¹ and stored under nitrogen before use,

- i. Petroleum ether (Petrol) was distilled and collected fractions correspond to a boiling point of 40-60°C
- ii. THF and ether were distilled over sodium / benzophenone
- iii. Dichloromethane over calcium hydride
- iv. Toluene over sodium.

All sensitive reactions were performed under an inert atmosphere and done in dried glassware.

All reactions were followed by thin layer chromatography (TLC) using normal phase silica plates which were revealed by UV (254 nm) for components with active chromophores or visualised by stains (phosphomolybdic acid in ethanol) and revealed by heating (heat-gun) or followed by gas Chromatography (GC) carried out on a Hewlett-Packard 5890 series II fitted with a 25 cm column and connected to a flame ionization detector.

Purification of the products was performed by flash column chromatography with normal phase silica gel (Kieselgel 40-60 μm silica) using an appropriate choice of eluent (or solvent system).

Infrared spectra were recorded as thin films between NaCl plates for liquids or as solutions in DCM for solids or using a golden gate (ATR) on a Perkin-Elmer FT-IR 1600 spectrometer.

¹H and ¹³C NMR spectra were acquired in CDCl₃ unless otherwise stated on a Varian Mercury 200 (¹H at 199.975 MHz, ¹³C at 50.289 MHz, ¹⁹F at 282.2 MHz), Bruker AM-250

(^1H at 250.133 MHz, ^{13}C at 62.896 MHz), Varian Unity 300 (^1H at 299.908 MHz, ^{13}C at 75.412 MHz, ^{19}F at 376 MHz) or Varian VXR-400 (^1H at 399.968 MHz, ^{13}C at 100.572 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 internal reference:

CHCl_3 $\delta_{\text{H}} = 7.26$ ppm; $\delta_{\text{C}} = 77.0$ ppm

CHD_2OD $\delta_{\text{H}} = 3.41$ ppm, 1.09 ppm; $\delta_{\text{C}} = 49.8$ ppm

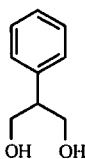
Assignment of stereochemistry was carried out with help of COSY, HSQC, HMBC and NOESY experiments.

Low Resolution Mass Spectra were obtained on a VG Analytical 7070E or VG Autospec Organic Mass spectrometer.

Gas-Chromatography Mass Spectra (GC-MS) were taken using a Hewlett Packard 5890 series II gas chromatograph equipped with a 25 cm column connected to a VG Mass Lab Trio 1000. Electrospray mass spectra (ES) were obtained on micromass LCT Mass Spectrometer. High-resolution mass spectra (HRMS) were performed on a Micromass Autospec Mass Spectrometer by Durham University Mass Spectroscopy service

4.2 Experimental details

2-Phenyl-propane-1,3-diol (1)



Molecular Formula: $\text{HOCH}_2\text{CH}(\text{C}_6\text{H}_5)\text{CH}_2\text{OH}$

mp: 53-56 °C (lit.)

Molecular Weight: 152.19

Hazard Codes: Xi

CAS Number: 1570-95-2

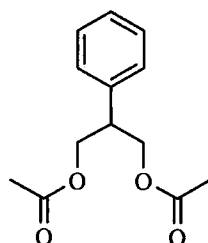
Risk Statements: 41

MDL number: MFCD00236056

Safety Statements: 26-39

The starting material (1) was obtained commercially from Lancaster-Avocado and then from Sigma Aldrich.

Acetic acid 3-acetoxy-2-phenyl-propyl ester (2)^{2,3}

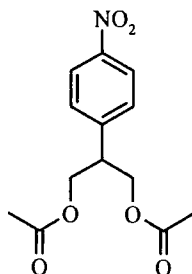


To a solution of (1) (10 g, 0.066 mol) in dry DCM (150 ml), was added Et_3N (91.4 ml, 0.66 mol, 10 eq.) and 4-DMAP (0.122 g, 13.14 mmol, 0.2 eq.). Acetic anhydride (24.9 ml, 0.26 mol, 4 eq.) was added dropwise to the reaction mixture. The reaction mixture was stirred for overnight at RT. After completion, the reaction mixture was transferred to an ice bath; 10 ml of 1M HCl were added to the reaction mixture and the phases were allowed to separate. The aqueous phase was re-extracted with EtOAc twice (2×10 ml). The combined organic phase was washed with brine, sat. NaHCO_3 and dried over dry MgSO_4 and filtered. The solvent was removed *in vacuo* yielding the crude product as viscous yellow oil. The crude product was purified by chromatography (cyclohexane/EtOAc, 95:5 then 8:2) to give to give (2). (13.8 g, 89% yield)

ν_{max} (thin film)/ cm^{-1} : 1733 (CO); 761, 700 (mono-substitution). δ_{H} (200 MHz): 7.35-7.19 (5H, m, *Ar-H*); 4.32 (4H, d, *J* 6.6, 2×*1-H*, 2×*3-H*); 3.30 (1H, m, *J* 6.6, *2-H*); 2.0 (6 H, s, 2×COCH₃). δ_{C} (62.9 MHz): 171.1 (2×OCOMe); 138.6 (*C-1'*); 128.9 (*C-2', C-6'*); 128.2 (*C-3', C-5'*); 127.7

(*C-4'*); 65.1 (*C-1, C-3*); 43.9 (*C-2*); 21.1 ($2\times\text{COCH}_3$). m/z (ES⁺): 259 (M+Na)⁺; 177 (M-OCOMe)

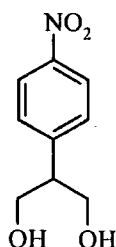
Acetic acid 3-acetoxy-2-(4-nitro-phenyl)-propyl ester (**3a**)^{2,3}



To a solution of (**2**) (12.27 g, 0.052 mol), (4.22 g, 1.012 eq.) of NH_4NO_3 in 100 ml of anhydrous chloroform, trifluoroacetic anhydride (29.4 ml, 4 eq.) was added dropwise. The mixture was stirred for 2 hours at 0 °C then allowed to warm to RT and stirred overnight. Once the reaction is complete, observed by complete dissolution of ammonium nitrate, it was poured to ice-water mixture and extracted with chloroform twice. The combined organic extracts were dried over MgSO_4 and solvent was evaporated *in vacuo* to yield a mixture of (**3**) and the *ortho* isomer (Ratio 3.8:1 respectively) as a greasy yellowish solid (13.0 g, 79% yield). Separation by column chromatography failed. Subsequent separation was possible *via* precipitation of the free diol of the major isomer from EtOAc upon cooling.

mp: 49–50°C (EtOAc). ν_{max} (ATR)/ cm^{-1} : 1733 (CO); 1525, 1345 (NO_2). δ_{H} (400 MHz): 8.20 (2H, d, J 8.9, 3'-H, 5'-H); 7.43 (2H, d, J 8.9, 2'-H, 6'-H); 4.35 (4H, d, J 6.6, 2×1-H, 2×3-H); 3.45 (1 H, p, J 6.6, 2-H); 2.02 (6H, s, $2\times\text{COCH}_3$). δ_{C} (100.5 MHz): 170.7 ($2\times\text{OCOMe}$); 146.6 (*C-4'*); 140.0 (*C-1'*); 130.6 (*C-2', C-6'*); 124.0 (*C-3', C-5'*); 64.0 (*C-1, C-3*); 42.0 (*C-2*); 22.2 ($2\times\text{COCH}_3$). m/z (ES⁺): 304 (M+Na)⁺

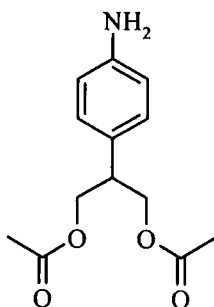
2-(4-Nitro-phenyl)-propane-1,3-diol (**4**)²



A mixture of (3) & the *ortho* isomer (5.7 g, 0.02 mol) was dissolved in dry MeOH to form **solution 'A'**. A 1M solution of NaOMe was prepared by dissolving (0.92 gm, 2 eq.) of Na metal in 40 ml of MeOH to form **solution 'B'**. **Solution 'B'** was added slowly to a stirred **solution 'A'**, and allowed to react at RT. The reaction was followed by TLC and needed 30 ~ 40 minutes to complete. Once completed, the solvent volume was reduced *in vacuo* and 5 ml of brine were added followed by extraction with EtOAc three times and continuous extraction overnight. The combined organic extracts were dried over MgSO₄ to give a mixture of (4) and the *ortho* isomer as yellow heavy oil (3.92 g, 98% yield). Dissolving the crude yield in a minimum amount of EtOAc and placing the resulting solution in ice bath led to precipitation of Compound (4) in pure form (3.43 g, 86% yield).

mp: 83–86°C (EtOAc). ν_{\max} (ATR)/cm⁻¹: 3500-3008 (b) (OH); 1513, 1345 (NO₂). δ_{H} (400 MHz): 8.20 (2H, d, *J* 8.8, 3'-H, 5'-H); 7.45 (2H, d, *J* 8.8, 2'-H, 6'-H); 4.05 (2H, dd, *J*₁=10.6, *J*₂=6.8, 1-H_a, 3-H_a); 4.00 (2H, dd, *J*₁=10.6, *J*₂=5.6, 1-H_b, 3-H_b); 3.20 (1H, tt, *J*₁=6.8, *J*₂=5.6, H-2); 1.90 (2H, bs, 2xOH). δ_{C} (100.5 MHz): 147.8 (C-1'); 147.2 (C-4'); 129.6 (C-2', C-6'); 124.2 (C-3', C-5'); 65.8 (C-1, C-3); 50.0 (C-2). *m/z* (ES⁺): 197 (M)⁺. **EA:** Found: C 54.51, H 5.57, N 6.84 %, C₉H₁₁NO₄ requires: C 54.82, H 5.62, N 7.10 %.

Acetic acid 3-acetoxy-2-(4-amino-phenyl)-propyl ester (5)^{3,4}

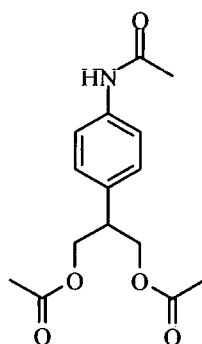


After successful separation of pure (4), compound (3) was re-prepared following the same procedure used for the protection of diol (1) to obtain pure *p*-isomer. To a solution of (3) (5.61 g, 20.0 mmol) in dry EtOH (25 ml) was added PtO₂.xH₂O 79% (127 mg, 0.440 mmol). A hydrogen gas source was attached to the reaction flask under 1 atm. The reaction mixture was stirred for 12 h at RT. Once finished, nitrogen gas was bubbled through the reaction mixture several times. Then the mixture was filtered through celite to remove the catalyst. The reaction solvent was

evaporated *in vacuo* yielding the crude product as yellowish solid. The crude product was purified by column chromatography (Petrol/EtOAc, 9:1 then 4:1) to give (5). (4.48 g, 89% yield)

mp: 73–75°C (EtOAc/Pet. ether). ν_{\max} (DCM solution)/ cm^{-1} : 3230, 3356 (NH₂); 1729 (CO) cm^{-1} . δ_{H} (300 MHz): 7.01 (2H, d, *J* 8.4, 3'-H, 5'-H); 6.63 (2H, d, *J* 8.4, 2'-H, 6'-H); 4.27 (4H, d, *J* 6.9, 1-H, 3-H); 3.64 (2H, bs, NH₂); 3.20 (1H, m, *J* 6.9, 2-H); 2.01 (6H, s, 2×COCH₃). δ_{C} (62.9 MHz): 170.9 (2×CO); 145.6 (C-1'); 128.5 (C-2', C-6'); 128.0 (C-4'); 115.4 (C-3', C-5'); 64.9 (C-1, C-3); 42.95 (C-2); 20.8 (2×COCH₃). *m/z* (ES⁺): 274 (M+Na)⁺. *m/z* (HRMS ES⁺): Found: 274.1072 (M+Na)⁺, C₁₃H₁₇NO₄ requires: 274.1055,

Acetic acid 3-acetoxy-2-(4-acetylamino-phenyl)-propyl ester (6)³

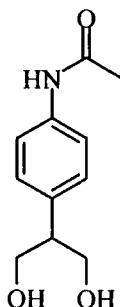


To a solution of (5) (3.87 g, 15.42 mmol) in dry DCM (30 ml), was added Et₃N (5.4 ml, 38.56 mmol, 2.5 eq.). AcCl (1.2 ml, 17 mmol, 1.1 eq.) was added dropwise to the reaction mixture. The reaction mixture was stirred for 12 h at RT. After completion of the reaction, 10 ml H₂O were added to the reaction mixture and the phases were allowed to separate. The aqueous phase was re-extracted with EtOAc twice (2×10 ml). The combined organic phase was washed with brine, dried over dry MgSO₄ and filtered. The solvent was removed *in vacuo* yielding the crude product as white solid. The crude product was purified by chromatography (Petrol/EtOAc, 9:1) to give (6). (4.3 g, 95% yield)

mp: 99–102°C (EtOAc/Pet. ether). ν_{\max} (DCM solution)/ cm^{-1} : 1735 (OCO); 1686 (NHCO). δ_{H} (500 MHz): 7.46 (2H, d, *J* 8.5, 3'-H, 5'-H); 7.19 (2H, d, *J* 8.5, 2'-H, 6'-H); 4.30 (4H, d, *J* 6.5, 1-H, 3-H); 3.28 (1H, m, *J* 6.5, 2-H); 2.18 (3H, s, NHCOCH₃); 2.03 (6H, s, 2×COCH₃). δ_{C} (62.9 MHz): 170.8 (2×OCOMe); 168.2 (NHCOMe); 137.2 (C-1'); 134.2 (C-4'); 128.5 (C-2', C-6');

120.1 (*C-3'*, *C-5'*); 64.8 (*C-1*, *C-3*); 43.3 (*C-2*); 24.5 (NHCOMe); 20.8 (2×COCH₃). *m/z* (ES⁺): 316 (M+Na)⁺, *m/z* (HRMS ES⁺): Found: 316.1152 (M+Na)⁺, C₁₁H₁₃NO₅Na requires: 316.1161

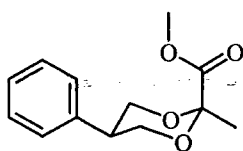
N-[4-(2-Hydroxy-1-hydroxymethyl-ethyl)-phenyl]-acetamide (7)



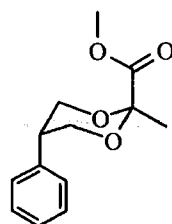
To a solution of (6) (2 g, 6.83 mmol) in dry MeOH (10 ml), 2 eq. of NaOMe solution was added as 1M solution in MeOH. The reaction mixture was stirred for 40 min at RT. Once completion of the reaction achieved, solvent volume was reduced under vacuum, (5 ml) of brine were added and the reaction mixture was extracted with EtOAc (4×20 ml). The combined organic phase was then dried over MgSO₄, filtered and solvent removed *in vacuo* to give the crude product which was purified by chromatography (DCM/MeOH, 9:1 then 4:1) to give to give to give (7). (1.382 g, 97% yield)

mp: 96–99°C (EtOAc). **v_{max} (ATR)/cm⁻¹:** 3266 (intramolecular H-bonded OH); 1635 (NHCO); 1602; 1545; 1514; 823 (*para*-substitution). **δ_H (500 MHz) CD₃OD:** 7.46 (2H, d, *J* 8.5, 3'-H, 5'-H); 7.19 (2H, d, *J* 8.5, 2'-H, 6'-H); 3.86 (2H, dd, *J*₁=6.5, *J*₂=11, 1-H_a, 3-H_a); 3.77 (2H, dd, *J*₁=6.5, *J*₂=11, 1-H_b, 3-H_b); 2.90 (1H, m, 2-H); 2.09 (3H, s, NHCOCH₃). **δ_C (62.9 MHz):** 171.3 (NHCOMe); 138.1 (*C-1'*); 137.9 (*C-4'*); 129.6 (*C-2'*, *C-6'*); 121.4 (*C-3'*, *C-5'*); 64.6 (*C-1*, *C-3*); 51.7 (*C-2*); 24.2 (NHCOMe). ***m/z* (ES⁺):** 232 (M+Na)⁺. ***m/z* (HRMS ES⁺):** Found: 232.09425 (M+Na)⁺, C₁₁H₁₅NO₃ requires: 232.09441

2-Methyl-5-phenyl-[1,3]dioxane-2-carboxylic acid methyl ester (8a/8b)²



(8a)



(8b)

To a stirred solution of (1) (10 g, 0.066 mol) and methyl pyruvate (12 ml, 0.132 mol, 2 eq.) in AcCN (80 ml), $\text{BF}_3 \cdot \text{OEt}_2$ (16.2 ml, 0.132 mmol, 2 eq.) was added dropwise. The reaction mixture was stirred at RT overnight. Using sat. aq. NaHCO_3 , the reaction was quenched and stirred for 30 min. The resulting mixture volume was reduced *in vacuo* to one third of original volume and then extracted with EtOAc (3×25 ml). The combined organic extracts were dried over MgSO_4 , filtered and concentrated and separated by chromatography (Petrol/EtOAc, 9:1) to give total of 13.82 g (89% yield) in the ratio (8a) major: (8b) minor equal 7:1

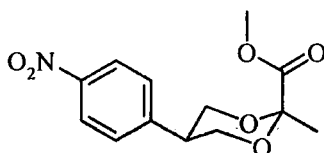
Characterization for (8a)

mp: 65–67°C (Cyclohexane). ν_{max} (ATR)/ cm^{-1} : 1724 (OCO); 1143 (COC); 724, 659 (*mono-substitution*). δ_{H} (500 MHz): 7.30 (3H, m, 3'-H, 4'-H, 5'-H); 7.13 (2H, d, J 7.5, 2'-H, 6'-H); 4.10 (2H, dd, $J_1=5$, $J_2=12.5$, 4- H_{eq} , 6- H_{eq}); 3.90 (2H, t, J 12.5, 4- H_{ax} , 6- H_{ax}); 3.89 (3H, s, COOCH_3); 3.25 (1H, tt, $J_1=5$, $J_2=12.5$, 5-H); 1.59 (3H, s, 2- CH_3). δ_{C} (125.7 MHz): 171.3 (COMe); 137.5 (C-1'); 129.1 (C-3', C-5'); 127.9 (C-2', C-6'); 127.8 (C-4'); 98.4 (C-2); 68.4 (C-4, C-6); 52.9 (COOMe); 40.2 (C-5); 26.3 (2-Me). m/z (ES+): 259 (M+Na)⁺. EA: Found: C 66.06, H 6.89 %, $\text{C}_{13}\text{H}_{16}\text{O}_4$ requires: C 66.07, H 6.84 %

Characterization for (8b)

mp: 55–57°C. δ_{H} (500 MHz): 7.49 (2H, d, J 1.5, 2'-H, 6'-H); 7.35 (2H, t, J 7.5, 3'-H, 5'-H); 7.27 (1H, t, J 7.5, 4'-H); 4.26 (2H, dd, $J_1=3.8$, $J_2=12.5$, 4- H_{eq} , 6- H_{eq}); 4.12 (2H, dd, $J_1=3$, $J_2=12.5$, 4- H_{ax} , 6- H_{ax}); 3.87 (3H, s, COOCH_3); 2.75 (1H, tt, $J_1=3.5$, $J_2=3$, 5-H); 1.61 (3H, s, 2- CH_3). δ_{C} (125.7 MHz): 171.1 (COMe); 141.9 (C-1'); 128.8 (C-3', C-5'); 128.4 (C-2', C-6'); 127.1 (C-4'); 98.5 (C-2); 67.1 (C-4, C-6); 52.9 (COOMe); 38.8 (C-5); 24.9 (2-Me). m/z (ES+): 259 (M+Na)⁺. EA: Found: C 66.02, H 6.87 %, $\text{C}_{13}\text{H}_{16}\text{O}_4$ requires: C 66.07, H 6.84 %

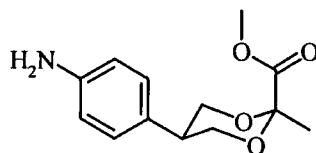
2-Methyl-5-(4-nitro-phenyl)-[1,3]dioxane-2-carboxylic acid methyl ester (9)⁵



To a solution of (**8a**) (10 g, 0.042 mol), (10.3 g, 1.012 eq.) of NH_4NO_3 in 85 ml of anhydrous chloroform, trifluoroacetic anhydride (29.9 ml, 4 eq.) was added dropwise. The mixture was stirred for 2 hours at 0°C then allowed to warm to RT and stirred overnight. Once the reaction is complete, it was poured to ice-water mixture and extracted with chloroform twice. The combined organic extracts were dried over MgSO_4 and solvent was evaporated *in vacuo* and purified by column chromatography (Petrol/EtOAc, 9:1) to yield (**9**) as a white solid re-crystallised from EtOAc (11.1 g, 93% yield).

mp: 119–121 $^\circ\text{C}$ (EtOAc). ν_{max} (ATR)/ cm^{-1} : 1743 (CO); 1514, 1350 (NO_2); 1143 (COC). δ_{H} (500 MHz): 8.18 (2H, d, $J=8.5$, 3'-H, 5'-H); 7.31 (2H, d, $J=8.5$, 2'-H, 6'-H); 4.11 (2H, dd, $J_1=5$, $J_2=12$, 4- H_{eq} , 6- H_{eq}); 3.93 (2H, t, J 12, 4- H_{ax} , 6- H_{ax}); 3.90 (3H, s, COOCH_3); 3.77 (1H, tt, $J_1=5$, $J_2=12$, 5-H); 1.60 (3H, s, 2- CH_3). δ_{C} (125.7 MHz): 170.9 (COMe); 147.6 (C-4'); 144.9 (C-1'); 128.8 (C-2', C-6'); 124.7 (C-3', C-5'); 98.4 (C-2); 67.7 (C-4, C-6); 53.1 (COOMe); 40.3 (C-5); 26.1 (2-Me). m/z (ES+): 304 (M+Na) $^+$. m/z (HRMS ES+): Found: 304.0808 (M+Na) $^+$, $\text{C}_{13}\text{H}_{15}\text{NO}_6$ requires: 304.0797

5-(4-Amino-phenyl)-2-methyl-[1,3]dioxane-2-carboxylic acid methyl ester (**10**)⁴

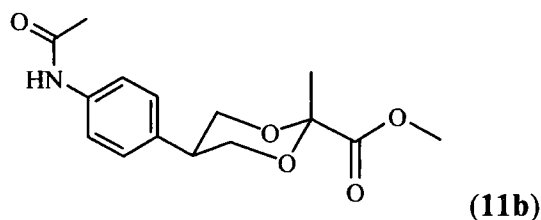
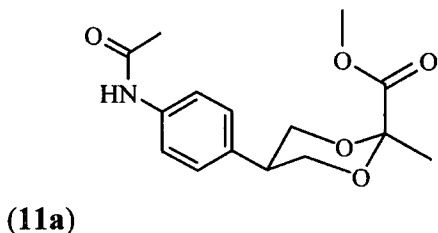


To a solution of (**9**) (4.8 g, 17.1 mmol) in dry Toluene (40 ml) was added $\text{PtO}_2 \cdot x\text{H}_2\text{O}$ 79% (316.5 mg, 1.1 mmol). A hydrogen gas source was attached to the reaction flask under atmospheric pressure. The reaction mixture was stirred for 48 h at RT. Once the reaction is completed, nitrogen gas was bubbled through the reaction mixture several times. Then it was filtered through celite to remove the catalyst. The reaction solvent was evaporated *in vacuo* yielding the crude product as yellowish solid which was purified by column chromatography (Petrol/EtOAc, 9:1 then 4:1) to give (**10**). (3.83 g, 89% yield)

mp: 79–82 $^\circ\text{C}$ (EtOAc). ν_{max} (ATR)/ cm^{-1} : 3476, 3402 (NH_2); 1742 (CO); 1143 (COC). δ_{H} (300 MHz): 6.92 (2H, d, J 8.4; 3'-H, 5'-H); 6.66 (2H, d, J 8.4; 2'-H, 6'-H); 4.04 (2H, dd, $J_1=4.8$ H-4, $J_2=12$, 4- H_{eq} , 6- H_{eq}); 3.88 (3H, s, COOCH_3); 3.82 (2H, t, J 12, 4- H_{ax} , 6- H_{ax}); 3.14 (1H, tt, $J_1=4.8$, $J_2=12$, 5-H); 1.58 (3H, s, 2- CH_3). δ_{C} (62.9 MHz): 171.5 (COMe); 146 (C-1'); 128.5 (C-

2', C-6'); 127 (C-4'); 116 (C-3', C-5'); 99.2 (C-2); 68.3 (C-4, C-6); 42.5 (COOMe); 39 (C-5); 26.2 (2-Me). m/z (ES⁺): 274 (M+Na)⁺ 252 (M+H)⁺. m/z (HRMS ES⁺): Found: 274.10446 (M+Na)⁺, C₁₃H₁₇NO₄ requires: 274.10498

5-(4-Acetylamino-phenyl)-2-methyl-[1,3]dioxane-2-carboxylic acid methyl ester (11a/11b)



▪ **Method I⁵**

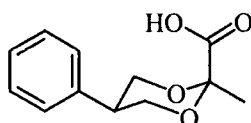
To a stirred suspension of (7) (300 mg, 1.44 mmol) and methyl pyruvate (2.16 ml, 2.87 mmol, 2 eq.) in AcCN (20 ml), BF₃·OEt₂ (0.35 ml, 2.87 mmol, 2 eq.) was added dropwise. The reaction mixture was stirred at RT for 48 h. Using sat. aq. NaHCO₃, the reaction was quenched and stirred for 30 min. The resulting mixture volume was reduced *in vacuo* to one third of the original volume and then extracted with EtOAc (3×25 ml). The combined organic extracts were dried over MgSO₄, filtered and concentrated. Both peaks of (11a) and (11b) could be detected in the ¹H NMR spectrum. Separation by chromatography failed. Crude yield was 45% with rough ratio of (11a) major : (11b) minor as 3 : 1 respectively.

▪ **Method II**

To a solution of (10) (4.2 g, 16.73 mmol) in dry DCM (30 ml), was added Et₃N (5.8 ml, 41.83 mmol, 2.5 eq.). AcCl (1.4 ml, 20.08 mmol, 1.2 eq.) was added dropwise to the reaction mixture. The reaction mixture was stirred for 12 h at RT. After completion of the reaction, 10 ml H₂O were added to the reaction mixture and the phases were allowed to separate. The aqueous phase was re-extracted with ethyl acetate twice (2×10 ml). The combined organic phase was washed with brine, dried over dry MgSO₄ and filtered. The solvent was removed *in vacuo* yielding the crude product as white solid. The crude product was purified by chromatography (Petrol/EtOAc, 9:1) and re-crystallised from EtOAc-hexane to yield (11a). (4.31 g, 88% yield)

Characterization for (11a)

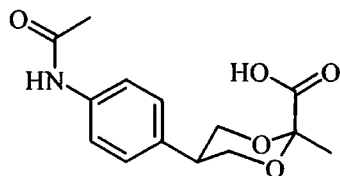
mp: 107–111°C (EtOAc-hexane). ν_{\max} (ATR)/ cm^{-1} : 3318 (NH); 1742 (CO); 1687 (NHCO). δ_{H} (300 MHz): 7.43 (2H, d, J 8.4, 3'-H, 5'-H); 7.20 (1H, broad s, CONH); 7.08 (2H, d, J 8.4, 2'-H, 6'-H); 4.06 (2H, dd, $J_1=4.5$, $J_2=12$, 4- H_{eq} , 6- H_{eq}); 3.88 (3H, s, COOCH₃); 3.85 (2H, t, J 12, 4- H_{ax} , 6- H_{ax}); 3.22 (1H, tt, $J_1=4.8$, $J_2=12$, 5-H); 2.16 (3H, s, NHCOCH₃); 1.58 (3H, s, 2-CH₃). δ_{C} (62.9 MHz): 171.5 (COOMe); 168.5 (NHCOMe); 137.5 (C-1'); 133.8 (C-4'); 128.2 (C-2', C-6'); 120.5 (C-3', C-5'); 99.1 (C-2); 68.2 (C-4, C-6); 42.7 (COOMe); 39.8 (C-5); 26.4 (2-Me); 25 (NHCOMe). m/z (ES⁺): 316 (M+Na)⁺ 294 (M+H)⁺. m/z (HRMS ES⁺): Found 316.11484 (M+Na)⁺, C₁₅H₁₉NO₅ requires: 316.11554

2-Methyl-5-phenyl-[1,3]dioxane-2-carboxylic acid (12)²

To a solution of (8a) (9.5 g, 40.2 mmol) in a 50 ml of a THF/H₂O 1:1 mixture, 4.5 eq. of 3M solution of NaOH were added. The reaction mixture was stirred for 2 h at RT. After completion of the reaction, the reaction mixture was transferred to ice bath, 2M HCl was added until pH 3 attained and the reaction mixture was extracted with EtOAc (3×20 ml). The combined organic phase was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give the product as white solid (12) and re-crystallised from EtOAc. (7.03 g, 80% yield)

mp: 132–135°C (EtOAc). ν_{\max} (ATR)/ cm^{-1} : 3260-2840 (COOH); 1735 (COOH). δ_{H} (500 MHz): 7.30 (3H, m, *Ar-H*); 7.16 (2H, d, J 8.5, 2'-H, 6'-H); 4.15 (2H, dd, $J_1=5$, $J_2=12.5$, 4- H_{eq} , 6- H_{eq}); 3.99 (2H, t, J 12, 4- H_{ax} , 6- H_{ax}); 3.28 (1H, tt, $J_1=5$, $J_2=11.5$, 5-H); 1.677 (3H, s, 2-CH₃). δ_{C} (125.7 MHz): 175.0 (COOMe); 137.2 (C-1'); 129.1 (C-3', C-5'); 127.9 (C-2', C-6'); 127.8 (C-4'); 98.1 (C-2); 68.5 (C-4, C-6); 40.1 (C-5); 26.3 (2-Me). m/z (ES⁻): 221 (M-H)⁻. *EA*: Found: C 64.81, H 6.38 %, C₁₂H₁₄O₄ requires: C 66.85, H 6.36 %

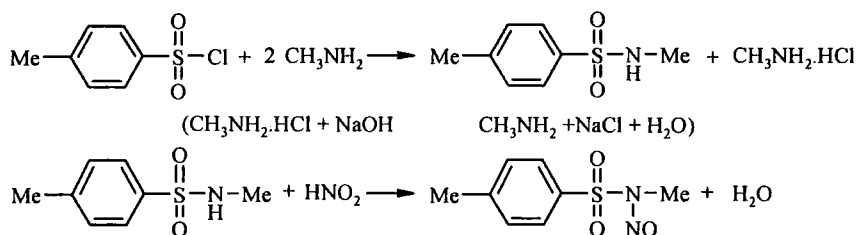
5-(4-Acetylamino-phenyl)-2-methyl-[1,3]dioxane-2-carboxylic acid (13)⁵



To a solution of (**11a**) (4.3 g, 14.68 mmol) in a 20 ml of a THF/H₂O 1:1 mixture, 4.5 eq. of 3M solution of NaOH were added. The reaction mixture was stirred for 2 h at RT. After completion of the reaction, the reaction mixture was transferred to ice bath, 2M HCl was added until pH 3 attained and the reaction mixture was extracted with EtOAc (3×20 ml). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo* to give the product as white solid (**13**) and re-crystallised from EtOAc. (3.82 gm, 93% yield)

mp: 160–164°C (EtOAc). ν_{\max} (ATR)/cm⁻¹: 3710-2700 (b) (COOH); 1761 (COOH monomer); 1710 (COOH dimer); 1680 (NHCO); 1109 (COC). δ_{H} (300 MHz): 7.47 (2H, d, *J* 8.4, 3'-H, 5'-H); 7.39 (1H, broad s, MeCONH); 7.09 (2H, d, *J* 8.4, 2'-H, 6'-H); 4.08 (2H, dd, *J*₁=3.9, *J*₂=11.4, 4-H_{eq}, 6-H_{eq}); 3.91 (2H, t, *J* 11.4, 4-H_{ax}, 6-H_{ax}); 3.22 (1H, tt, *J*₁=5.4, *J*₂=11.6, 5-H); 2.19 (3H, s, NHCOCH₃); 1.65 (3H, s, 2-CH₃). δ_{C} (62.9 MHz): 173.6 (COOMe); 168.9 (NHCOMe); 144.1 (C-1'); 133.2 (C-4'); 128.4 (C-2', C-6'); 120.6 (C-3', C-5'); 98.1 (C-2); 68.4 (C-4, C-6); 39.5 (C-5); 26.1 (2-Me); 24.8 (NHCOMe). *m/z* (ES⁺): 302 (M+Na)⁺ 280 (M+H)⁺. *m/z* (HRMS ES⁺): Found: 280.11835 (M+H)⁺, C₁₄H₁₇NO₅ requires: 280.11795

Diazald® (*p*-Tolylsulfonylmethylnitrosamide) preparation⁶



A total of 20 g (0.105 mol) of *p*-toluenesulfonyl chloride was divided to 3 portions of 11.88, 5.63 and 2.5 g. A 25M solution of NaOH (4.38 g) was prepared by dissolving the amount in 4.4 ml H₂O with cooling. The first portion (11.88 g) was added over 5 minutes to 10.88 ml of 40% solution of methylamine. The temperature was kept at 80–90 °C in order to maintain the

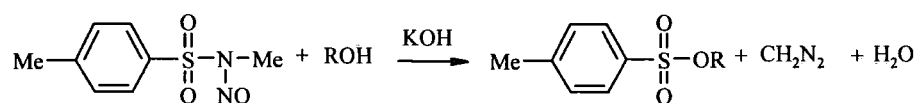
sulfonylmethylamine (m.p. 78 °C) in molten condition. The reaction mixture was stirred monitored by universal pH indicator until it becomes acidic (pH 5~6). Once the mixture had become acidic, 3.1 ml of the alkali solution was added, followed by immediate addition of the second portion (5.63 g) of the *p*-toluenesulfonyl chloride. Once again the solution had become acidic; 1.6 ml of the alkali was added followed by the final portion of the *p*-toluenesulfonyl chloride. When the reaction mixture became acidic, the remainder amount of NaOH was added.

The walls of the reaction flask were rinsed with 5 ml of H₂O and the mixture was heated at 100 °C for 15 minutes. The hot mixture was carefully poured into 94 ml of glacial acetic acid and the original flask was rinsed with 15.6 ml of acetic acid.

The resultant solution was cooled to 7 °C and a solution of 7.75 g of NaNO₂ dissolved in 15.63 ml of H₂O was added slowly *via* a dropping funnel over 45 minutes. Temperature was kept below 10 °C. The reaction mixture was stirred for more 15 minutes after addition was complete. The nitroso compound separates as yellow crystalline product.

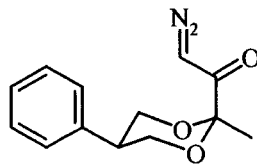
62.5 ml of H₂O was added to the mixture and the product was separated by suction filtration and washed with 31.25 ml H₂O. The product was washed again until complete absence of acetic acid odour and dried under vacuum. (Yield 19.49 g 87%)

Diazomethane – non-ethanolic preparation⁷



A solution of Diazald[®] (10 g, 46.7 mmol) in 60 ml of anhydrous ether was slowly dripped into a mixture of KOH (2.8 g, 50 mmol) and di(ethyleneglycol)methyl ether (16.4 ml, 140 mmol) in 9.4 ml of a 1:1 mixture H₂O/ether at temperature of 60 °C. The resultant diazomethane was distilled as an ethereal solution. Additional amount of ether (20~60 ml) was dripped to the distilling mixture until the distillate was colourless. The resultant ethereal solution is assumed to have 32.7 mmol of diazomethane according to the literature (yield 70%).

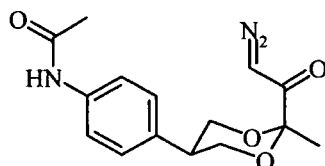
2-Diazo-1-(2-methyl-5-phenyl-[1,3]dioxan-2-yl)-ethanone (14)²



A solution of **(12)** (3.33 g, 0.015 mol) and Et₃N (2.5 ml, 1.2 eq.) in anhydrous CH₂Cl₂ (50ml) was cooled to -20 °C and isobutylchloroformate (2.3 ml, 1.2 eq.) was added dropwise *via* syringe at -20 °C. The reaction mixture was stirred until complete formation of the mixed anhydride then an excess of an ethereal solution of diazomethane was added *via* syringe and the reaction mixture allowed to warm to RT overnight. When the reaction was complete, argon was bubbled through the solution with rigorous stirring to remove the excess of diazomethane and a small amount of dilute acetic acid was added. The resulting mixture was then extracted with EtOAc and washed with NH₄Cl (3×25 ml), NaHCO₃ (3×25 ml) and brine (3×25 ml). The combined organic extracts were then dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by chromatography (Petrol/EtOAc, 95:5 then 4:1) to provide **(14)** as a white solid. (2.564 g, 69% yield).

mp: 78–82°C (EtOAc). ν_{\max} (DCM Solution)/cm⁻¹: 2111 (CHN₂); 1653 (COCHN₂). δ_{H} (400 MHz): 7.30 (3H, m, *Ar-H*); 7.13 (2H, m, *2'-H*, *6'-H*); 5.78 (1H, s, COCHN₂); 4.06 (2H, dd, $J_1=4.8$, $J_2=12$, *4-H_{eq}*, *6-H_{eq}*); 3.93 (2H, t, J 12, *4-H_{ax}*, *6-H_{ax}*); 3.23 (1H, tt, $J_1=4.8$, $J_2=12$, *5-H*); 1.51 (3H, s, *2-CH₃*). δ_{C} (62.9 MHz): 194.3 (COCHN₂); 137.4 (*C-1'*); 129.1 (*C-3'*, *C-5'*); 127.9 (*C-2'*, *C-6'*); 127.8 (*C-1'*); 100.6 (*C-2*); 68.1 (*C-4*, *C-6*); 54.1 (COCHN₂); 40.5 (*C-5*); 26.4 (*2-Me*). m/z (ES⁺): 269 (M+Na)⁺. *EA*: Found: C 63.31, H 5.74, N 11.37 %, C₁₃H₁₄N₂O₃ requires: C 63.39, H 5.74, N 11.38 %

N-{4-[2-(2-Diazo-acetyl)-2-methyl-[1,3]dioxin-5-yl]phenyl}-acetamide **(15)**⁵

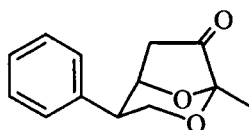


A solution of **(13)** (2 g, 7.17 mmol) and Et₃N (1.2 ml, 8.6 mmol, 1.2 eq.) in anhydrous CH₂Cl₂ (24ml) was cooled to -20 °C and isobutylchloroformate (1.2 ml, 8.6 mmol, 1.2 eq.) was added dropwise *via* syringe at -20 °C. The reaction mixture was stirred until complete formation of the

mixed anhydride then an excess of an ethereal solution of diazomethane was added *via* syringe and the reaction mixture allowed to warm to RT overnight. When the reaction was complete, argon was bubbled through the solution with rigorous stirring to remove the excess of diazomethane and a small amount of dilute acetic acid was added. The resulting mixture was then extracted with EtOAc and washed with NH₄Cl (3×25 ml), NaHCO₃ (3×25 ml) and brine (3×25 ml). The combined organic extracts were then dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by chromatography (Petrol/EtOAc, 9:1 then 4:1) to provide (15) as a white solid. (1.716 g, 79% yield).

mp: 162–163°C (EtOAc). ν_{\max} (DCM Solution)/cm⁻¹: 2116 (CHN₂); 1654 (NHCO). δ_{H} (300 MHz): 7.43 (2H, d, *J* 8.4, 3'-H, 5'-H); 7.15 (1H, broad s, MeCONH); 7.08 (2H, d, *J* 8.4, 2'-H, 6'-H); 5.77 (1H, s, COCHN₂); 4.03 (2H, dd, *J*₁=4.5, *J*₂=11.4, 4-H_{eq}, 6-H_{eq}); 3.88 (2H, t, *J* 11.4, 4-H_{ax}, 6-H_{ax}); 3.19 (1H, tt, *J*₁=4.5, *J*₂=11.4, 5-H); 2.17 (3H, s, NHCOCH₃); 1.50 (3H, s, 2-CH₃). δ_{C} (62.9 MHz): 194.1 (COCHN₂); 168.9 (NHCOMe); 137.5 (C-1'); 133.7 (C-4'); 128.4 (C-2', 6'-H); 120.6 (C-3', C-5'); 100.4 (C-2); 68.1 (C-4, C-6); 54.2 (COCHN₂); 39.8 (C-5); 26.3 (2-Me); 24.7 (NHCOMe). *m/z* (ES⁺): 326 (M+Na)⁺ 276 (M-N₂+H)⁺ *m/z* (HRMS ES⁺): Found: 326.11048 (M+Na)⁺, C₁₅H₁₇N₃O₄ requires: 326.11113,

1-Methyl-4-phenyl-2,8-dioxa-bicyclo[3.2.1]octan-7-one (16)²

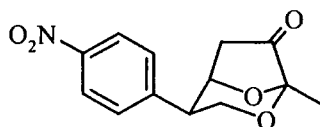


To a flame dried flask under nitrogen was added Rh₂(OAc)₄ (10 mg) and CH₂Cl₂ (20 ml) to form a solution of 1 mmol/L concentration of the Rh(II) catalyst. A solution of (14) (242 mg, 1 mmol) in anhydrous (10 ml) was then added *via* syringe pump over 20 hours and the reaction mixture stirred at room temperature. On completion of the reaction, the reaction mixture was filtered. The filtrate was then washed with sat. NaHCO₃ (3×25 ml), dried on MgSO₄, filtered and concentrated *in vacuo*. The resulting residue was then purified by chromatography (Petrol/EtOAc, 9:1) to give (16) as a white solid. (80.2 mg, 37% yield)

mp: 78–80°C (EtOAc). ν_{\max} (DCM Solution)/cm⁻¹: 1766 (CO); 1602; 1184 (COC). δ_{H} (300 MHz): 7.38-7.28 (3H, m, 3'-H, 4'-H, 5'-H); 7.13 (2H, d, *J* 12, 2'-H, 6'-H); 4.90 (1H, dd,

$J_1=3.3$, $J_2=7.2$, **5-H**); 4.22 (2H, d, J 7.2, **3-H**); 3.81 (1H, ddd, $J_1=3.3$, $J_2=7.2$, $J_3=10.5$, **4-H**); 2.59 (1H, dd, $J_1=7.2$, $J_2=18.3$, **6-H_a**); 2.42 (1H, d, J 18.3, **6-H_β**); 1.43 (3H, s, **1-CH₃**). δ_C (125.7 MHz): 210.9 (**C-7**); 136.5 (**C-1'**); 129.3 (**C-2'**, **C-6'**); 127.8 (**C-4'**); 127.4 (**C-3'**, **C-5'**); 98.4 (**C-1**); 76.4 (**C-5**); 64.3 (**C-3**); 42.4 (**C-4**); 36.6 (**C-6**); 18.4 (**1-Me**). m/z (ES⁺): 316 (M+Na+H₂O)⁺; 298 (M+Na)⁺. m/z (HRMS ES⁺): Found: 218.0865 (M+Na)⁺, C₁₃H₁₄O₃ requires: 218.0941

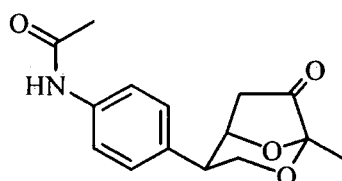
1-Methyl-4-(4-nitro-phenyl)-2,8-dioxa-bicyclo[3.2.1]octan-7-one (17)²



To a solution of (16) (0.11 g, 0.504 mmol), (0.409 g, 1.012 eq.) of NH₄NO₃ in 5 ml of anhydrous chloroform, trifluoroacetic anhydride (0.285 ml, 4 eq.) was added dropwise. The mixture was stirred for 2 hours at 0°C then allowed to warm to RT and stirred for 72 hours. Once the reaction is complete, it was poured to ice-water mixture and extracted with chloroform twice. The combined organic extracts were dried over MgSO₄ and solvent was evaporated *in vacuo* to yield (17) as a yellowish white solid (60 mg, 45% yield) after purification with flash chromatography (Petrol/EtOAc, 9:1).

mp: 148–150°C (EtOAc). ν_{\max} (DCM Solution)/cm⁻¹: 1766 (CO); 1602; 1517, 1347 (NO₂); 1184 (COC). δ_H (500 MHz): 8.22 (2H, d, J 8.5, **3'-H**, **5'-H**); 7.32 (2H, d, J 8.5, **2'-H**, **6'-H**); 4.94 (1H, dd, $J_1=3.5$, $J_2=7.5$, **5-H**); 4.24 (2H, m, **3-H**); 3.91 (1H, td, $J_1=3.5$, $J_2=7$, **4-H**); 2.64 (1H, dd, $J_1=7.5$, $J_2=18.5$, **6-H_a**); 2.29 (1H, d, J 18.5, **6-H_β**); 1.44 (3H, s, **1-CH₃**). δ_C (125.7 MHz): 209.8 (**C-7**); 147.9 (**C-4'**); 143.9 (**C-1'**); 128.4 (**C-2'**, **C-6'**); 124.5 (**C-3'**, **C-5'**); 98.3 (**C-1**); 75.8 (**C-5**); 63.8 (**C-3**); 42.4 (**C-4**); 36.5 (**C-6**); 18.2 (**1-Me**). m/z (ES⁺): 316 (M+Na+H₂O)⁺; 298 (M+Na)⁺

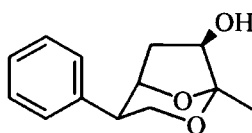
N-[4-(1-Methyl-7-oxo-2,8-dioxa-bicyclo[3.2.1]oct-4-yl)phenyl]-acetamide (19)^{5,7}



To a flame dried flask under nitrogen was added $\text{Rh}_2(\text{OAc})_4$ (10 mg) and CH_2Cl_2 (20 ml) to form a solution of 1 mmol/L concentration of the Rhodium catalyst. A solution of (15) (303 mg, 1 mmol) in anhydrous (10 ml) was then added *via* syringe pump over 20 hours and the reaction mixture stirred at room temperature. On completion of the reaction, the reaction mixture was filtered. The filtrate was then washed with sat. NaHCO_3 (aq.) (3×5 ml), dried on MgSO_4 , filtered and concentrated *in vacuo*. The resulting residue was then purified by chromatography (Petrol/EtOAc, 9:1 then 3:2) to give (19) as a white solid. (81.4 mg, 30% yield)

mp: 205–09°C (EtOAc). ν_{max} (DCM Solution)/ cm^{-1} : 3336 (NH); 1764 (OCO); 1654 (NHCO); 1601; 1516; 1182 (COC); 821 (*para*-substitution). δ_{H} (500 MHz): 7.47 (2H, d, J 8.5, 3'-H, 5'-H); 7.14 (1H, broad s, NHCOMe); 7.08 (2H, d, J 8.5, 2'-H, 6'-H); 4.86 (1H, dd, $J_1=3.5$, $J_2=7.5$, 5-H); 4.18 (2H, d, J 9, 3-H); 3.76 (1H, td, $J_1=3.5$, $J_2=9$, 4-H); 2.52 (1H, dd, $J_1=7.5$, $J_2=18.5$, 6-H $_{\alpha}$); 2.39 (1H, d, J 18.5, 6-H $_{\beta}$); 2.18 (3H, s, NHCOCH $_3$); 1.42 (3H, s, 1-CH $_3$). δ_{C} (62.9 MHz): 210.5 (C-7); 168.9 (NHCOMe); 137.5 (C-4'); 133.7 (C-1'); 128.2 (C-2', C-6'); 120.1 (C-3', C-5'); 98.4 (C-1); 76.2 (C-5); 64.1 (C-3); 42.1 (C-4); 36.2 (C-6); 24.8 (NHCOMe); 18.3 (1-Me). m/z (ES $^+$): 316 (M+Na+H $_2$ O) $^+$ 298 (M+Na) $^+$. m/z (HRMS ES $^+$): Found: 298.1051 (M+Na) $^+$, C $_{15}$ H $_{17}$ NO $_4$ Na requires: 298.1049; Found: 316.1157 (M+Na+H $_2$ O) $^+$, C $_{15}$ H $_{19}$ NO $_5$ Na requires: 316.1155

(R)-1-Methyl-4-phenyl-2,8-dioxa-bicyclo[3.2.1]octan-7-ol (20a) 2

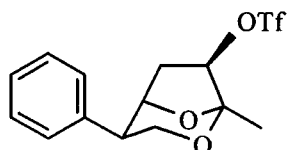


To a solution of (16) (25 mg, 0.66 mmol) in MeOH (15 ml), NaBH_4 (120 mg, 0.55 mmol, 2 eq.) was added and the reaction mixture was stirred at RT overnight. The reaction mixture was then extracted with EtOAc (3×20 ml), dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Petrol/EtOAc, 4:1 then 7:3) to provide (20) as a white solid (105 mg, 87% yield).

mp: 109–112°C (EtOAc). ν_{max} (DCM Solution)/ cm^{-1} : 3600–3150 (OH); 1596; 1517; 1116 (COC); 755, 700 (*mono*-substitution). δ_{H} (500 MHz): 7.45 (2H, m, 3'-H, 4'-H, 5'-H); 7.17 (2H,

d, J 8 Hz, **2'-H**, **6'-H**); 4.57-4.53 (2H, m, **5-H**, **7-H**); 4.22-4.18 (2H, m, **3-H**); 3.56 (1H, m, **4-H**); 2.50 (1H, ddd, $J_1=7.5$, $J_2=11$, $J_3=13.5$, **6-H $_{\alpha}$**); 2.09 (1H, d, $J=5$, **7-OH**); 1.86 (1H, dd, $J_1=4$, $J_2=13.5$, **6-H $_{\beta}$**); 1.49 (3H, s, **1-CH $_3$**). δ_C (125.7 MHz): 137.7 (**C-1'**); 129.0 (**C-2'**, **C-6'**); 127.6 (**C-3'**, **C-5'**); 127.4 (**C-4'**); 102.9 (**C-1**); 78.8 (**C-5**); 75.6 (**C-7**); 64.2 (**C-3**); 42.6 (**C-4**); 33.5 (**C-6**); 22.2 (**1-Me**). m/z (CI, NH_3): 238 ($\text{MH}+\text{NH}_4$)⁺, 221 (MH)⁺. m/z (HRMS ES⁺): Found: 243.0967 ($\text{M}+\text{Na}$)⁺, $\text{C}_{13}\text{H}_{14}\text{O}_3\text{Na}$ requires: 243.0997

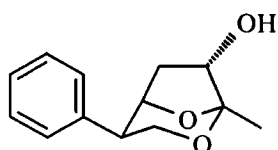
(R)-1-Methyl-4-phenyl-2,8-dioxa-bicyclo[3.2.1]octan-7-yl trifluoromethane sulfonate (20b)



A solution of the alcohol (**20a**) (160 mg, 0.72 mmol) and 2,6-lutidine (0.25 ml, 2.15 mmol, 3 eq.) in CH_2Cl_2 (10 ml) was cooled to 0°C and trifluoromethane sulfonic anhydride (0.38 ml, 2.15 mmol, 3 eq.) was added dropwise and the reaction was allowed to warm up to RT and stirred overnight. The reaction was quenched with sat. NaCl solution. The aqueous phase was extracted with DCM, dried over MgSO_4 , filtered and the solvent was evaporated *in vacuo* yielding (**20b**) in a good yield (202 mg, 80%) as a viscous oily residue subsequently used without purification.

ν_{max} (thin film)/ cm^{-1} : 1414+1202 (OSO_2), 1596; 1517; 1116 (COC); 755, 700 (*mono-substitution*). δ_H (400 MHz): 7.35 (2H, t, J 8.0, **3'-H**, **5'-H**); 7.28 (1H, t, J 8.0, **4'-H**); 7.12 (2H, d, J 8.0 Hz, **2'-H**, **6'-H**); 5.00 (1H, dd, $J_1=11.1$, $J_2=3.8$, **7-H**); 4.63 (1H, ddd, $J_1=7.5$, $J_2=3.1$, $J_3=1.5$, **5-H**); 4.37 (1H, t, J 11.8, **3-H $_{ax}$**); 4.23 (1H, ddd, $J_1=11.8$, $J_2=5.9$, $J_3=1.5$, **3-H $_{eq}$**); 3.60 (1H, ddd, $J_1=11.8$, $J_2=5.9$, $J_3=3.1$, **4-H**); 2.61 (1H, ddd, $J_1=14.6$, $J_2=11.1$, $J_3=7.5$, **6-H $_{\alpha}$**); 2.12 (1H, dd, $J_1=14.6$, $J_2=3.8$, **6-H $_{\beta}$**); 1.55 (3H, s, **2-Me**); 1.49 (3H, s, **1-CH $_3$**). δ_F (282.2 MHz): -74.48 (CF_3). δ_C (100.5 MHz): 136.6 (**C-1'**); 129.2 (**C-3'**, **C-5'**); 127.7 (**C-4'**); 127.2 (**C-2'**, **C-6'**); 119.0 (q, J 320, CF_3); 101.3 (**C-1**); 86.6 (**C-7**); 78.3 (**C-5**); 63.7 (**C-3**); 41.7 (**C-4**); 30.9 (**C-6**); 22.0 (**1-Me**). m/z (ES⁻): 284.7 ($\text{M}-\text{CF}_3+\text{H}$)⁺. m/z (HRMS ES⁺): Found: 375.0483 ($\text{M}+\text{Na}$)⁺, $\text{C}_{14}\text{H}_{15}\text{O}_5\text{F}_3\text{Na}_1\text{S}_1$ requires: 375.0485

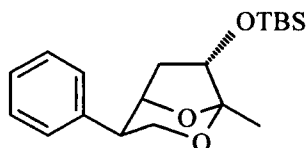
(S)-1-Methyl-4-phenyl-2,8-dioxa-bicyclo[3.2.1]octan-7-ol (20c)²



To a solution of **(20b)** (0.215 mmol) in DMF, KOH (24 mg, 0.43 mmol, 2 eq.) and 18-crown-6 (114mg, 0.43 mmol, 2 eq.) were added and the reaction mixture was stirred at reflux temperature for 16 hours. Once the reaction was complete, an ice-cooled solution of NH_4Cl was added and the mixture was extracted with EtOAc (3×10 ml). The combined organic extracts were dried on MgSO_4 , filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (Petrol/EtOAc, 4:1 then 7:3) to yield **(20c)** as white solid (28 mg, 60%).

mp: 115–119°C (EtOAc). ν_{max} (DCM Solution)/ cm^{-1} : 3680-3197 (broad *OH*); 1596; 1517; 1116 (*COC*); 755, 700 (*mono-substitution*). δ_{H} (500 MHz): 7.37-7.29 (3H, m, *3'-H*, *4'-H*, *5'-H*); 7.10 (2H, d, J 7.6, *2'-H*, *6'-H*); 4.72 (1H, ddd, $J_1=7.5$, $J_2=3.0$, $J_3=1.1$, *5-H*); 4.35 (1H, dd, $J_1=7.5$, $J_2=2.8$, *7-H*); 4.12 (1H, ddd, $J_1=11.6$, $J_2=5.3$, $J_3=1.1$, *3-H_{eq}*); 3.98 (1H, t, J 11.6, *3-H_{ax}*); 3.43 (1H, ddd, $J_1=11.6$, $J_2=5.3$, $J_3=3$, *4-H*), 2.47 (1H, dd, $J_1=14.1$, $J_2=7.5$, *6-H_{\alpha}*); 1.81 (1H, ddd, $J_1=5$, $J_2=7.5$, $J_3=2.8$, *6-H_{\beta}*); 1.56 (1H, bs, *7-OH*); 1.52 (3H, s, *1-CH_3*). δ_{C} (125.7 MHz): 137.0 (*C-1'*); 129.0 (*C-2'*, *C-6'*); 127.6 (*C-3'*, *C-5'*); 127.4 (*C-4'*); 106.7 (*C-1*); 78.6 (*C-5*); 75.5 (*C-7*); 63.2 (*C-3*); 42.3 (*C-4*); 36.4 (*C-6*); 19.8 (*1-Me*). m/z (ES^+): 243.1 ($\text{M}+\text{Na}$) $^+$, m/z (HRMS ES^+): Found: 243.0995 ($\text{M}+\text{Na}$) $^+$, $\text{C}_{13}\text{H}_{14}\text{O}_3\text{Na}$ requires: 243.0997

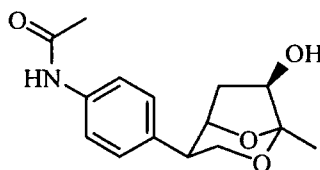
(S)-1-Methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (20d)



To a 1M solution of **(20c)** (17mg, 0.077 mmol) in DCM (5 ml), 2,6-lutidine (0.036 ml, 0.309 mmol, 4 eq.) and *tert*-butyldimethylsilyltriflate (0.04 ml, 0.232 mmol, 3 eq.) were added dropwise. The reaction mixture was stirred at RT overnight. The reaction was purified by flash chromatography (Petrol/EtOAc, 95:5 then 9:1) and gave the protected alcohol **(20d)** as yellowish white oil. (19.35 mg, 75% yield)

ν_{\max} (thin film)/ cm^{-1} : 2932 (OSiMe); 1606; 1252 + 838 (SiMe); 1163 (COC); 1077 (OSi). δ_{H} (300 MHz): 7.35 (2H, t, J 8, 3'-H, 5'-H); 7.26 (1H, t, J 8, 4'-H); 4.75 (1H, m, 5-H); 4.32 (1H, dd, $J_1=6.5$, $J_2=2.5$, 7-H); 4.13 (1H, m, 3- H_{eq}); 4.00 (1H, t, J 11.5, 3- H_{ax}); 3.44 (1H, m, 4-H); 2.32 (1H, dd, $J_1=13.5$, $J_2=7.5$, 6- H_{a}); 1.86 (1H, ddd, $J_1=13.5$, $J_2=7.5$, $J_3=3$, 6- H_{b}); 1.47 (3H, s, 1- CH_3); 0.92 (9H, s, SiCMe₃); 0.12 (3H, s, SiMe₁); 0.10 (3H, s, SiMe₂). δ_{C} (62.9 MHz): 137.9 (C-1'); 129.0 (C-2', C-6'); 127.4 (C-3', C-5'); 127.2 (C-4'); 107.3 (C-1); 78.8 (C-5); 75.8 (C-7); 63.3 (C-3); 42.3 (C-4); 37.2 (C-6); 26.9 (SiCMe₃); 20.3 (1-Me); 25.9 (SiC); -4.4 (SiMe₁); -4.7 (SiMe₂). m/z (ES⁺): 357.2 (M+Na)⁺. m/z (HRMS ES⁺): Found: 357.18541 (M+Na)⁺, C₁₉H₃₀O₃SiNa requires: 357.18564

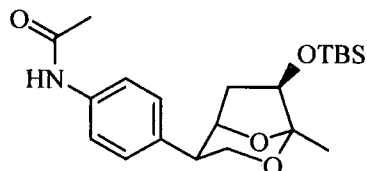
N-[4-((R)-7-Hydroxy-1-methyl-2,8-dioxabicyclo[3.2.1]oct-4-yl)-phenyl]-acetamide (21)



To a solution of (19) (75 mg, 0.273 mmol) in MeOH (15 ml), NaBH₄ (20.4 mg, 0.545 mmol, 2 eq.) was added and the reaction mixture was stirred at RT overnight. The reaction mixture was then extracted with EtOAc (3×20 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Petrol/EtOAc, 9:1 then 3:2) to provide (21) as a white solid. (60.3 mg, 80% yield)

mp: 145–149°C (EtOAc). ν_{\max} (DCM Solution): 3200-3500 (alcoholic OH); 1666 (NHCO); 1596; 1517; 1116 (COC); 816 (*para*-substitution). δ_{H} (500 MHz): 7.45 (2H, d, J 8.5, 3'-H, 5'-H); 7.14 (1H, broad s, NHCOMe); 7.10 (2H, d, J 8.5, 2'-H, 6'-H); 4.49 (2H, m, $J_1=3.9$, $J_2=11.5$, 5-H, 7-H); 4.16 (2H, m, 3-H); 3.76 (1H, m, 4-H); 2.52 (1H, ddd, $J_1=7.5$, $J_2=11.5$, $J_3=13.6$, 6- H_{a}); 2.17 (3H, s, NHCOCH₃); 2.10 (1H, d, J 5, 7-OH); 1.80 (1H, dd, $J_1=3.9$, $J_2=13.6$, 6- H_{b}); 1.46 (3H, s, 1- CH_3). δ_{C} (62.9 MHz): 168.9 (NHCOMe); 137.4 (C-4'); 133.8 (C-1'); 128.3 (C-2', C-6'); 120.2 (C-3', C-5'); 102.5 (C-1); 78.2 (C-5); 75.8 (C-7); 64.1 (C-3); 42.2 (C-4); 33.7 (C-6); 24.7 (NHCOMe); 22.2 (1-Me). m/z (ES⁺): 300 (M+Na)⁺. m/z (HRMS ES⁺): Found: 300.1207 (M+Na)⁺, C₁₅H₁₉NO₄Na requires: 300.1206

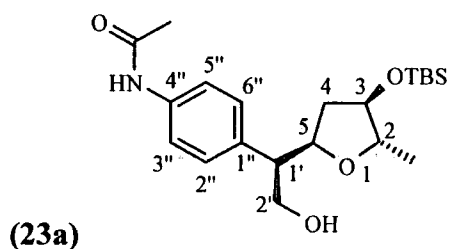
N-{4-[(R)-7-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-2,8-dioxabicyclo[3.2.1]oct-4-yl]-phenyl}-acetamide (22)



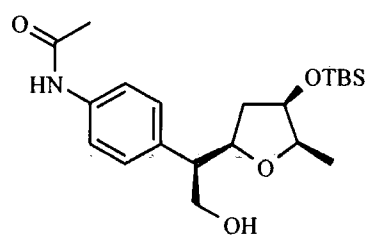
To a 1M solution of (21) (60mg, 2.17 mmol) in AcCN (15 ml), 2,6-lutidine (0.05 ml, 0.43 mmol, 2 eq.) and *tert*-butyldimethylsilyltriflate (0.075 ml, 0.325 mmol, 1.5 eq.) were added dropwise. The reaction mixture was stirred at RT overnight. The reaction was purified by flash chromatography (Petrol/EtOAc, 9:1 then 4:1) and gave the protected alcohol (22) as yellowish white solid. (75.5 mg, 89% yield)

mp: 162–167°C (EtOAc). ν_{\max} (DCM Solution)/ cm^{-1} : 3472 (NH); 2940 (OSiMe); 1654 (NHCO); 1606; 1265 + 848 (SiMe); 1156 (COC); 1074 (OSi); 804 (*para*-substitution). δ_{H} (300 MHz): 7.45 (2H, d, J 8.4, 3'-H, 5'-H); 7.09 (2H, d, J 8.4, 2'-H, 6'-H); 4.64 (1H, t, J 11.7, 3-H_{ax}); 4.46 (1H, m, 5-H); 4.08 (1H, dd, $J_1=6$, $J_2=11.7$, 3-H_{eq}); 4.05 (1H, dd, $J_1=3.3$, $J_2=11.2$, 7-H); 3.46 (2H, m, 4-H); 2.37 (1H, ddd, $J_1=5.7$, $J_2=11.2$, $J_3=13.2$, 6-H_α); 2.17 (3H, s, NHCOCH₃); 1.65 (1H, dd, $J_1=3.3$, $J_2=13.2$, 6-H_β); 1.40 (3H, s, 1-CH₃); 0.94 (9H, s, SiCMe₃); 0.10 (3H, s, SiMe₁); 0.09 (3H, s, SiMe₂). δ_{C} (62.9 MHz): 172.4 (NHCO); 141.7 (C-4'); 139.5 (C-1'); 132.4 (C-2', C-6'); 125.1 (C-3', C-5'); 107.3 (C-1); 83.6 (C-5); 80.7 (C-7); 68.2 (C-3); 47.1 (C-4); 39.6 (C-6); 30.9 (SiCMe₃); 29.3 (NHCOMe); 27.3 (1-Me); 23.1 (SiC); 0.2 (2×SiMe). m/z (ES⁺): 414 (M+Na)⁺ 391 (M+H)⁺ 261 (M-TBSO+H)⁺. m/z (HRMS ES⁺): Found: 414.2079 (M+Na)⁺, C₂₁H₃₃NO₄SiNa requires: 414.2071

N-(4-{(R)-1-[(2R, 4R, 5S^(23a) / 5R^(23b)]-4-(*tert*-Butyl-dimethyl-silanyloxy)-5-methyl-tetrahydrofuran-2-yl]-2-hydroxy-ethyl}-phenyl)-acetamide (23a/23b)^{2,4,6}



(23a)



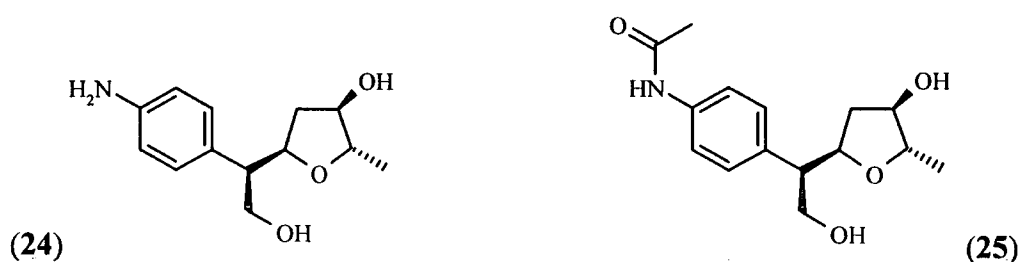
(23b)

To a solution of the bicyclic acetal (**22**) (15.6 mg, 0.039 mmol) in DCM cooled to $-78\text{ }^{\circ}\text{C}$, Et_3SiH (0.025 ml, 0.159 mmol, 4 eq.) was added. Later, 1M solution of TiCl_4 in DCM (0.092 ml, 1.2 eq.) was added dropwise and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 6 hours. Once completed, the reaction mixture was poured into 2N HCl and extracted with EtOAc (3×10 ml). The combined organic extracts were dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo* and purified by column chromatography (Petrol/EtOAc, 95:5 then 4:1) to give (**23a**) as the major isomer as white solid (2.5 mg, 16% yield). The isomer (**23b**) could not be isolated and only detected in the ^1H NMR spectrum of the crude yield of the reaction.

Characterization for (**23a**)

mp: $107\text{--}111\text{ }^{\circ}\text{C}$ (EtOAc). ν_{max} (DCM Solution)/ cm^{-1} : 3200-3450 (alcoholic OH); 2926 (OSiMe); 1676 (NHCO); 1596; 1262 + 844 (SiMe); 1072 (OSi). δ_{H} (500 MHz) CD_3OD : 7.45 (2H, d, J 8.4, 3''-H, 5''-H); 7.22 (2H, d, J 8.4, 2''-H, 6''-H); 4.64 (1H, m, 5-H); 4.46 (1H, m, $J_1=6.5$, $J_2=8$, 3-H); 4.08 (1H, m, 2'-H); 4.05 (1H, dd, $J_1=5.5$, $J_2=12.5$, 2-H); 3.46 (2H, dd, $J_1=6$, $J_2=12.5$, 1'-H); 2.37 (1H, m, $J_1=6.5$, $J_2=12$, 4-H $_{\alpha}$); 2.06 (3H, s, NHCOCH_3); 1.65 (1H, ddd, $J_1=8$, $J_2=9$, $J_3=12$, 4-H $_{\beta}$); 1.06 (3H, d, J 5.5, 1-CH $_3$); 0.85 (9H, s, SiCMe_3); 0.04 (3H, s, SiMe_1); 0.04 (3H, s, SiMe_2). δ_{C} (62.9 MHz): 170.6 (NHCOMe); 137.2 (C-4''); 129.5 (C-3'', C-5''); 128.2 (C-1''); 119.9 (C-2'', C-6''); 80.1 (C-2); 77.9 (C-3); 76.9 (C-5); 63.8 (C-2'); 51.8 (C-1'); 38.7 (C-4); 25.4 (SiCMe_3); 22.6 (NHCOMe); 17.6 (2-Me); 17.4 (SiCMe_3); -5.8 ($2\times\text{SiMe}$). m/z (ES $^+$): 416 ($\text{M}+\text{Na}$) $^+$ 412 ($\text{M}+\text{H}+\text{H}_2\text{O}$) $^+$ 411 ($\text{M}+\text{H}_2\text{O}$) $^+$ 394 ($\text{M}+\text{H}$) $^+$ 376 ($\text{M}-\text{OH}+\text{H}$) $^+$ 274 ($\text{M}-\text{TBSO}+\text{H}$) $^+$. m/z (HRMS ES $^+$):, Found: 416.2225 ($\text{M}+\text{Na}$) $^+$, $\text{C}_{21}\text{H}_{35}\text{NO}_4\text{SiNa}$ requires: 416.2228

Quenching the reaction with 2N HCl, led the formation of two more compounds (**24**) and (**25**). Due to the high polarity especially in acidic medium where the aromatic *para* amino group of (**24**) can be ionised, they could not be extracted by the extracting solvent.

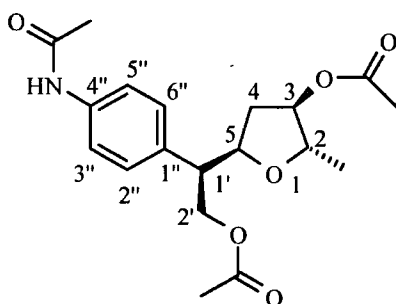


Raising the pH of the aqueous phase to pH 8 and re-extraction with EtOAc (4×10 ml), the combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*, to give (24) and (25) as white solid (7 mg).

δ_{H} (500 MHz) (24): 7.05 (2H, d, *J* 8, 3''-H, 5''-H); 7.03 (2H, d, *J* 8, 2''-H, 6''-H); 4.40 (1H, m, 5-H); 3.85 (1H, m, 3-H); 3.77 (1H, m, 2'-H); 3.42 (1H, m, 2-H); 2.83 (1H, dt, *J*₁=6, *J*₂=12.5, 1'-H); 2.20 (1H, m, 4-H_a); 1.65 (1H, m, 4-H_β); 1.16 (3H, d, *J* 6.5, 2-Me).

δ_{H} (500 MHz) (25): 7.45 (2H, d, *J* 8, 3''-H, 5''-H); 7.23 (2H, d, *J* 8, 2''-H, 6''-H); 4.40 (1H, m, 5-H); 3.85 (1H, m, 3-H); 3.77 (1H, m, 2'-H); 3.42 (1H, m, 2-H); 2.75 (1H, dt, *J*₁=6, *J*₂=12.5, 1'-H); 2.20 (1H, m, 4-H_a); 2.12 (3H, s, NHCOCH₃); 1.65 (1H, m, 4-H_β); 1.16 (3H, d, *J* 6.5, 2-Me).

Acetic acid (2S, 3R, 5R)-5-[(R)-2-acetoxy-1-(4-acetylamino-phenyl)-ethyl]-2-methyl-tetrahydrofuran-3-yl ester (26) :



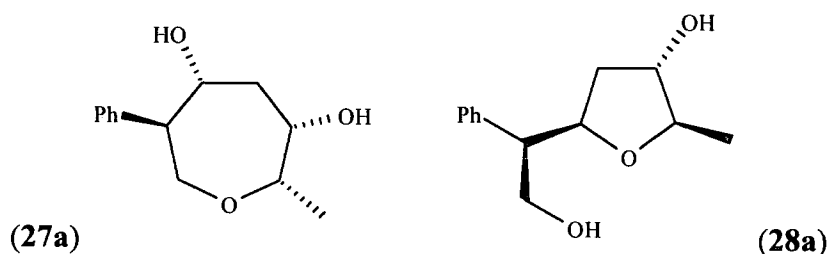
Without purification, to a solution of the mixture of (24) and (25) (5 mg, 0.021 mmol -calculated as 23), Et₃N (0.012 ml, 0.084 mmol, 10 eq.) and DMAP (1.5 mg, 0.6 eq.) in AcCN (5 ml), AcCl (0.011 ml, 0.152 mmol, 7.2 eq.) was added dropwise. The reaction mixture was stirred at RT overnight. After the reaction went to completion, it was quenched with 1 ml of brine solution and extracted with EtOAc (3×5 ml). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (Petrol/EtOAc, 95:5 then 9:1) to give (26) as a colourless oily residue (2 mg, 26% yield).

ν_{max} (thin film)/cm⁻¹: 1735 (OCO); 1693 (NHCO) cm⁻¹. δ_{H} (500 MHz): 7.45 (2H, d, *J* 8, 3''-H, 5''-H); 7.23 (2H, d, *J* 8, 2''-H, 6''-H); 4.79 (1H, m, *J*₁=4.5, *J*₂=5, 3-H); 4.40 (1H, m, *J*₁=7, 5-H); 4.36 (1H, m, *J*₁=12.5, 2'-H); 3.92 (1H, m, *J*₁=4.5, *J*₂=6.5, 2-H); 3.06 (1H, m, *J*₁=6, *J*₂=12.5, 1'-H); 2.43 (1H, m, *J*₁=7, *J*₂=14.5, 4-H_a); 2.18 (3H, s, NHCOCH₃); 1.99 (3H, s, 3-OCOCH₃); 1.95

(3H, s, 2'-OCOCH₃); 1.70 (1H, m, $J_1=5$, $J_2=14.5$, 4-H_β); 1.16 (3H, d, J 6.5, 2-Me). δ_C (125.7 MHz): 171.1 (2'-OCOMe); 170.5 (3-OCOMe); 168.2 (NHCOMe); 136.9 (C-4''); 134.6 (C-1''); 130.0 (C-2'', C-6''); 119.8 (C-3'', C-5''); 78.6 (C-3); 78.4 (C-2); 77.1 (C-5); 66.0 (C-2'); 48.6 (C-1'); 35.1 (C-4); 24.3 (NHCOMe); 21.4 (2'-OCOMe, 3-OCOMe); 18.2 (2-Me). *m/z* (ES⁺): 386 (M+Na)⁺. *m/z* (HRMS ES⁺):, Found: 386.1585 (M+Na)⁺, C₁₉H₂₅NO₆Na requires: 386.1574

(2R,3S,5R,6R)-2-methyl-6-phenyloxepane-3,5-diol (27a)

(2S,3S,5R,6R)-2-methyl-6-phenyloxepane-3,5-diol (28a)



To a solution of the bicyclic alcohol (**20c**) (30 mg, 0.136 mmol) in DCM cooled to -78 °C, Et₃SiH (0.09 ml, 0.55 mmol, 4 eq.) was added. Later, 1M solution of TiCl₄ in DCM (0.018 ml, 1.2 eq.) was added dropwise and the reaction mixture was stirred at -78 °C for 6 hours. Once completed, the reaction mixture was poured into 2N HCl and extracted with EtOAc (3×10 ml). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo* and purified by column chromatography (Petrol/EtOAc 7:3 then 3:7) to give (**27a**) (major oxepane isomer) and (**28a**) (major THF isomer) as a white solid of a non-separable mixture (19.7 mg, 65% yield). Minor isomers could not be isolated.

Characterization for (27a)

mp (Mixture): 87–91°C (EtOAc). **v_{max}** (DCM Solution)/cm⁻¹ (Mixture): 3603 (b, free OH); 3556-3222 (vb, H-Bonded OH); 1602; 1376; 1260; 1080. δ_H (500 MHz): 7.25 (5H, m, *Ar-H*); 4.55 (1H, ddd, $J_1=9$, $J_2=6$, $J_3=4.5$, 5-H); 4.03 (1H, dd, $J_1=11$, $J_2=7$, 7-H_β); 3.92 (1H, dd, $J_1=11$, $J_2=7$, 7-H_α); 3.83 (1H, qd, $J_1=6.5$, $J_2=3$, 2-H); 3.75 (1H, ddd, $J_1=6$, $J_2=3$, $J_3=3$, 3-H); 3.0 (1H, td, $J_1=7$, $J_2=4.5$, 6-H); 2.75 (1H, bs, OH); 2.45 (1H, bs, OH); 1.80 (1H, m, 4-H_α, 4-H_β); 1.10 (3H, d, J 6.5, 2-Me). δ_C (125.7 MHz): 138.8 (C-1'); 129.3 (C-2', C-6'); 128.1 (C-3', C-5'); 127.1 (C-4'); 82.5 (C-2); 79.1 (C-5); 77.1 (C-3); 64.5 (C-7); 51.5 (C-6); 37.5 (C-4); 19.4 (2-Me). *m/z*

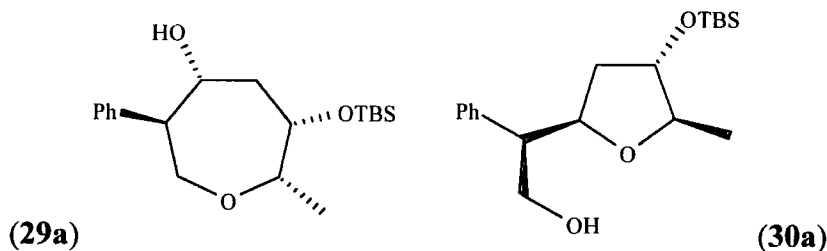
(ES⁺): 245.2 (M+Na)⁺. *m/z* (HRMS ES⁺): Found: 233.1328 (M+H)⁺, C₁₃H₁₉O₃ requires: 223.1329; Found: 245.1146 (M+Na)⁺, C₁₃H₁₈O₃Na requires: 245.1146

Characterization for (28a)

mp (Mixture): 87–91°C (EtOAc). **v_{max}** (DCM Solution)/cm⁻¹ (Mixture): 3603 (b, free OH); 3556-3222 (vb, H-Bonded OH); 1602; 1376; 1260; 1080. **δ_H** (500 MHz): 7.25 (5H, m, *Ar-H*); 4.68 (1H, ddd, *J*₁=5, *J*₂=3, *J*₃=2, *5-H*); 4.04 (2H, m, *7-H_β*, *7-H_α*); 3.83 (1H, m, *2-H*); 3.74 (1H, m, *3-H*); 2.9 (1H, dt, *J*₁=3.5, *J*₂=2, *6-H*); 2.34 (1H, dt, *J*₁=5, *J*₂=3, *4-H_α*); 1.95 (1H, dd, *J*₁=5, *J*₂=3, *4-H_β*); 1.19 (3H, d, *J* 3, *2-Me*). **δ_C** (125.7 MHz): 138.8 (*C-1'*); 129.7 (*C-2'*, *C-6'*); 128.7 (*C-3'*, *C-5'*); 127.1 (*C-4'*); 82.5 (*C-2*); 78.8 (*C-3*); 77.8 (*C-5*); 73.8 (*C-7*); 52.3 (*C-6*); 38.9 (*C-4*); 14.6 (*2-Me*). ***m/z*** (ES⁺): 245.2 (M+Na)⁺. ***m/z*** (HRMS ES⁺): Found: 233.1328 (M+H)⁺, C₁₃H₁₉O₃ requires: 223.1329; Found: 245.1146 (M+Na)⁺, C₁₃H₁₈O₃Na requires: 245.1146

(2R,3S,5R,6R)-3-tert-Butyldimethylsilanyloxy-2-methyl-6-phenyloxepane-5-ol (29a)

(2S,3S,5R,6R)-3-tert-Butyldimethylsilanyloxy-2-methyl-6-phenyloxepane-5-ol (30a)



To a solution of the bicyclic acetal (**20d**) (60 mg, 0.27 mmol) in DCM cooled to -78 °C, Et₃SiH (0.04 ml, 1.1 mmol, 4 eq.) was added. Later, 1M solution of TiCl₄ in DCM (0.173 ml, 1.2 eq.) was added dropwise and the reaction mixture was stirred at -78 °C for 6 hours. Once completed, the reaction mixture was poured into 2N HCl and extracted with EtOAc (3×10 ml). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo* and purified by column chromatography (Petrol/EtOAc 7:3 then 3:2) to give (**29a**) (major oxepane isomer) and (**30a**) (major THF isomer) as a viscous oily residue of non-separable mixture (42.2 mg, 70% yield). Minor isomers could not be isolated.

Characterization for (29a)

ν_{\max} (thin film)/ cm^{-1} (Mixture): 3200-3450 (alcoholic *OH*); 2926 (*OSiMe*); 1596; 1262 + 844 (*SiMe*); 1072 (*OSi*). δ_{H} (500 MHz): 7.35-7.23 (5H, m, *Ar-H*); 4.57 (1H, m, *5-H*); 4.05 (1H, dd, $J_1=11$, $J_2=7$, *7-H β*); 3.60 (1H, dd, $J_1=11$, $J_2=7$, *7-H α*); 3.74 (1H, qd, $J_1=6.5$, $J_2=4.5$, *2-H*); 3.54 (1H, dt, $J_1=4.5$, $J_2=6.5$, *3-H*); 3.0 (1H, td, $J_1=7$, $J_2=4$, *6-H*); 1.83-1.64 (2H, m, *4-H α* , *4-H β*); 1.11 (3H, d, J 6.5, *2-Me*). δ_{C} (125.7 MHz): 138.8 (*C-1'*); 129.8 (*C-2'*, *C-6'*); 127.6 (*C-3'*, *C-5'*); 126.5 (*C-4'*); 82.5 (*C-2*); 79.1 (*C-5*); 77.8 (*C-3*); 64.5 (*C-7*); 51.9 (*C-6*); 38.2 (*C-4*); 26.1 (*SiCMe₃*); 19.5 (*2-Me*); 7.5 (*SiCMe₃*); -4.3 ($2\times\text{SiMe}$). m/z (ES⁺): 337.2 (M+H)⁺; 359.3 (M+Na)⁺. m/z (HRMS ES⁺): Found: 337.2194 (M+H)⁺, C₁₉H₃₃O₃Si requires: 337.2194; Found: 359.2013 (M+Na)⁺, C₁₉H₃₂O₃SiNa requires: 359.2013

Characterization for (30a)

ν_{\max} (thin film)/ cm^{-1} (Mixture): 3200-3450 (alcoholic *OH*); 2926 (*OSiMe*); 1596; 1262 + 844 (*SiMe*); 1072 (*OSi*). δ_{H} (500 MHz): 7.35-7.23 (5H, m, *Ar-H*); 4.57 (1H, m, *5-H*); 4.0 (1H, dd, $J_1=11$, $J_2=7$, *7-H β*); 3.82 (1H, dd, $J_1=11$, $J_2=7$, *7-H α*); 3.64 (1H, qd, $J_1=6.5$, $J_2=4.5$, *2-H*); 3.43 (1H, dt, $J_1=4.5$, $J_2=6.5$, *3-H*); 2.9 (1H, ddd, $J_1=7$, $J_2=4$, $J_3=3$, *6-H*); 2.2 (1H, dt, $J_1=5$, $J_2=3$, *4-H α*); 1.22 (1H, dd, $J_1=5$, $J_2=3$, *4-H β*); 1.06 (3H, d, J 6.5, *2-Me*). δ_{C} (125.7 MHz): 140.1 (*C-1'*); 130.0 (*C-2'*, *C-6'*); 128.0 (*C-3'*, *C-5'*); 126.8 (*C-4'*); 82.0 (*C-2*); 79.2 (*C-5*); 77.0 (*C-3*); 64.6 (*C-7*); 53.5 (*C-6*); 39.2 (*C-4*); 26.1 (*SiCMe₃*); 18.3 (*2-Me*); 6.5 (*SiCMe₃*); -4.2 ($2\times\text{SiMe}$). m/z (ES⁺): 337.2 (M+H)⁺; 359.3 (M+Na)⁺. m/z (HRMS ES⁺): Found: 337.2194 (M+H)⁺, C₁₉H₃₃O₃Si requires: 337.2194; Found: 359.2013 (M+Na)⁺, C₁₉H₃₂O₃SiNa requires: 359.2013

4.3 References

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