Stereocontrolled synthesis of highly functionalised tetrahydrofurans,

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ABSTRACT

Stereocontrolled Synthesis of Highly Functionalised Tetrahydrofurans

Amel Garbi, PhD, June 2005

Polysubstituted tetrahydrofurans appear in a large variety of bioactive structures of both natural and unnatural origin. The stereochemistry of the substituents has a profound effect on function; therefore, the development of new methodology for the stereoselective construction of tetrahydrofuran rings is very attractive.

A tandem methodology for the stereoselective synthesis of 2,3,5-trisubstituted tetrahydrofurans is reported here. This involves a catalytic C-H insertion of diazocarbonyl acetal templates followed by the stereoselective reductive cleavage of the resultant bicyclic acetals.

A key area of this project is the formation and reaction of diazoketones. The diazoketones were prepared in good yields (70-85%) by acylation of diazomethane with a mixed anhydride, which involves the initial activation of the acid group of the corresponding acid acetal precursors. Alternatives to the use of diazomethane have been examined but proved to be less efficient. Two routes towards the synthesis of the acid acetals have been examined. A one-pot process involving the treatment of 1,3- and 2,2-disubstituted-propane-1,3-diols with pyruvic acid gave poor yields (30-38%). A two-step procedure involving the initial synthesis of pyruvate ester acetals, by ketalisation of 2-substituted-propane-1,3-diols followed by their hydrolysis, led to the formation of acid acetals in good yield (~ 75% after 2 steps). Rhodium (II) acetate is an efficient catalyst for the decomposition of diazoketones leading to transition metal-carbenoids (or metallocarbenes), reactive intermediates susceptible to insertion into a C-H bond. Determination of the optimum conditions for the C-H insertion process has been achieved and electronic effects of the substituents on the C-H insertion process have been examined. The reaction was regioselective, occurring at the C-H bond α to the oxygen, and a variety of bicyclic ketones were prepared in moderate but reproducible yields.

The bicyclic core intermediate, present in naturally occurring bioactive molecules, is also a target for synthesis. An attempt to synthesize sordidin, an aggregation pheromone released by male banana weevils, is reported. Finally, the reductive cleavage of these bicyclic ketones, upon Et_3SiH/Lewis Acid treatment, has been examined. In all cases, the reactions were stereoselective leading to 2,3-*anti*-3,5-*cis*-trisubstituted tetrahydrofurans. The stereoselectivity increased with the size of the OR group at C-3.

Declaration :

The work in this thesis was carried out in the Department of Chemistry at the University of Durham between 1st April 2001 and 30th July 2004. It has not been submitted for any other degree and is the author's own work, except where acknowledged by reference.

Copyright :

I left it for last and I am really pleased now to write these few pages...

You might wonder why ?!

Well... to be honest it is just that now I realize that I have finally manage ! That I have done it ! Like many other PhD students, the writing up had its ups and downs. Sometimes you can't see the end ... but it does happen ☺ and it is a great feeling !

I just would like to say to the one that are writing or will have to write their thesis and they are a bit down ... to keep on, to keep having faith there is a light at the end of the tunnel ;-) Good luck !

Of course now it is time to thank all the people that have played a role in this ... euh ... how can I call it ?!...achievement ?! without being pedantic, I do feel it as an achievement ... Well anyway for the moment ☺.

I would like to thank my supervisor, Dr Patrick Steel, first of all for the fantastic opportunity he gave me to do a PhD in Durham, which has hopefully permitted to improve my English (☺) but definitely my personality. I would like to thank you, Patrick, for your guidance, the theoretical and practical advices you have given me in the lab, for the general organic chemistry knowledge gained during the group meetings all over the three years but also for your patience towards the "frenchie" and for trying to teach me some time management ☺!

I would like to thank my industrial supervisor, Dr Sadie Vile from GSK for her advices, help and attention during the three months placement down in Stevenage, during our regular meetings and all over these three years. Thank you, Sadie for your assistance in the lab and improving my safety spirit ☺. I would like also to thank you for the time you have spent correcting my thesis and for the valuable comments and corrections you have given me.

I would like to thank GSK for funding and for permitting me to use the advanced facilities available in Industry.

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Thanks to Dr Alan Kenwright, Katherine Heffernan and Ian McKeag for all the NMR work and mostly for all the nOesy, COSY experiments permitting the determination of the stereochemistry of my compounds. Thanks to Dr Mike Jones and Lara Turner for the mass spectrometry, to Dr Ritu Kataky, Lenny Lauchlan and Jaroslava Dostal for the GC's and elemental analysis. Thanks to all the technical staff members of the department

(Elizabeth, Joe, Jim, Tony and Gary from the stores, Peter and Malcom, the glassblowers etc.) for their professionalism, their kindness and smiles !!! If the department is 5* it is thanks to you !!! Thanks to Dave Hunter for all the nice "meetings" (around a coffee and a cake ☺), the nice and helpful conversations about Life and the hugs that helped me to keep going when I was down !

I would like to thank my labmates : Andy, Ed, Ganesh, Ishmael, John, Jonathan, Jun, Kathryn, Laila, Lisa, Ollie, Wendy and Ximo for making the lab and the office such a nice place to work in but also for the social life ! "Special dedicace" to my labmates but moreover close friends : Pete, Dan and Chris for the fantastic group spirit, laughs, fun, mental support etc. I left Paris and left my two brothers but I arrived in Durham and found three brothers !!! Thanks guys, I owe you loads !!!

Thanks to the PhD I have learnt a lot in Chemistry and in the lab but it also permitted me to meet a lot of people from all over the world. But most of all, I have met good friends, close friends and best friends !!! To all of you (and I am sure that you will recognized yourselves) I would like to say thanks and to express my gratitude for your unconditional support, love etc. You have always been there for me and without you I would have never been able to do it ! Thank you so much !

And at last but not the least, I would like to dedicate this thesis to my parents ! Thank you Mum and Dad for your support, for your love, for always being there for me and for believing in me ... I love you !!!!

Ac :	Acetyl
acac :	Acetylacetonate
acam :	Acetamide
aliph :	Aliphatic
aq. :	Aqueous
Ar :	Aryl
atm :	Atmosphere (1 atm = 1.013×10^5 Pascal)
ATR :	Attenuated total reflectance
BINAP :	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn :	Benzyl
Boc :	*t*-Butoxycarbonyl
b.p. :	Boiling point
Bu :	Butyl
Bz :	Benzoyl
c.a. :	*circa*, about
cap :	Caprolactam
cat. :	Catalyst
Cbz :	Benzyloxycarbonyl
CI :	1a,2,3,5-tetrahydro-1H-cycloprop[1,2-c]indol-5-one
c-hex :	Cyclohexyl
cf :	Confer
cm :	Centimetre
conc. :	Concentrated
COSY :	^{1}H-^{1}H Correlation spectroscopy
δ / ppm :	Chemical shift / Parts per million
δ^+ :	Partial positive charge
δ^- :	Partial negative charge
Δ :	Heat
d :	Doublet
dba :	Dibenzylideneacetone
DBU :	1,8-Diazabyciclo[5.4.0]undec-7-ene
DCM :	Dichloromethane (CH_2Cl_2)
dd :	Doublet of doublets

ddd : Doublet of doublet of doublets

DEAD : Diethyl azodicarboxylate

DIAD : Diisopropyl azodicarboxylate

Dibal-H : Diisobutylaluminium hydride

DMAP : 4-Dimethylaminopyridine

DMF : N,N-Dimethylformamide

D^{t}BPF : 1,1-Bis(di-*tert*-butylphosphino)ferrocene

e.e. / % : Enantiomeric excess / %

e.g. : For example

eq. : Equivalents

Et : Ethyl

EDG : Electron donating group

EWG : Electron withdrawing group

g. : Gram

GC : Gas chromatography

GC / MS : Gas chromatography / Mass spectroscopy

h. : Hours

hfacac : Hexafluoroacetylacetonate

hν : Light

HMBC : Heteronuclear shift correlations *via* multiple bond connectivities

HSQC : Heteronuclear single quantum correlation

i.e. : *in extenso*

iPr : Isopropyl

IR : Infra-red

J / Hz : Coupling constant / Hertz

K_a : Acid dissociation constant

kcal : Kilocalorie

kJ : Kilojoule

L.A. : Lewis acid

LDA : Lithium diisopropylamide

LiHMDS : Lithium bis(trimethylsilyl)amide

Ln : n Ligands

m : Multiplet

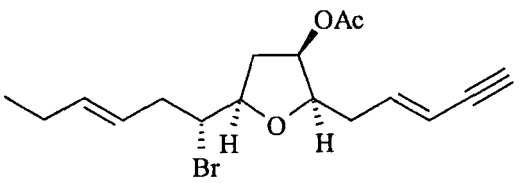
M :	mol/L
[M] :	Transition metal catalyst
MAD :	Methyl aluminium bis(2,6-di-*tert*-butyl-4-methyl phenoxide)
Me :	Methyl
MEM :	2-Methoxyethoxymethyl
5R-MEPY :	Methyl 2 pyrrolidone-5(R)-carboxylate
5S-MEPY :	Methyl 2 pyrrolidone-5(S)-carboxylate
5S-MEOX :	Methyl 2-oxazolidone-4(S)-carboxylate
min :	Minutes
mL :	Millilitres
m.p. :	Melting point
Ms :	Mesyl (methanesulphonyl)
N/A :	Not available
n/c :	Not communicated
NMR :	Nuclear magnetic resonance
nOe :	Nuclear Overhauser effect
nOesy :	Nuclear Overhauser effect spectroscopy
Nu :	Nucleophile
oct :	Octanoate
p :	Pentet
pfb :	Perfluorobutyrate
pH :	$-\text{Log}[H^+]$
Ph :	Phenyl
Piv. :	Pivaloyl (2,2-dimethylacetyl)
pK_a :	$-\text{Log}\ (K_a)$
Py :	Pyridine
q :	Quartet
qdd :	Quartet of doublet of doublets
[Red] :	Reduction
r.t. / R.T. :	Room temperature
s :	Singlet
S-DOSP :	(S)-(N)-*p*-Dodecylbenzenesulfonylprolinate
SM :	Starting material

S_N1 :	Unimolecular nucleophilic substitution
S_N2 :	Bimolecular nucleophilic substitution
S-TBSP :	(S)-(N)-*p-tert*-Butylbenzenesulfonylprolinate
Sub :	Substrate
TBDMS :	*tert*-Butyldimethylsilyl
t :	Triplet
tBu :	*tert*-Butyl
Temp. :	Temperature
Tf :	Triflate (trifluoromethanesulfonyl)
tfa :	Trifluoroacetate
tfacac :	Trifluoro acetylacetonate
TFEA :	Trifluoroethyl trifluoroacetate
tfm :	Trifluoromethane sulfonamide
THF :	Tetrahydrofuran
TIPS :	Triisopropylsilyl
TLC :	Thin layer chromatography
TMS :	Trimethylsilyl
Tol-BINAP :	*p*-Toluyl-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
tpa :	Triphenylacetate
tpp :	Tetraphenylporphyrin
TPP :	Triphenylphosphine
Ts :	Tosyl (*p*-toluenesulfonyl)
1D :	Unidimensional
2D :	Bidimensional
% w/w :	Weight percentage
18-crown-6 :	1,4,7,10,13,16-Hexaoxacyclooctadecane

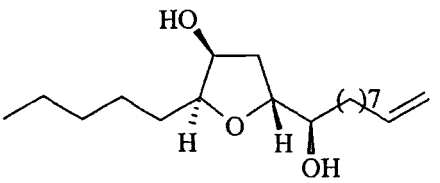
CHAPTER I:
INTRODUCTION

1.1-General introduction :

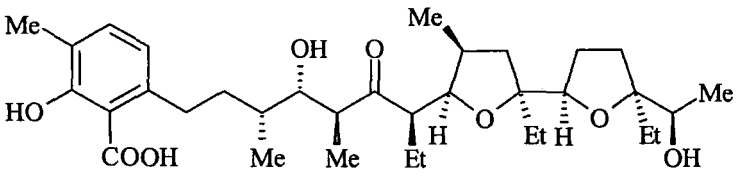
Polysubstituted tetrahydrofurans are commonly found in bioactive naturally occuring compounds such as lignans[1] (e.g. *trans*-kumausyne), marine natural products[2] (e.g. C19 lipid diol from *Notheia anomala*), polyether antibiotics[3] (e.g. isolasalocid A) and annonaceous acetogenins[4,5] (e.g. solamin, reticulatacin) (Scheme 1.1).



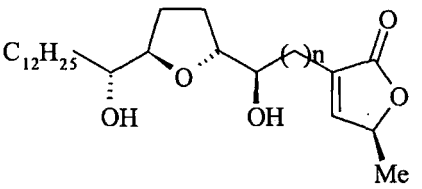
(+)- *trans*-kumausyne



C_{19} lipid diol from*Notheia anomala*



isolasalocid A

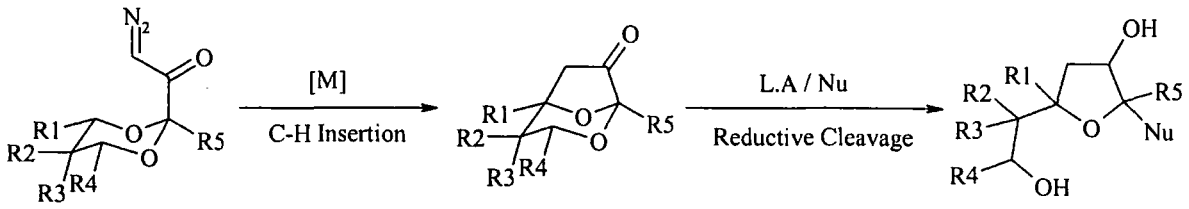


solamin : n=12
reticulatacin : n=14

Scheme 1.1

Due to their potent biological activities (cytotoxic, pesticidal, antimalarial, antiparasitic and antimicrobial) and their low natural abundance, preparation methods using multistep methodologies have been intensively studied. Biological activity depends upon the stereochemistry of the substitutents. Therefore, the development of new methodologies for the stereoselective construction of tetrahydrofuran cores is still very attractive.
Most methods have been concerned with the construction of 2,5-disubstituted tetrahydrofurans[6] while fewer focused on 2,3,5-trisubstituted tetrahydrofurans[7].

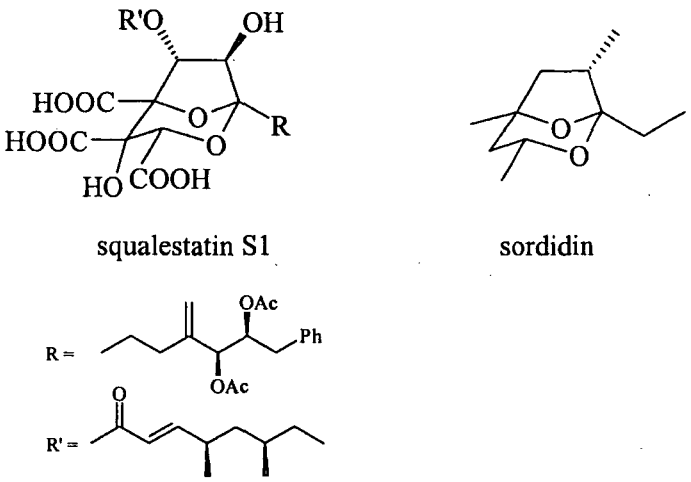
The aim of this project was to develop a methodology for the synthesis of highly functionalised 2,3,5-trisubstituted tetrahydrofurans. The strategy adopted was a tandem methodology, which involved a catalytic C-H insertion of diazocarbonyl acetal templates **(I)** followed by a stereoselective reductive cleavage of the resultant bicyclic acetals **(II)** (Scheme 1.2).



(I) (II) (III)

Scheme 1.2

The bicyclic acetals **(II)** are useful intermediates but also targets for total synthesis. Indeed, this core structure is present in both squalestatin S1 and sordidin (Scheme 1.3).



squalestatin S1 sordidin

Scheme 1.3

Isolated by Merck[8] in 1992, from a soil fungus in Spain and by Glaxo[9] in Portugal, squalestatin S1 belongs to a class of fungal metabolites, also including zaragozic acid, which are inhibitors of squalene synthetase in the biosynthesis of cholesterol. Isolated and identified by Ducrot[10] in 1995, sordidin is a volatile aggregation pheromone released by the male of the banana weevil, a widespread and highly destructive pest of banana trees. Field trials have shown that sordidin lures in traps led to a high capture rate of weevils and offered a viable method for controlling the population of this pest.[11] But since the natural abundance of this pheromone is very low (1500 weevils yield *c.a.* 100 μg),

synthesis provides the only practical method for producing significant quantities of sordidin.

After an overview of C-H activation, and more specifically and thoroughly of C-H activation by means of metallocarbenes in this introduction chapter, the three following chapters will describe the optimisation studies for the preparation of the bicyclic acetal core, the attempt towards the synthesis of sordidin and the reductive cleavage of the bicyclic acetals formed. After a general conclusion, Chapter 6 will detail the experimental procedures and the analytical data of the products formed during this work.

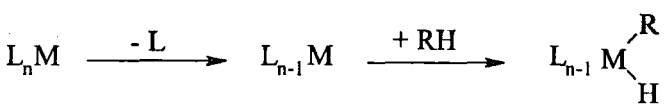
1.2-C-H activation :

Over the last two decades, the dirhodium (II)-catalyzed decomposition of α-diazocarbonyl compounds, and the subsequent C-H insertion of the resulting rhodium carbenoid intermediates, has emerged as a particularly powerful methodology for the construction of carbocylic and heterocyclic rings. However, C-H activation by means of metal-carbenoid-induced C-H insertion is generally not included in the literature reviews on C-H activation.

1.2.1-Transition-metal catalyzed activation of C-H bonds :

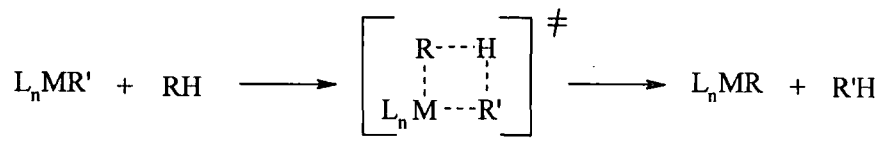
One of the most extensively studied strategies for the formation of carbon-carbon bonds has been the generation of highly reactive metal complexes. They have been developed to activate C-H bonds and to form C-C bonds in a single preparative step combining economy and efficiency. Palladium and ruthenium catalysts are frequently used. However, the biggest challenge has been to regenerate the reactive catalyst. Nevertheless, over the years a great knowledge has been gained on the process of C-H bond activation and three main mechanisms have been identified : oxidative addition, σ-bond metathesis and electrophilic substitution.

- Oxidative addition[12] :



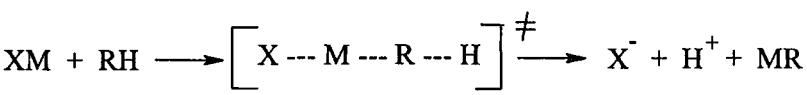
Late transition metals (right side of the transition series) oxidatively add a C-H unactivated bond leading to the hydrido (alkyl) metal complex.

- σ-bond metathesis[13] :



A [2+2]-σ-bond metathesis mechanism involving a 4-center transition state is suggested for early transition lanthanide and actinide metals. Bercaw[14] and Marks[15] have shown that C-H bonds with more *s*-orbital character react faster than those with more p-orbital character ($sp>sp^2>sp^3$).

- Electrophilic substitution[16] :

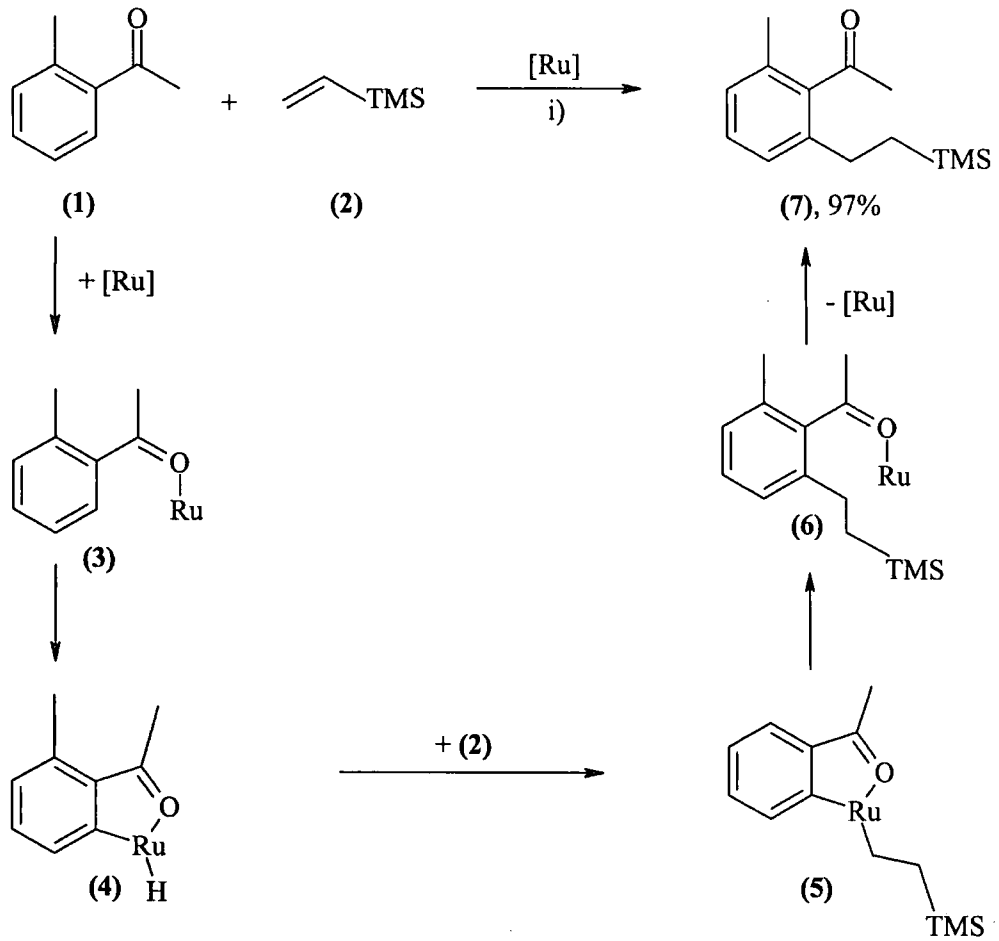


This mechanism is typical of zirconium, titanium, tantalum and vanadium complexes.

In the case of the intramolecular C-H activation, three different processes have been identified : the transition metal can be precoordinated to a suitable functional group prior to the C-H bond activation by cyclometallation, the transition metal forms a σ-bond with the carbon (cyclometallation) or the transition metal is considered as an organometallic base responsible for the C-H activation without cyclometallation.

1.2.1.1-Intramolecular C-H activation by a precoordinated transition metal : Murai *et al*[17]. in 1995 reported a highly efficient ruthenium-catalyzed addition of aromatic C-H bonds to olefins where ketones were used as precoordinating functional groups (Scheme 1.4). The transition metal is precoordinated to the carbonyl function of **(1)** and in a favorable position for the cleavage of the C-H bond. Cyclometallation leads to the ruthenium hydride complex **(4)** as reactive intermediate. After coordination of the olefin **(2)**, an insertion reaction probably occurs leading to the formation of **(5)**. The C-C bond is

then formed by reductive elimination and gives **(6)**. Subsequent decomplexation of **(6)** leads to the final product **(7)** and liberates the active catalyst.

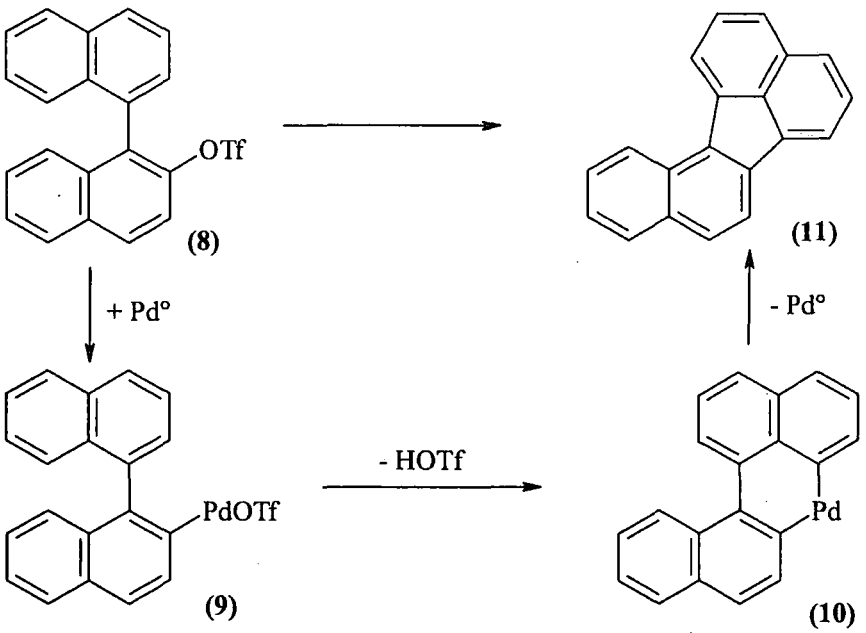


i) reaction conditions : 2 mol% $[RuH_2(CO)(PPh_3)_3]$, toluene reflux, 2h.

Scheme 1.4

1.2.1.2-Intramolecular C-H activation through carbon-bound transition metals :

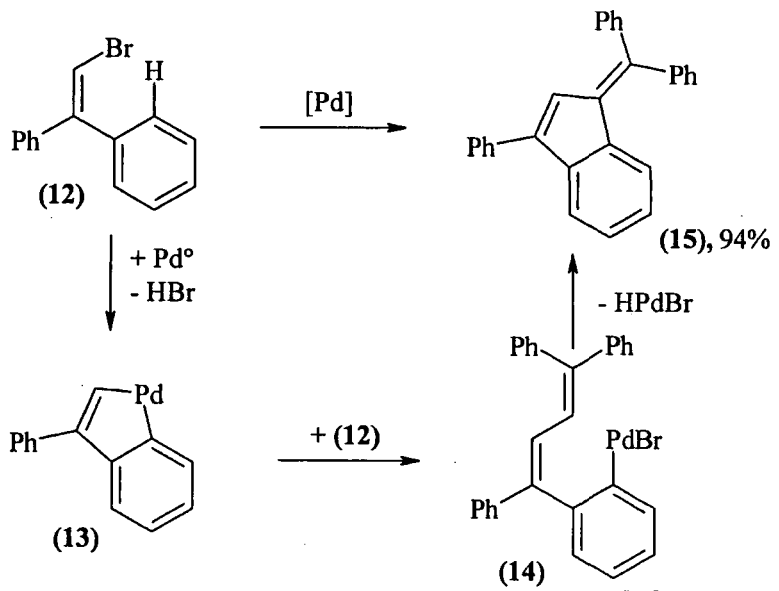
The formation of the fluoroanthene derivative **(11)** by Rice and Cai[18] is a good illustration of this type of reaction (Scheme 1.5). Pd^{II} catalysts are firstly reduced *in situ* to Pd°. The first carbon-palladium σ-bond is formed by oxidative addition of Pd° catalyst to the aryltriflate **(8)**. The electrophilic Pd^{II} species **(9)** is responsible for the intramolecular C-H activation during which the second palladium-carbon σ-bond is formed. Subsequent reductive elimination gives the five-membered ring **(11)**.



reaction conditions : 10 mol% $[PdCl_2(PPh_3)_2]$, LiCl, DBU, DMF, 140°C, 10h.

Scheme 1.5

This type of intramolecular aryl-aryl coupling is classed as an established and useful method for the construction of five- and six-membered carbocyclic and heterocyclic systems and clearly a domain of palladium chemistry. It is worth noting that five-membered palladacycles react differently (Scheme 1.6).



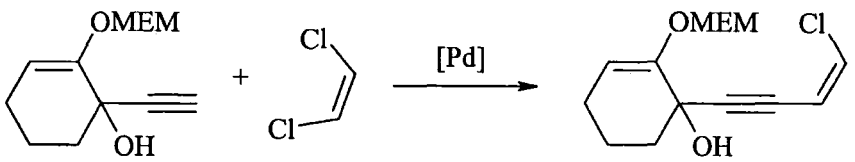
reaction conditions : 1 mol% $Pd(OAc)_2$, K_2CO_3, nBu$_4$NBr, DMF, 100°C, 3days

Scheme 1.6

After oxidative addition followed by C-H activation, the phenyl-substituted bromoethene **(12)** forms the 5-membered palladacycle **(13)**. In this case, the reductive elimination of Pd° is inhibited because a highly strained and antiaromatic benzocyclobutadiene would be formed. Instead, the palladacycle **(13)** adds to a further equivalent of starting material **(12)** leading to the Pd^{II} intermediate **(14)**. Ring closure under an intramolecular Heck reaction occurs to give product **(15)**.[19]

1.2.1.3-C-H activation without cyclometallation :

Since the early 1980s, transition metal complexes have been known to be capable of oxidative addition to alkane C-H bonds. However, the metal catalyst is also an organometallic base responsible for the C-H activation. The Stevens-Castro-Sonogashira reaction[20] (e.g. coupling of **(16)** with **(17)** to give **(18)**, Scheme 1.7) is a good illustration of this type of reaction.



(16) **(17)** **(18)**, 80%

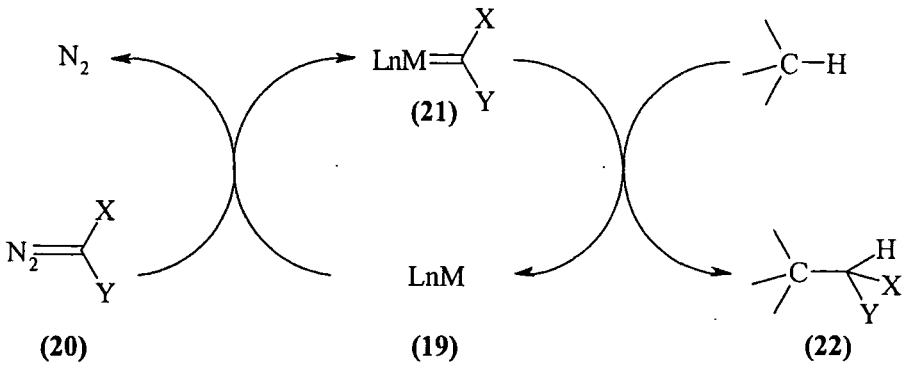
reaction conditions : 5 mol% $[Pd(PPh_3)_4]$, 15 mol% CuI, $nBuNH_2$, 20°C

Scheme 1.7

Additional bases such as amines or carbonates are always present; however, their main purpose is the regeneration of the active Pd° catalyst from the hydridopalladium halide complex intermediate.

1.2.2-C-H activation by means of metallocarbenes :

Even though the C-H insertion of metal-carbenoids is not generally included in the literature reviews on C-H activation, this process does lead to the functionalization of an unactivated C-H bond. The metal atom is not thought to interact directly with the C-H bond. A metal-carbenoid undergoes the insertion. A major advantage of metal-carbenoid-induced C-H insertion is its catalytic cycle process (Scheme 1.8).



Scheme 1.8

Decomposition of the carbene precursor, typically a diazo-compound **(20)**, upon metal complex catalysis generates molecular nitrogen and a high-energy carbenoid intermediate **(21)**. Subsequent C-H insertion gives the functionalized product **(22)** and regenerates the starting catalyst **(19)**, which allows the catalytic cycle to continue.

The following sections will describe the preparation, structural types and typical reactions of metallocarbenes after a more general section about carbenes.

1.3-Metallocarbenes :

1.3.1-Generality :

Carbenes may be defined as neutral 'divalent' carbon intermediates in which a carbon atom has two covalent bonds to other groups and two non-bonding electrons. Carbenes exist in two spin states. The *singlet* carbene has two electrons with antiparallel spins in an sp^2-orbital leaving a vacant *p*-orbital. In the *triplet* carbene, both the sp^2- and *p*-orbitals contain one electron each, with parallel spins, and it can therefore be considered as a diradical (Scheme 1.9).

singlet state triplet state

Scheme 1.9

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

A closer inspection of the chemistry of carbenes indicates the existence of three distinct classes :

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

Free carbenes were the first to be investigated in some detail. They have long been known to be capable of inserting into C-H bonds but their high reactivity is responsible for low yields and low selectivity which have limited their use.[21]

Carbenes can be stabilized by steric and/or electronic effects. Thus, in 1991, a distillable red oil phosphinosilyl carbene[22] and the first crystalline carbene (1,3-di-1-adamantylimidazol-2-ylidene)[23] have been reported.

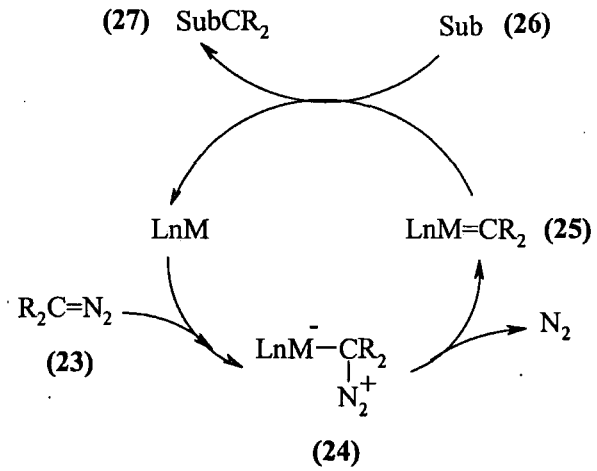
Finally, transition metal carbenoids or metallocarbenes describe carbenes complexed with transition metals. Unlike free carbenes, these species acquire stabilization by interaction with the metal and are more selective in their behaviour because of this interaction. This type of carbene is generally generated by catalytic decomposition of diazocarbonyl compounds. The metal catalyst needs to have an accessible site for coordination with the diazo-compound. After coordination, molecular nitrogen is lost and the carbenoid intermediate formed. The metal catalyst binds to the carbene through strong σ-acceptor interactions and weak π-back-donor interactions, which stabilize the carbene without affecting its electrophilic character. The degree of electrophilicity of the metallocarbenoids and their stability are governed by the nature of the metal catalyst and its ligands but also by the nature of the substituents adjacent to the carbene carbon.

The following section of this introduction will describe, in more detail, the generation and the different structural types of the metallocarbenes as well as their typical reactions.

1.3.2-Metallocarbenes :

1.3.2.1-Generation of metallocarbenes :

During the early investigation of diazo chemistry,[24] it was discovered that transition metals could catalytically decompose diazocarbonyl compounds and generate metallocarbenes. Early work in this area made use of insoluble copper catalysts (Cu powder, Cu bronze, Cu_2O, CuO, $CuSO_4$, CuCl and CuBr).[25] Although these catalysts are still employed today, their use has decreased significantly with the use of homogeneous copper catalysts (e.g. Cu (I) triflate, $Cu(acac)_2$).[26] In the late 1970s, Teyssie and co-workers[27] discovered that rhodium carboxylates also facilitate nitrogen loss, and since then a wide range of transition metal complexes (rhodium, palladium and cobalt) have been extensively studied and used for the decomposition of α-diazocarbonyl compounds. Although this catalytic decomposition had been known since the early part of the last century, the mechanism involved was not proposed until 1952 (Scheme 1.10).[28]



Scheme 1.10

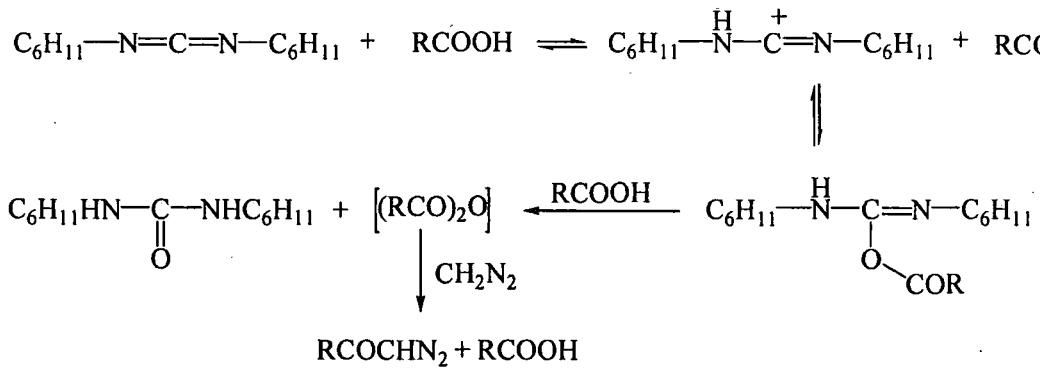
The first step is the attack of the diazo functionality **(23)** at the metal to form a zwitterionic metallo intermediate **(24)**. The nitrogen is then extruded to form the metal carbenoid **(25)**, which can react with various electron-rich substrates **(26)** (alkenes, C-H bonds etc.) producing the observed product **(27)** and regenerating the initial catalyst.

1.3.2.2-Preparation of metallocarbene precursors :

As mentioned above, diazocompounds are used as carbene precursors. The first synthesis of an α-diazocarbonyl dates back to 1883, when Curtius[29] prepared an ethyl diazoacetate by diazotization ($NaNO_2$, HNO_2 or N_2O_4) of glycine, a natural amino acid. However, simple diazocarbonyl compounds only became readily available in the late 1920s. There are two major strategies for the preparation of diazocarbonyl compounds. These involve either acylation of diazoalkanes or diazo-transfer reactions.

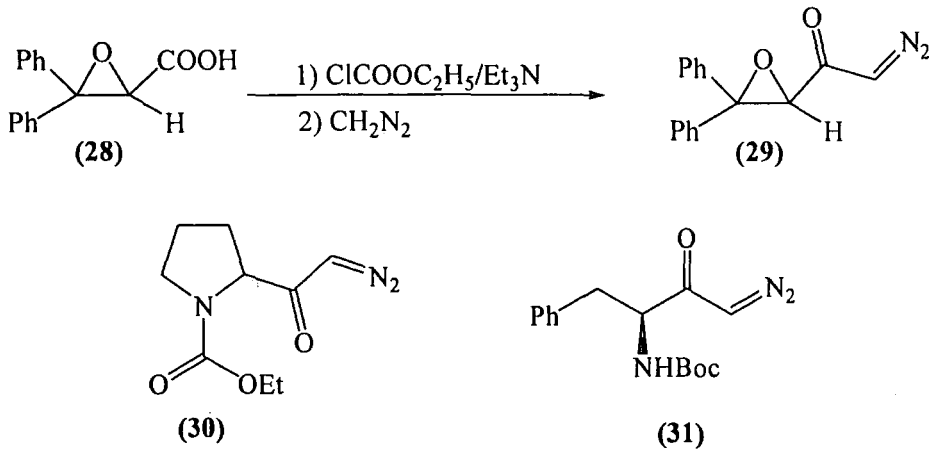
1.3.2.2.1-Acylation of diazoalkanes :

Arndt and Eistert[30] and Bradley and Robinson[31] showed that acylation of diazomethane with an acyl chloride leads to diazocarbonyl compounds when using a sufficient excess of diazomethane in order to avoid the addition of hydrogen chloride to the diazoketone formed. Anhydrides are also suitable acylating agents.[32] A convenient procedure involves treatment of the carboxylic acid with dicyclohexyl carbodiimide to form the anhydride, which is then allowed to react with ethereal diazomethane (Scheme 1.11).[33]



Scheme 1.11

A convenient *in situ* procedure to form mixed anhydrides involves anhydride formation between a carboxylic acid and a chloroformate ester. Contrary to the previous method, all the acid is converted into the diazoketone. This route has been applied to the synthesis of 3-diazoacetyl-2,2-diphenyloxirane **(29)**[34] and to the formation of homochiral-α-diazoketones **(30,31)**[35] from N-protected amino-acids (proline, phenylalanine) (Scheme 1.12).

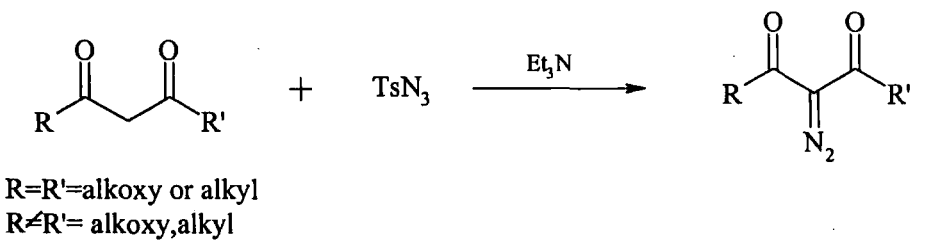


Scheme 1.12

Acylation of diazomethane is the most important route to acyclic terminal α-diazoketones. Nevertheless this method is not applicable to cyclic α-diazoketones.

1.3.2.2.2-Diazo-transfer reaction :

Regitz[36] in 1967 introduced a diazo-transfer technique, which became a standard route not only to cyclic α-diazoketones but also to many acyclic systems. The method in the broadest sense refers to the transfer of a complete diazo group from a donor (a sulfonyl azide) to an acceptor (an acid or a ketone derivative) (Scheme 1.13).

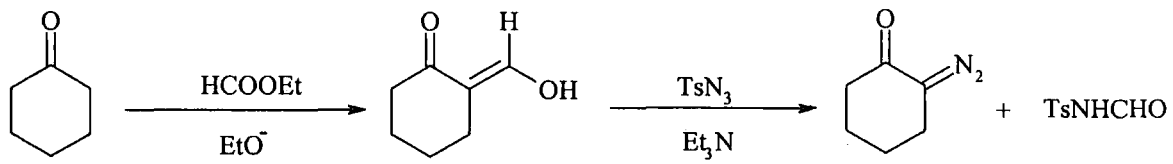


R=R'=alkoxy or alkyl
R≠R'= alkoxy,alkyl

Scheme 1.13

In the case of malonic esters, β-keto esters and β-diketones, simple treatment by tosyl azide in dry chloroform or ethanol using triethyl amine as a base is enough for the diazotransfer to occur since the α-methylene position is acidic enough. The diazo-transfer works well when the reaction site is activated by two carbonyl functions but generally fails when the methylene group is activated by a single carbonyl group. The efficiency of

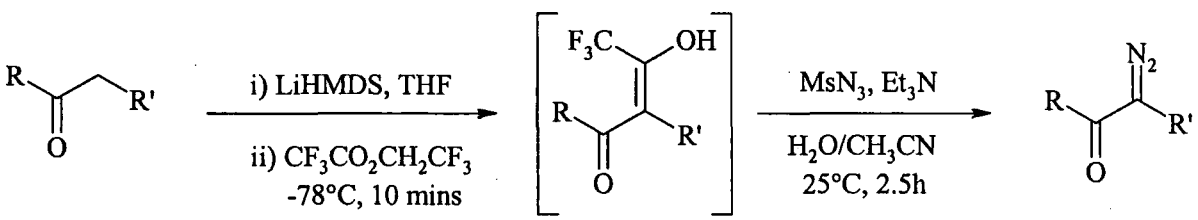
the diazo-transfer reaction can be improved, in that later case, by activation of the ketone precursor prior to diazotransfer (Scheme 1.14).



Scheme 1.14

The reaction involves a Claisen condensation of the ketone with ethyl formate introducing a strongly activating formyl group released as the sulfonamide after diazotransfer. A number of acyclic and cyclic α-diazo ketones have been synthesized this way.[37] However, the harsh conditions required for the Claisen condensation step are particularly problematic for base-sensitive substrates such as α,β-enones.

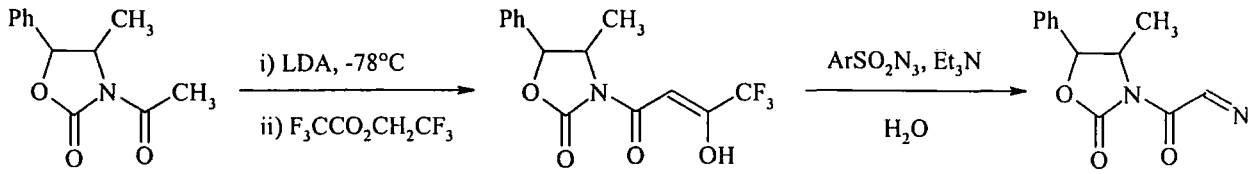
To overcome this problem, Danheiser[38] developed an improved method where the ketone **(32)** was activated as the corresponding α-trifluoroacetyl derivative **(33)** prior to the diazo-transfer (Scheme 1.15).



(32) **(33)** **(34)**

Scheme 1.15

Doyle[39] used these conditions to achieve the diazotransfer to a base sensitive N-acyloxazolidinone derivative **(35)** using a similar strategy (Scheme 1.16).



(35) (36) (37)

Scheme 1.16

1.3.2.3-Metallocarbene structural types :

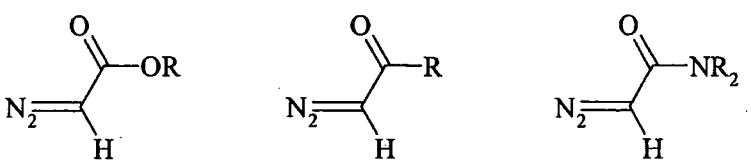
The nature of the substituents can dramatically influence the stability, and thus the reactivity, of the metallocarbene complex. An acceptor group will tend to make the carbenoid more electrophilic and reactive, whereas a donor group will make the carbenoid more stable and so more chemoselective.

On the basis of the nature of the substituents, Davies has classified the metallocarbenoids into three groups : [40]

- acceptor-substituted carbenoids,
- acceptor-acceptor-substituted carbenoids,
- donor-acceptor-substituted carbenoids.

1.3.2.3.1-Acceptor-substituted carbenoids :

This category groups carbenoids derived from diazo compounds with a single electron-withdrawing substituent (Scheme 1.17).



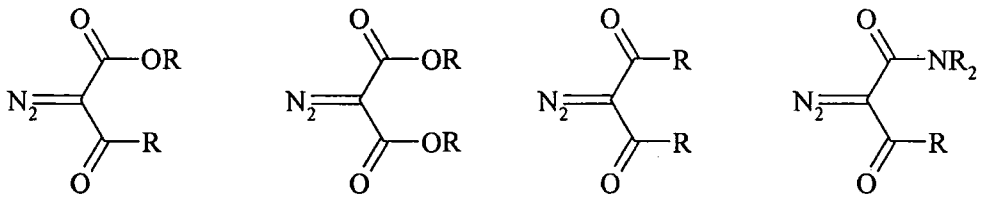
diazoacetate diazoketone diazoacetamide

Scheme 1.17

Their decomposition leads to the formation of highly reactive metallocarbenoid species. Carbenoids from diazoketones are more reactive than carbenoids from diazoacetates, which are more reactive than carbenoids from diazoacetamides. The common side reaction for this group is the dimerization of the carbene.

1.3.2.3.2-Acceptor-acceptor-substituted carbenoids :

This category groups carbenoids derived from diazo compounds with two electron-withdrawing substituents (Scheme 1.18).



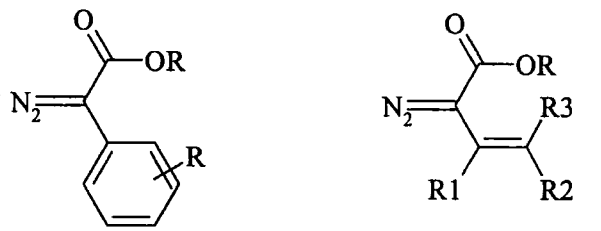
diazoacetoacetate diazomalonate diazodiketone diazoacetoacetamide

Scheme 1.18

Due to the added stabilization of the diazo compound by the second electron-withdrawing group, very active catalysts are required for the decomposition.[39,41] Once formed, the carbenoid is highly electrophilic and easily undergoes C-H activation. The common side reactions for this group are carbene dimerization and hydride transfer.

1.3.2.3.3-Donor-acceptor-substituted carbenoids :

In this group, a donor substituent such as a vinyl or aryl group is stabilizing the carbenoid through resonance (Scheme 1.19).



aryldiazoacetate vinyldiazoacetate

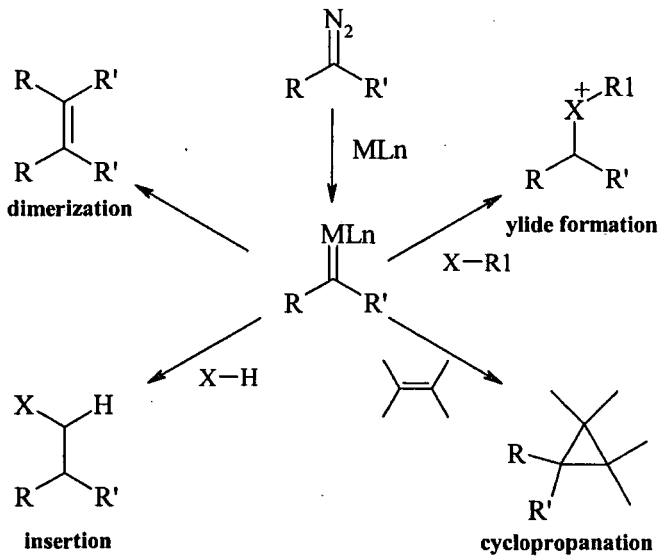
Scheme 1.19

Very active catalysts are required for effective decomposition of this class of diazo compounds. Davies[42] reported the first example of C-H activation with this group of carbenoids in 1997. As a result of the work of Davies[43] over the past few years, this group

of carbenoids has been recognized as capable of undergoing highly chemoselective intermolecular C-H activation.[44]

1.3.2.4-Typical reactions of metallocarbenes.

Transition-metal catalyzed decomposition of α-diazocarbonyl compounds has been widely studied. Thus, transition metal carbene complexes (or metallocarbenes) are now widely used in organic synthesis. They can undergo a large spectrum of useful transformations including cyclopropanation, ylide generation and insertion reactions (Scheme 1.20).



X = C, Si, O, S, N ; R = H, alkyl, aryl, COR, CN, NO_2 ; R' = H, alkyl, aryl, OR, NR_2

Scheme 1.20

Transition metal complexes of copper (I) and dirhodium (II) are the most effective catalysts for diazodecomposition.[40,45] There is now general understanding that metal and ligand modifications induce electronic and steric interactions in product formation that provide substantial control of chemo, regio- and stereoselectivity.[46] Dirhodium (II) carboxylates and carboxamidates have proven to be the most versatile for highly selective metal carbene transformations.[47]

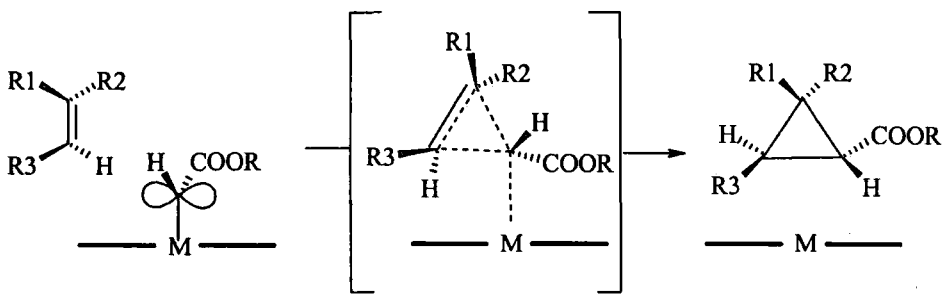
The following sections will describe in more detail the main reactions of metallocarbenes (cyclopropanation, ylide formation, Wolff rearrangement and insertion) and the different

factors that have an effect on the selectivity. However, it should be noted that, because the object of interest of this thesis is the C-H insertion, the chemo-, regio- and stereoselectivity of the other transformations will not be discussed in detail.

1.3.2.4.1-Cyclopropanation :

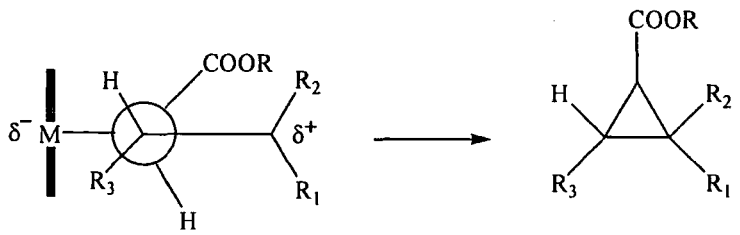
The formation of cyclopropanes by the 1,2-addition of carbenes to alkenes was first reported by Doering[48] in 1954. The process, which is probably the most characteristic reaction of carbene intermediates, provides a powerful means of constructing cyclopropanes.

A lot of research has been done to understand the mechanism of catalytic cyclopropanation.[49] The highly electrophilic metal carbene intermediate is believed to commence bond formation by attacking as an electrophile with its vacant *p*-orbital. The direct approach of a carbene to a double bond is forbidden due to antibonding interactions. Therefore, the carbene adopts a sideways approach. The orientation of the olefin approaching the carbene center controls the relative stereochemistry. The orientation itself is controlled by the carbene substituents and the catalyst face constituted by a "wall" of ligands limiting steric interactions between the carbene substituent (COR') and the alkene substituents. (Scheme 1.21).



Scheme 1.21

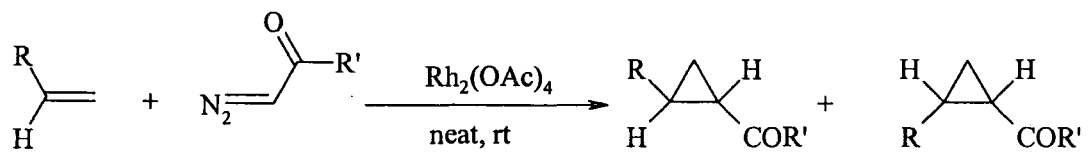
Maximum overlap occurs through the alignment described for **(38)**, and the olefin is moving away from the catalyst face as its proximity to the carbene carbon increases. The optimum transition-state orientation can be representated by **(40)** (Scheme 1.22).



(40)

Scheme 1.22

Doyle[50] studied in some detail the steric influences of the substituents of both olefin and carbene on diastereoselectivity. Thus, the use of the more hindered *t*-butyl substituent influences the diastereoselectivity and favours the formation of the *trans*-cyclopropane **(41)** as shown on the following scheme (Scheme 1.23, Table 1.1).

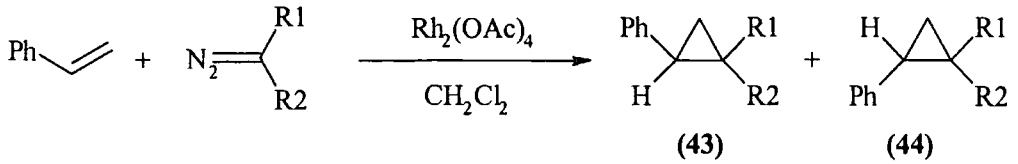


(41) (42)

alkene	Yield (%)	trans/cis ratio
R=Ph	93	1.6
R=OEt	88	1.7
R=tBu	87	4.2

Scheme 1.23, Table 1.1

Greater variation in diastereoselectivity results from changes in the carbene substituents and is due to electronic influences (Scheme 1.24, Table 1.2).



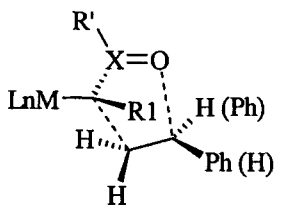
(43) (44)

Entry	R1	R2	Yield (%)	Ratio **(43)** : **(44)**
1	H	Ph	38	23 : 77
2	H	COOEt	93	62 : 38
3	H	$CONMe_2$	74	69 : 31
4	H	NO_2	54	71 : 29
5	Ph	COOEt	94	95 : 5
6	HC=CHPh	COOEt	94	> 95 : 5
7	HC=CHCOOEt	COOEt	96	89 : 11

Scheme 1.24, Table 1.2[51]

The more polar substituent (NO_2 > $CONMe_2$ > COOEt > Ph) determines the predominant stereochemistry, **(43)** > **(44)** (entries : 1-4). And, the introduction of a second polar substituent favors even more the formation of **(43)** (entries : 5-8).

Doyle postulated that the nucleophilic oxygen of the polar carbene substituent could stabilize the developing electropositive center of the reacting alkene, which increases the diastereoselectivity (Scheme 1.25).

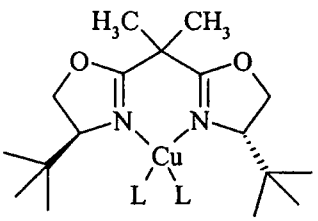


Scheme 1.25

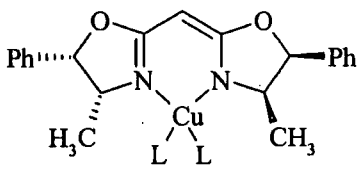
Finally, the catalyst, and more specifically the metal ligands, can also have a significant influence on diastereoselectivity. Historically, the use of various copper catalysts[52] was prevalent but strongly challenged by the use of group VIII metals[53] in the late 1960s and early 1970s. A systematic screening of common metal complexes revealed that rhodium (II) species were also efficient catalysts for cyclopropanation.[54] As reported by Doyle,[55]

among carboxylate and carboxamidate ligands for rhodium, the greater the acid strength of the ligand's conjugate acid, the higher is the reactivity of the catalyst and lower is its selectivity. The catalyst effectiveness order for diastereocontrol is therefore : $Rh_2(cap)_4$, $Rh_2(acam)_4$ > $Rh_2(OAc)_4$, $Rh_2(oct)_4$, $Rh_2(NHCOCF_3)_4$ > $Rh_2(tfa)_4$, $Rh_2(pfb)_4$.
Regioselectivity in cyclopropanation depends on electronic and steric factors.[51,56] The more electron-rich double bond will react preferentially : $ROCH{=}CH_2$ > $PhCH{=}CH_2$ > $RCH{=}CH_2$, R=alkyl and $R_2C{=}CH_2$ > $RCH{=}CH_2$. Electron deficient olefins (i.e : α,β-unsaturated) often fail to generate cyclopropanes but rather form pyrazolines. Conjugated dienes and trienes are also reactive and cyclopropanation at the more nucleophilic double bond is predominant.[57]

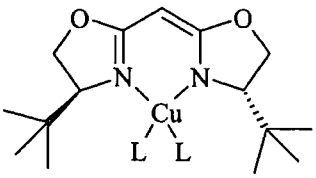
The first report of an homogeneous chiral catalyst inducing asymmetry was published in 1966 by Nozaki,[58] albeit with low e.e (10%), using a chiral salicylaldimine for the reaction of styrene with ethyl diazoacetate. Since then, extensive efforts in chiral ligands design was promoted by several other groups. Bis(oxazoline)-copper catalysts have been synthesized by Evans[59] **(45)**, Masamune[60] **(46)** and Pfaltz[61] **(47)**, and bipyridine-copper catalysts by Katsuki[62] **(48)** (Scheme 1.26).



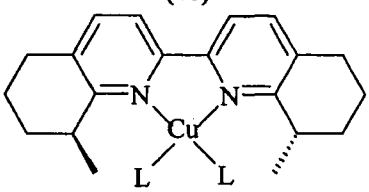
(45)



(46)



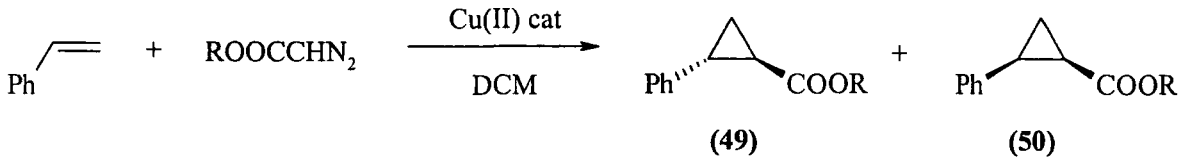
(47)



(48)

Scheme 1.26

These copper catalysts showed high enantiocontrol for intermolecular cyclopropanation reactions (Scheme 1.27).

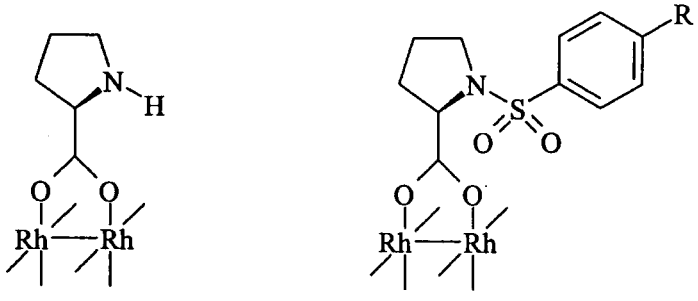


(49) **(50)**

substituent R	catalyst	ratio **49/50**	enantioselectivity (e.e.)
Et	**45**	73 : 27	**49**, 99% **50**, 97%
Et	**46**	75 : 25	**49**, 48% **50**, 36%
Et	**47**	77 : 23	**49**, 98% **50**, 93%
t-Bu	**48**	72 : 28	**49**, 77% **50**, 73%

Scheme 1.27

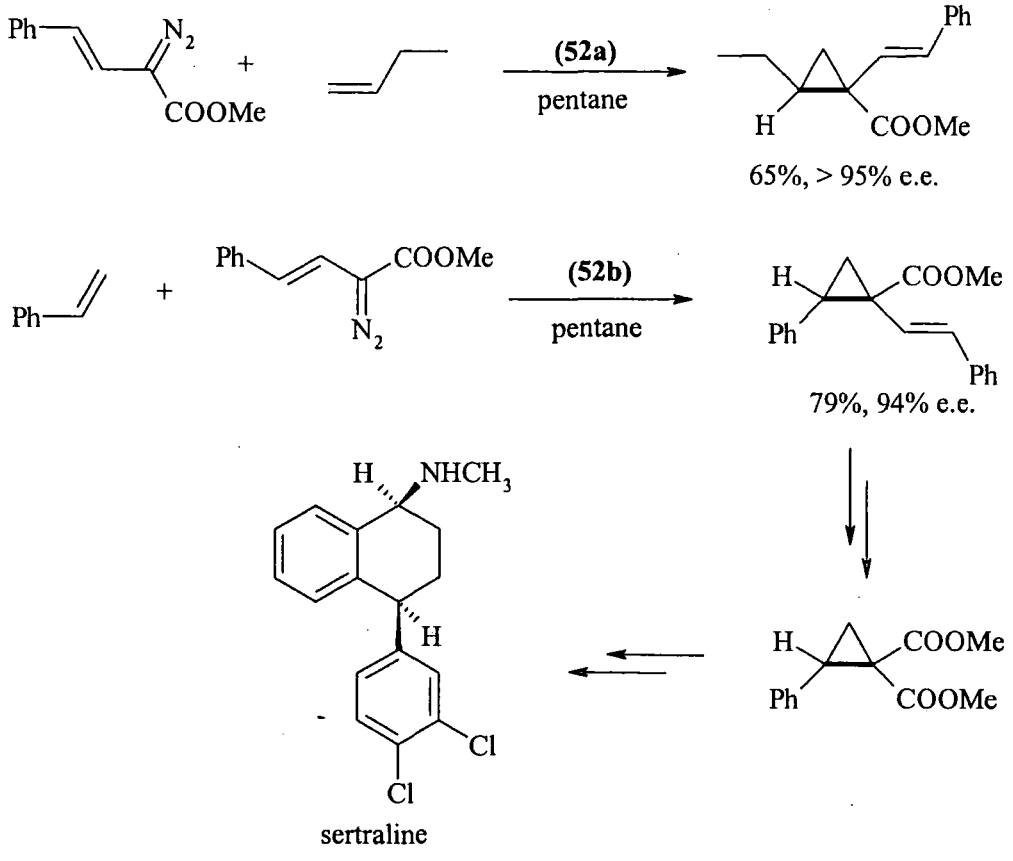
Chiral dirhodium (II) carboxamidates **(51)** and **(52a)** (Scheme 1.28), developed by McKervey[63] and Davies[64] respectively, showed high enantiocontrol.



(51) **(52a,b)** a : R = tBu, Rh_2(S-TBSP)$_4$
b : R = $nC_{12}H_{25}$, Rh_2(S-DOSP)$_4$

Scheme 1.28

Corey employed (Rh_2(S-DOSP)$_4$, **52b**) with great success for the synthesis of the antidepressant sertraline.[65] (Scheme 1.29).



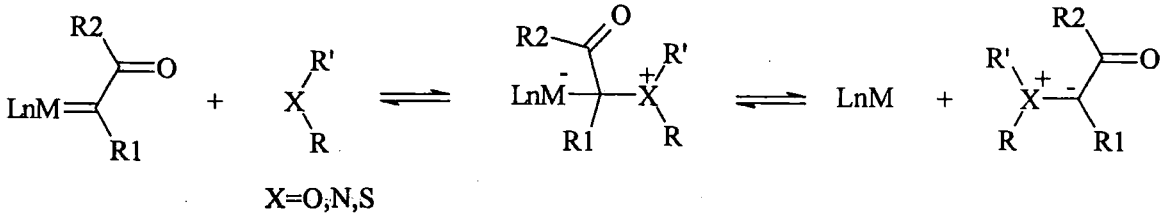
Scheme 1.29

Extensive research, in particular by Doyle,[66] has shown that the use of chiral dirhodium (II) carboxamidates led to high enantiocontrol. The optimum catalysts for the intermolecular cyclopropanation are Rh_2(S-TBSP)$_4$ and Rh_2(S-DOSP)$_4$.

1.3.2.4.2-Ylide formation and subsequent reactions :

1.3.2.4.2.1-Ylide formation :

Metallocarbenes are highly electrophilic species and therefore can readily react with nucleophiles to form ylides (Scheme 1.30).

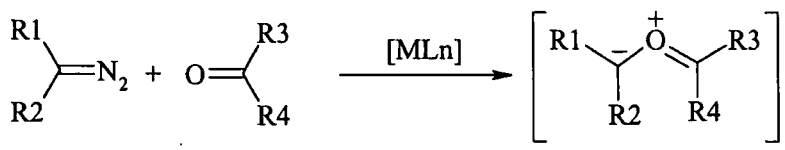


Scheme 1.30

Three categories of ylides exist : oxonium, sulfur and nitrogen ylides. It is worth noting that sulfur[67] and nitrogen ylides[68] can be easily formed without the presence of a metal catalyst. However, the formation of oxonium ylides requires the use of rhodium carboxylates or homogeneous copper complexes.[69] Oxonium ylides are highly reactive and short-lived intermediates compared to the other ylides.

Ylides are reactive intermediates, which are known to undergo a number of useful transformations[70] such as [2,3]-sigmatropic rearrangement, [1,2] insertion (Stevens rearrangement) and β-hydride elimination.

Another category of great importance exists: the carbonyl ylides. These ylides are generated through the reaction of the metallocarbenes with the polarized carbonyl bond of an aldehyde, ketone, amide or imide (Scheme 1.31).



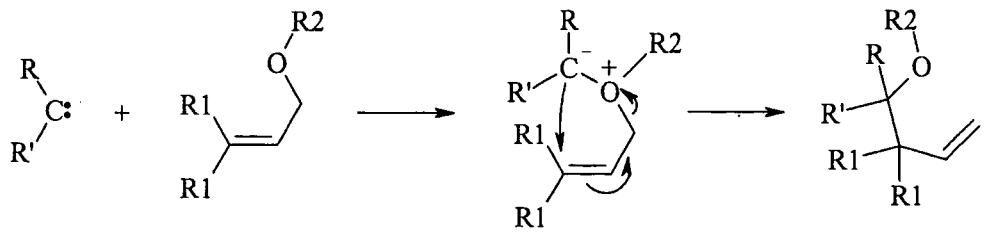
Scheme 1.31

They can be readily trapped inter- or intramolecularly with π-bonds (i.e. aldehydes, ketones, alkenes or alkynes) via a 1,3-dipolar cycloaddition reaction, to afford oxygen containing cyclic or polycyclic systems.[71] This process has shown great versatility in the synthesis of natural products and some examples will be given in the following section concerning the subsequent reactions of ylides.

1.3.2.4.2.2-Subsequent reactions of ylides :

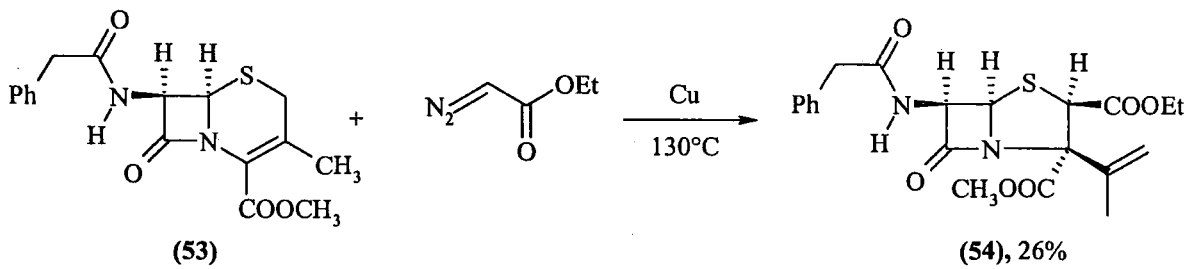
- **[2,3]-sigmatropic rearrangement :**

The [2,3]-sigmatropic rearrangement is a thermal, concerted, orbital-symmetry allowed process,[72] observed in the case of allylic or propargylic oxygen, nitrogen or sulphur ylides (Scheme 1.32). The rearrangement makes a new C-C σ-bond at the expense of a C-O σ-bond, *via* a 5-membered ring transition state, although the C-O bond is stronger. This is due to the fact that the oxyanion in the product is more stable than the carbanion in the starting material.



Scheme 1.32

The tandem inter- or intramolecular catalytic ylide formation followed by [2,3]-sigmatropic rearrangement has found wide synthetic applications. In one of the first examples, the [2,3]-sigmatropic rearrangement was used to convert cephalosporin **(53)** into penicillin **(54)** (Scheme 1.33).[73]

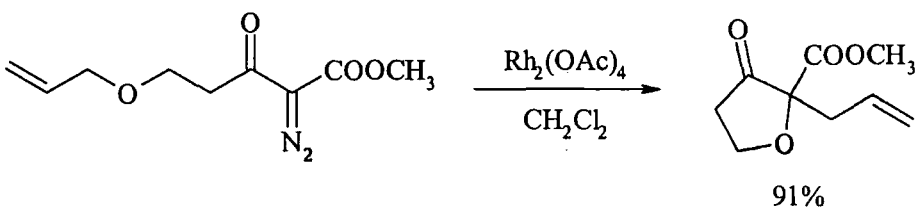


(53) **(54)**, 26%

Scheme 1.33

Copper catalysts were not particularly successful for this transformation, possibly because of the high temperature often required.[74] However, the high electrophilic copper (II) hexafluoroacetyl acetonate emerged as the catalyst of choice for this rearrangement by minimising competing C-H insertion.[75] Rhodium (II) acetate showed also a great potential, mostly because the diazo decomposition takes place under milder conditions.

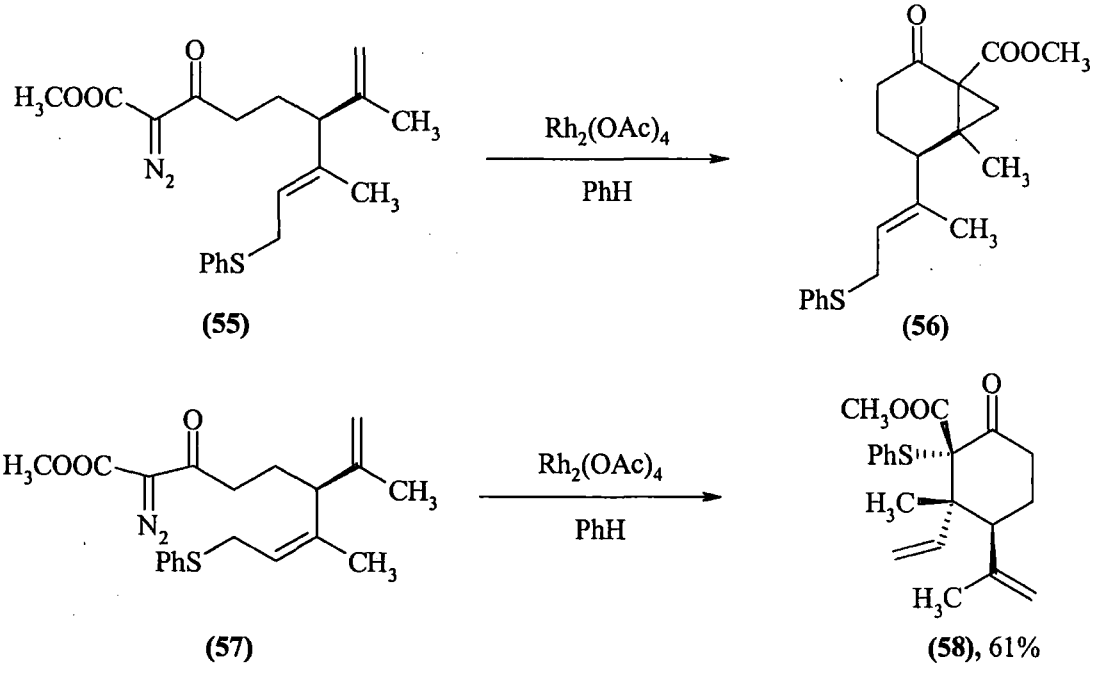
The [2,3]-sigmatropic rearrangement of oxonium ylides offers an approach to the construction of substituted carbocycles and cyclic ethers (Scheme 1.34).[76,77]



91%

Scheme 1.34

The major competing reaction is cyclopropanation. Several studies showed that the chemoselectivity is strongly dependent upon the nature of the diazocarbonyl compound, the choice of metal catalysts, the olefin geometry[78] and the allylic substituents.[79] Indeed, examples are known where intramolecular reactions of metal carbenes with allyl sulfides result in competition between formation of the cyclic sulfonium ylide and cyclopropanation. The following example illustrates the influence of the olefin geometry (Scheme 1.35).

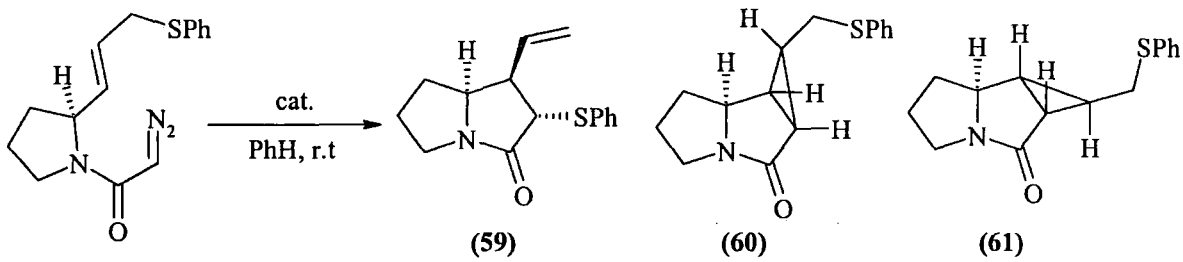


Scheme 1.35

The rhodium acetate catalyzed-decomposition of α-diazo-β-ketoester **(55)** bearing an (E)-olefinic bond afforded the cyclopropane derivative **(56)** leaving the allylic sulfide group intact whereas the corresponding (Z)-olefinic bond α-diazo-β-ketoester **(57)** yielded the cyclohexanone **(58)**.

Doyle[80] has also shown that the metal catalyst choice was important. Thus, he showed that the rhodium-catalyzed reaction of allylic sulfides and amines with ethyldiazoacetate produced the [2,3]-sigmatropic rearrangement products while the copper-catalyzed reaction of amine ylides led mostly to cyclopropanation products.

Studies realised by Chappie[81] have also shown that the choice of catalyst is critical in addition to the olefin geometry and the solvent (Scheme 1.36, Table 1.3).



(59) (60) (61)

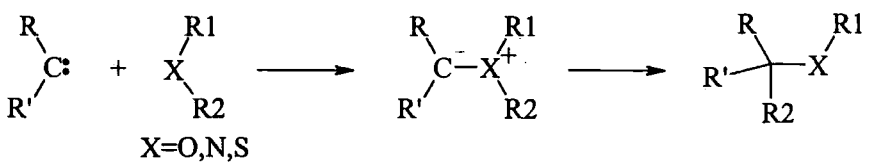
catalyst	Yield (%)	(59)/(60)/(61)
$Rh_2(OAc)_4$	70	0 : 69 : 31
$Cu(hfacac)_2$	68	0 : 68 : 32
$Pd(OAc)_4$	78	0 : 78 : 27
$Rh_2(cap)_4$	71	90 : 0 : 10

Scheme 1.36, Table 1.3

The *trans*-diazoamide was not expected to undergo a [2,3]-sigmatropic rearrangement because the allylic nucleophile was supposed to be too distant to react with the electrophilic carbenoid centre. However, upon decomposition with the electron rich $Rh_2(cap)_4$, the diazoamide formed the unexpected *anti* pyrrolizidine **(59)** whereas rhodium, copper and palladium catalysts with electron-withdrawing ligands produced only cyclopropanes **(60,61)**.

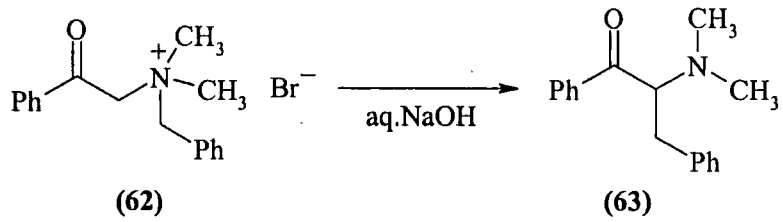
- **[1,2] insertion or Stevens rearrangement :**

The second major rearrangement is the [1,2]-insertion or Stevens rearrangement (Scheme 1.37).



Scheme 1.37

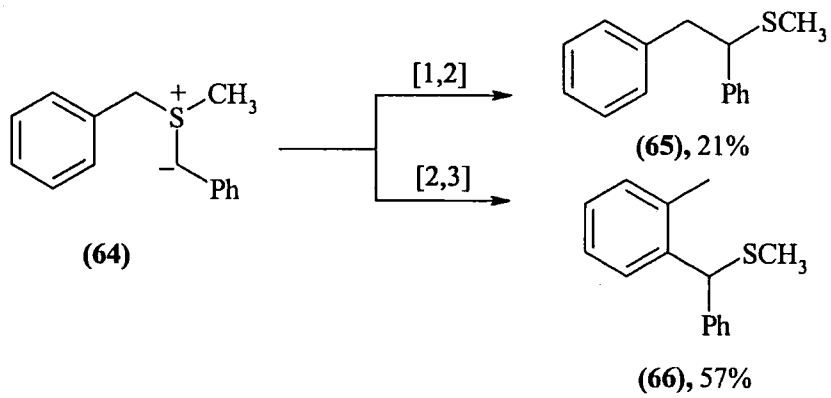
In 1928, Stevens[82] reported that upon treatment with aqueous NaOH, phenacyl benzyl dimethyl ammonium bromide **(62)** was converted into 1-benzoyl-2-benzyldimethyl amine **(63)** (Scheme 1.38).



(62) **(63)**

Scheme 1.38

Although widely studied from a mechanistic point of view,[83] the Stevens rearrangement of ylides has a limited extent and only few synthetic uses. The major problem is the co-occurrence of the [2,3]-sigmatropic rearrangement. For example, the rearrangement of the ylide **(64)** gave the [1,2]- and [2,3]- rearrangement products, **(65)** and **(66)** respectively, in 1:3 ratio (Scheme 1.39).[84]

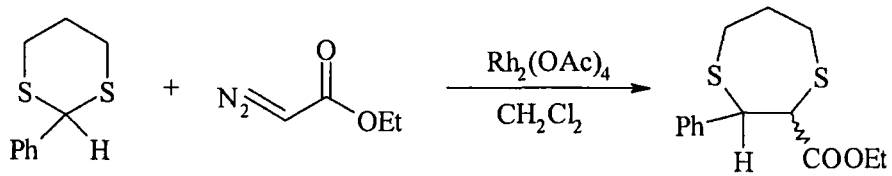


(64) **(65)**, 21% **(66)**, 57%

Scheme 1.39

This result was consistent with the greater probability for the concerted, symmetry-allowed [2,3]-sigmatropic rearrangement to occur against the [1,2]-rearrangement, forbidden by Woodward-Hoffmann rules.[85]

One of the few synthetic uses of the Stevens rearrangement is the formation of ring-expanded products as illustrated in the following scheme (Scheme 1.40).[76]



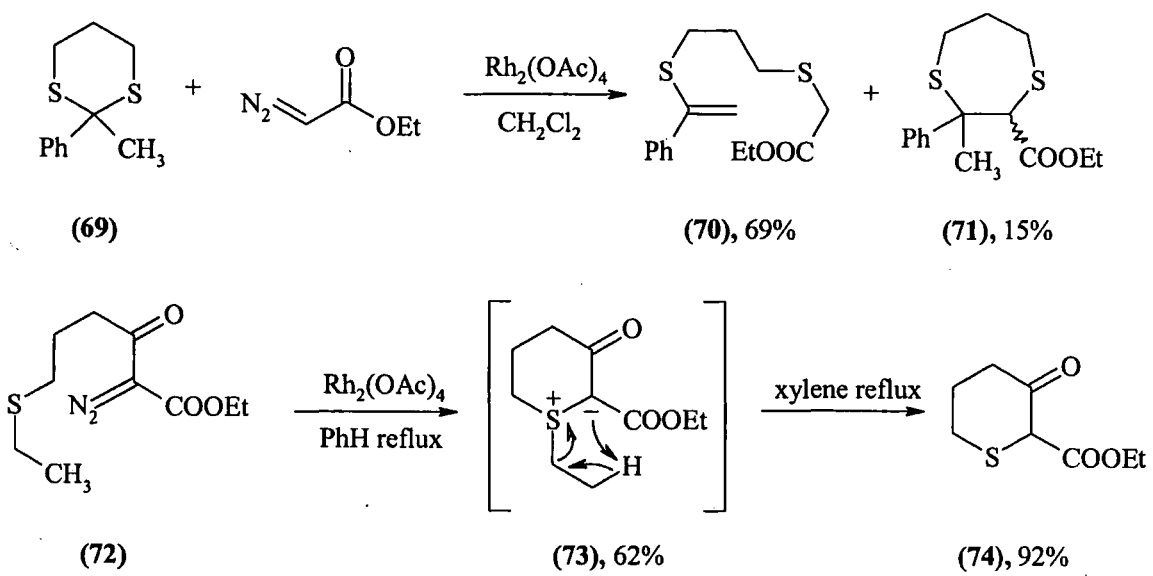
(67) **(68),** 73% (1:1)

Scheme 1.40

In presence of rhodium (II) acetate, the 2-phenyl-1,3-dithiane **(67)** underwent ylide generation with ethyldiazoacetate, and subsequent Stevens rearrangement led to the ring-expanded product **(68)**.

➢ **β-hydride elimination :**

In addition to [2,3]- and [1,2]-rearrangements, the other major reaction pathway for decomposition of ylides is the β-elimination. Some sulfonium ylides undergo thermal intramolecular eliminations, especially those carrying large alkyl groups on the sulfur atoms. Representative examples of β-elimination in both intra and intermolecular schemes are shown below (Scheme 1.41).[76,86]



(69) **(70),** 69% **(71),** 15%

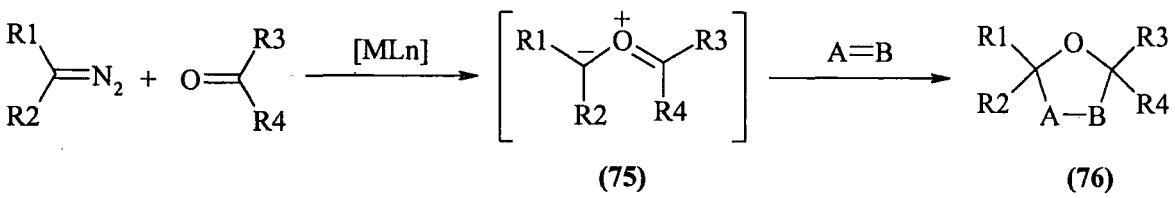
(72) **(73),** 62% **(74),** 92%

Scheme 1.41

The reaction of ethyl diazoacetate with 2-phenyl-2-methyl-1,3-dithiane **(69)** in the presence of rhodium (II) acetate gave the β-elimination product **(70)** in competition with Stevens rearrangement. Decomposition of S-ethyl diazosulfide **(72)** in refluxing benzene in the presence of rhodium (II) acetate gave the ylide **(73)**, which on further heating in xylene, eliminated ethylene to give ethyl-3-oxothiane-2-carboxylate **(74)** in good yield.

➢ **Dipolar cycloaddition :**

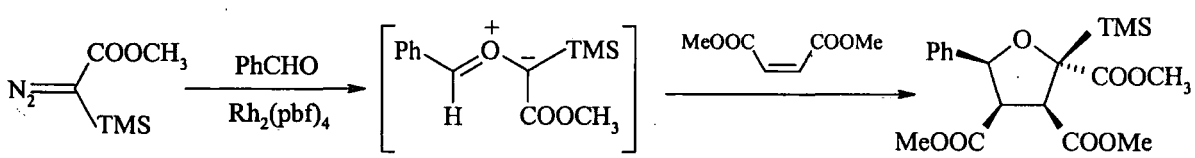
As mentioned in the previous section, the carbonyl ylide **(75)** generated through the reaction of a metallocarbene with a carbonyl group can be readily trapped with a π-bond to form an oxygen-containing carbocyclic system **(76)** (Scheme 1.42).



(75) **(76)**

Scheme 1.42

The tandem carbonyl ylide generation and 1,3-dipolar cycloaddition strategy has been used for the formation of tetrahydrofurans as illustrated in the following scheme (Scheme 1.43).

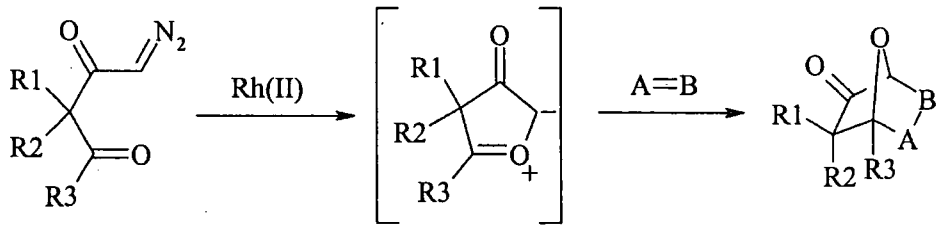


(77) **(78)** **(79), 49%**

Scheme 1.43

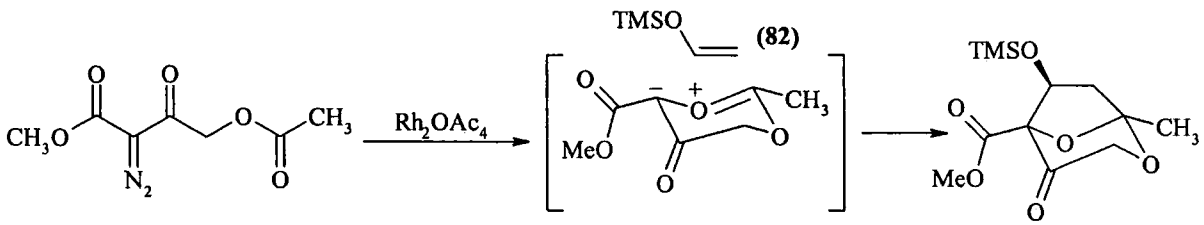
The rhodium-catalyzed decomposition of the diazoester **(77)** in the presence of benzaldehyde generated the carbonyl ylide **(78)**, which was trapped with dimethyl maleate to give tetrahydrofuran **(79)**.[87]

The intramolecular formation of a carbonyl ylide followed by intermolecular reaction with a π-bond has been initially described by Ibata[88] and well extended by Padwa.[89] This method has been widely used and permitted the construction of a diverse set of highly functionalized bicyclic compounds (Scheme 1.44).



Scheme 1.44

Koyama[90] successfully used this strategy for the formation of an analogue of the zaragozic core **(83)** (Scheme 1.45).



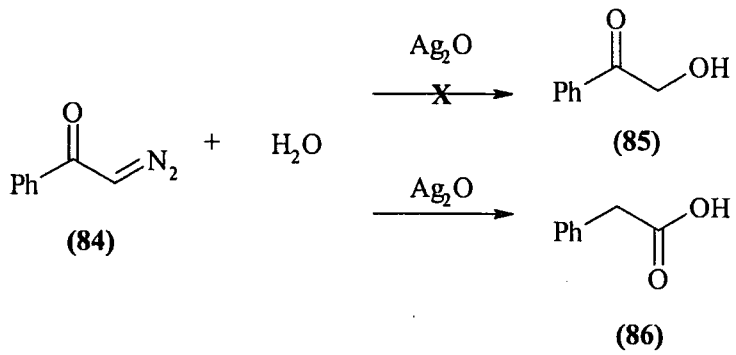
(80) **(81)** **(83), 66%**

Scheme 1.45

The carbonyl ylide **(81),** formed intramolecularly by decomposition of the diazoester **(80)** in presence of rhodium acetate, further reacted with the enol ether **(82)** leading to the compound **(83)** in good yield.

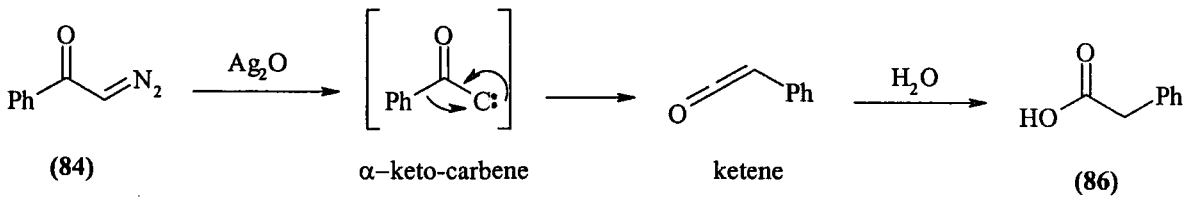
1.3.2.4.3-Wolff rearrangement :

In 1912 during a study of the chemistry of α-diazo ketones, Wolff[91] found that treatment of diazoacetophenone **(84)** with water in the presence of silver oxide gave not the hydroxyketone **(85)** as expected but phenylacetic acid **(86)**, the rearrangement product (Scheme 1.46).



Scheme 1.46

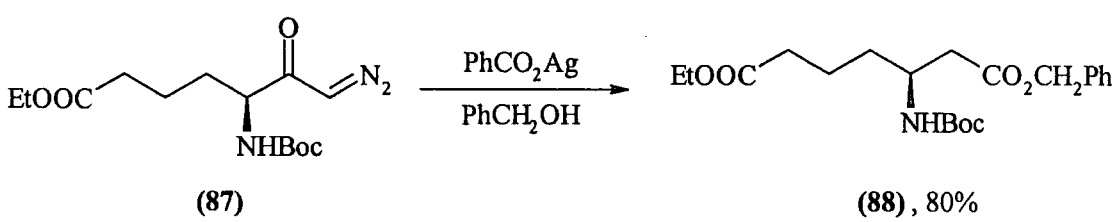
The diazocarbonyl compound **(84)**, with no β-hydrogen, undergoes a specific 1,2-rearrangement to form a ketene, which further reacts with H_2O to give the homologous acid **(86)** (Scheme 1.47).



Scheme 1.47

The Wolff rearrangement of α-diazocarbonyl compounds ($RCOCHN_2$, R=H, alkyl, aryl, OR) has a great synthetic importance because the ketenes formed generally react smoothly with water, alcohols, amines and thiols leading to acids, esters, amides and thioesters respectively.

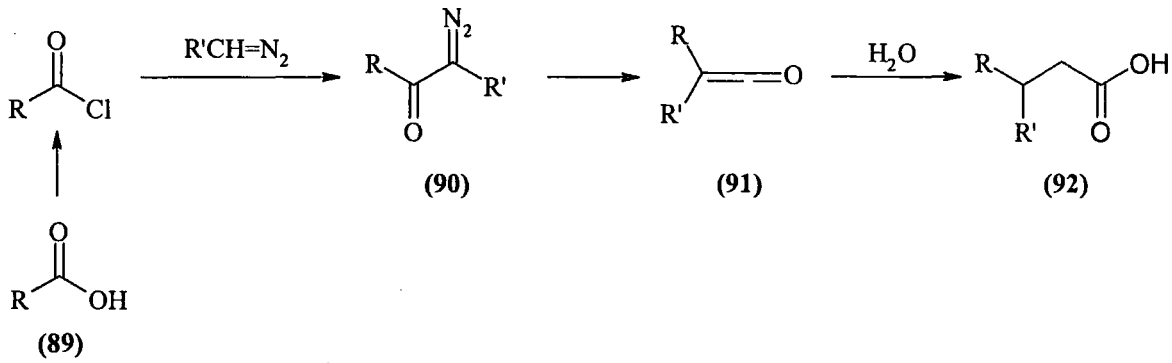
Studies with optically active diazoketones have shown predominant or complete retention of configuration of the migrating group (Scheme 1.48).[92]



Scheme 1.48

In general, the standard conditions use silver benzoate catalysis, which affords exclusively the Wolff rearrangement product.[93] However, the Wolff rearrangement can also be achieved with others transition metal catalysts (such as rhodium (II) acetate), thermally or photochemically.[94]

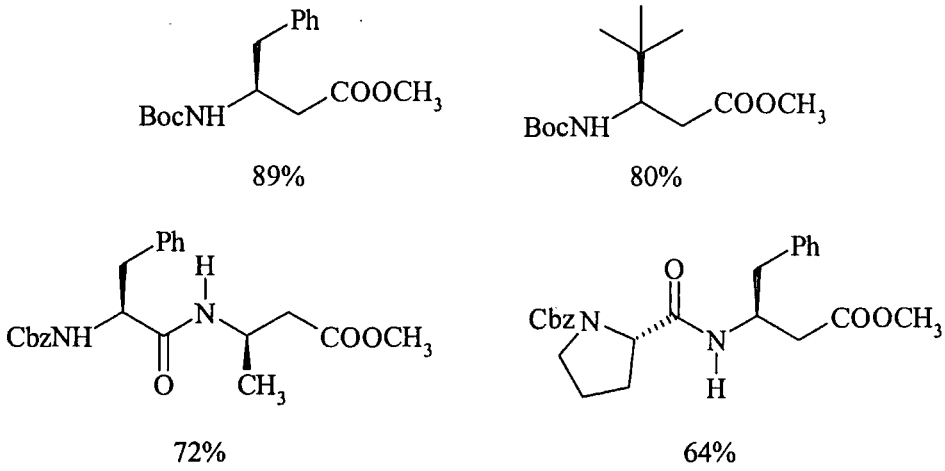
An early application of the Wolff rearrangement is the chain extension of acyl chlorides to their homologous acids or esters, known as the Arndt-Eistert reaction[95] (Scheme 1.49).



Scheme 1.49

The reaction starts from the acyl chloride of the acid **(89),** which then reacts with diazomethane (R'=H) to lead to an α-diazoketone **(90).** Wolff rearrangement and subsequent hydrolysis of the ketene intermediate **(91)** leads to the homologous carboxylic acid **(92).**

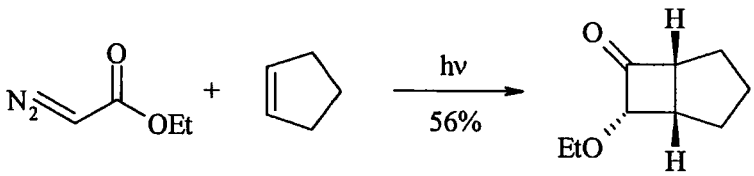
The Arndt-Eistert homologation has been widely used in amino acid and peptide modification, in particular for the transformation of optically pure α-amino-acids into their corresponding β-amino acids. β-Amino acids are components of some natural products[96] including peptides.[97] Thus, Podlech, Seebach[98] and McKervey[99] used this procedure to produce a selection of optically pure β-amino acids and methylesters (Scheme 1.50).



Scheme 1.50

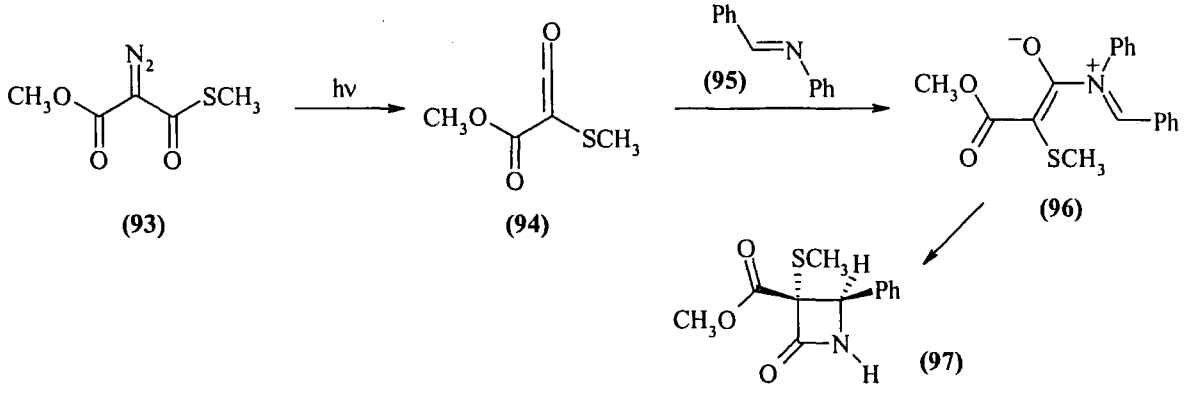
It is worth noting that, when the Wolff rearrangement is conducted in inert solvents (i.e. in absence of weak acids, alcohols etc.), stabilized ketenes can be isolated.[100] Further reaction with activated alkenes, dienes or alkynes by [2+2]-cycloaddition can then happen.

Thermal cycloaddition of ketenes to olefins are well understood and have been used for the synthesis of four-membered rings.[101] A representative example is shown below (Scheme 1.51).



Scheme 1.51

Trapping the ketene by cycloaddition to C=N, N=N and C=O has also been achieved.[92] Staudinger[102] reported the first example of ketene addition to a carbon-nitrogen double bond to give the first synthesis of a β-lactam in 1907 (Scheme 1.52).



Scheme 1.52

This cycloaddition is a two-step process where the ketene **(94)** derived from the α-diazo thioester **(93)**, adds to an imine **(95)** leading to the zwitterionic species **(96),**[103] which then gives the β-lactam **(97).**

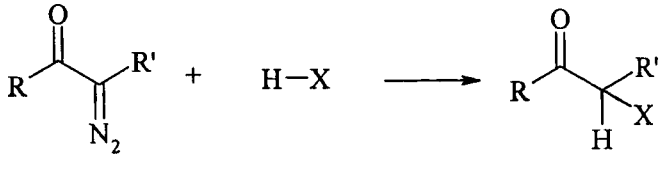
As outlined during this introduction, the range of transformations mediated by transition metal catalyzed decomposition of diazo compounds is large. The last transformation to be discussed in the following section is the insertion reaction, the object of interest of this thesis.

1.3.2.4.4-Insertion reactions :

Catalytically generated metal carbenes have proven to be highly versatile for insertion into C-H and X-H (ie : O, S, N, Se, P, halogen) bonds.[104] It is worth noting that C-H and Si-H bond insertion have to be separated from the other heteroatom-hydrogen bond insertion reactions. Indeed, their low polarity separates them mechanistically from the other group of insertion reactions.

1.3.2.4.4.1-X-H insertion reactions :

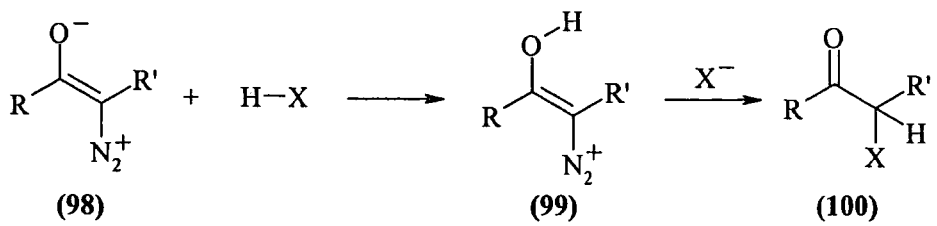
Diazocarbonyl compounds undergo an array of X-H insertions where X is a nitrogen, oxygen, sulfur, selenium, phosphorus or halogen atom (Scheme 1.53).



Scheme 1.53

The process overall represents a general approach to the α-functionalization of a ketone, in many cases under neutral conditions.

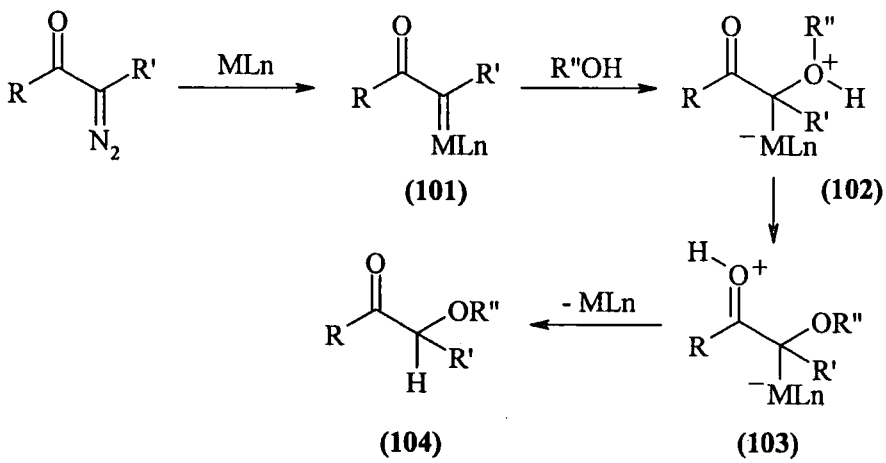
In the case of hydrogen halides, where catalysts are not required, the process starts by protonation of the diazocarbonyl compound **(98)** to form a diazonium salt **(99)** followed by attack by the halide ion and extrusion of nitrogen (Scheme 1.54).



(98) **(99)** **(100)**

Scheme 1.54

For weaker acids such as water, alcohols and phenols, the reaction requires catalytic assistance. The alternative mechanism is shown below (Scheme 1.55).



(101) **(102)** **(103)** **(104)**

Scheme 1.55

After formation of the carbenoid species **(101)**, the nucleophilic attack by R"OH on the electrophilic metal carbene forms an oxonium ylide **(102)** which rearranges into **(103).** Subsequent 1,2-rearrangement with regeneration of catalyst gives the product **(104).**
The mechanism of N-H, S-H, Se-H and P-H insertions are believed to be similar to the catalyzed insertion into the O-H bond.

The X-H insertion reactions have many synthetic uses and represent a useful way of introducing oxygen, nitrogen or sulfur containing substituents adjacent to carbonyl groups in ketones or esters.[105] But they are not of primary focus in this thesis and will therefore not be discussed further.

1.3.2.4.4.2-C-H insertion reactions :

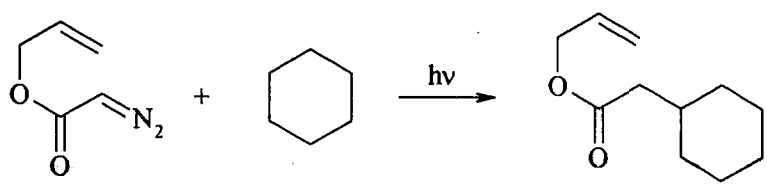
The insertion of carbenes into an unactivated C-H bond is a well-known transformation of "free" carbenes and has attracted much attention[106] since their first discovery by Meerwein, Rathjen and Werner.[107] However, both low yields and lack of chemical control have limited their use.

This limitation has been overcome by the use of metal catalysis and in particular by the introduction of rhodium (II) catalysts by Teyssié[108] and Taber.[109] From their independent studies, it appeared clearly that the choice of the metal and its ligands is crucial to achieve insertion into an unactivated C-H bond. An appropriate level of electrophilicity at the metallocarbene carbon center is required in order for the C-H insertion to happen. Poor regio- and stereocontrol are expected to be obtained if the carbenoid intermediate is too electrophilic, and other reaction pathways will then occur. On the other hand, if the carbenoid is not electrophilic enough, then it will not be reactive enough to insert into the unactivated C-H bond. The degree of electrophilicity is governed by the nature of the metal catalyst.

C-H insertions have been studied in both inter- and intramolecular schemes and both processes will be discussed separately below.

*** Intermolecular C-H insertion :**

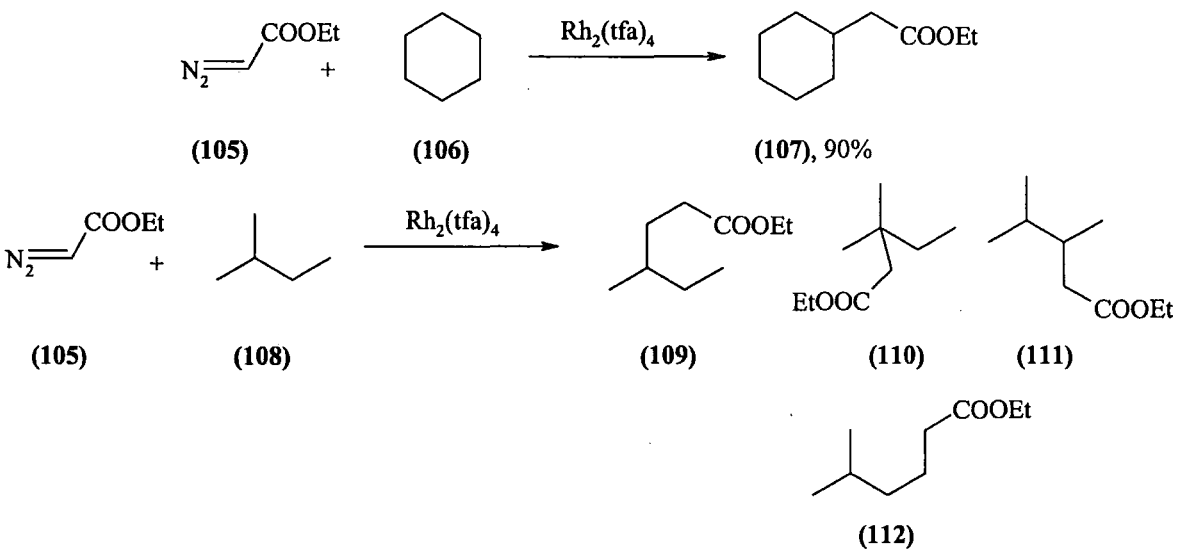
Intermolecular C-H insertions are prevalent in thermally or photochemically generated carbenes (Scheme 1.56).[107a]



Scheme 1.56

Initial attempts at inducing intermolecular C-H insertion by decomposition of α-diazocarbonyl compounds in the presence of copper bronze or its salts showed poor insertion.

An important step was achieved with the introduction of rhodium (II) tetracarboxylate catalysts.[107,108] In addition to their catalytic activity for diazodecomposition, they also showed a greater tendency towards C-H insertion compared to copper catalysts. The most widely studied carbenoids were derived from alkyl diazoacetates. However, these diazocompounds were not very chemoselective in intermolecular C-H insertion[110] as illustrated below (Scheme 1.57).

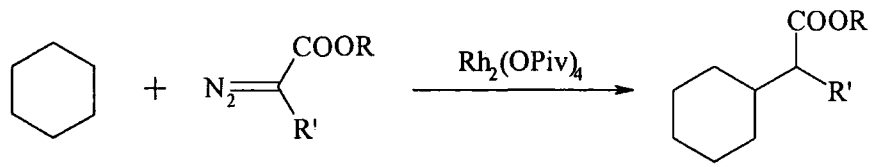


Scheme 1.57

Using the electron deficient dirhodium tetratrifluoroacetate $Rh_2(tfa)_4$ as catalyst, and very slow addition of the diazo compound *via* a syringe pump to avoid dimerization, the insertion reaction of ethyl diazoacetate **(105)** with cyclohexane **(106)** proceeded in a good yield. However, the reaction with 2-methylbutane **(108)** showed poor chemoselectivity and four products **(109-112)** in (5:25:66:4) ratio were obtained.

Davies showed that this poor chemoselectivity can be overcome by using rhodium carbenoid intermediates which contain both donor and acceptor substituents.[111] The presence of the donor group stabilizes the highly electron-deficient carbenoid and the reactions were much more selective than with the carbenoids which lack the donor group. Thus, under identical conditions using dirhodium tetrapivalate as catalyst,

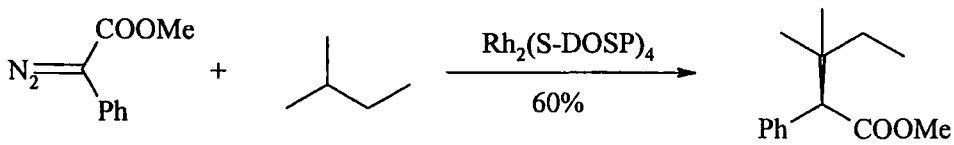
phenyldiazoacetate **(113)** formed the C-H insertion product **(114)** in 94% yield while only 10% yield of **(116)** was obtained from the reaction with ethyldiazoacetate **(113)** (Scheme 1.58).



R=Me, R'=Ph **(113)** **(114)**, 94%
R=Et, R'=H **(115)** **(116)**, 10%

Scheme 1.58

Donor-acceptor-substituted metallocarbenes (aryl and vinyldiazoacetates) showed good chemo- and enantioselectivity. These metallocarbenes appeared to be the best reagents for intermolecular C-H insertion reactions.[112] In addition, good regiocontrol has been achieved using Rh_2(S-DOSP)$_4$ as catalyst for the reaction of phenyl diazoacetate **(113)** and 2-methylbutane **(108)** leading to only one product **(117)** (Scheme 1.59)[113] while the reaction with ethyldiazoacetate **(105)** gave four different insertion products when using Rh_2(tfa)$_4$ (Scheme 1.57).



(113) **(108)** **(117)**, 68% e.e.

Scheme 1.59

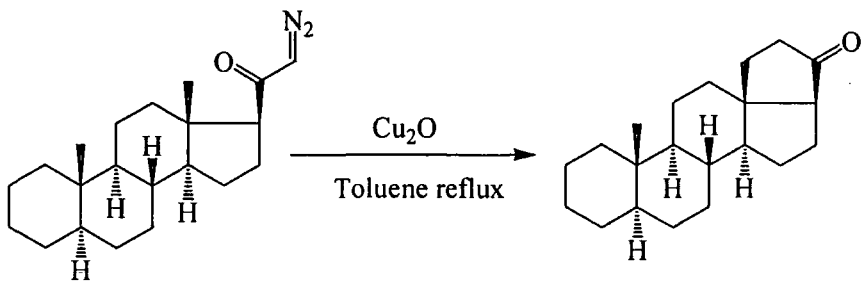
In summary, Davies developed carbenoid intermediates with improved chemoselectivity and achieved high asymmetric induction with the use of dirhodium tetraprolinate catalysts.[43c,112,114]

However, until recently, and particularly before the work reported by Davies,[115] intermolecular C-H insertion reactions were not generally considered useful from a synthetic point of view because of the low selectivity observed in contrast to the

intramolecular reactions. The intramolecular C-H insertion has gained strategic importance in organic synthesis over the intermolecular process by providing a convenient and valuable method for the synthesis of carbocyclic and heterocyclic systems.

1.3.3-Intramolecular C-H insertion :

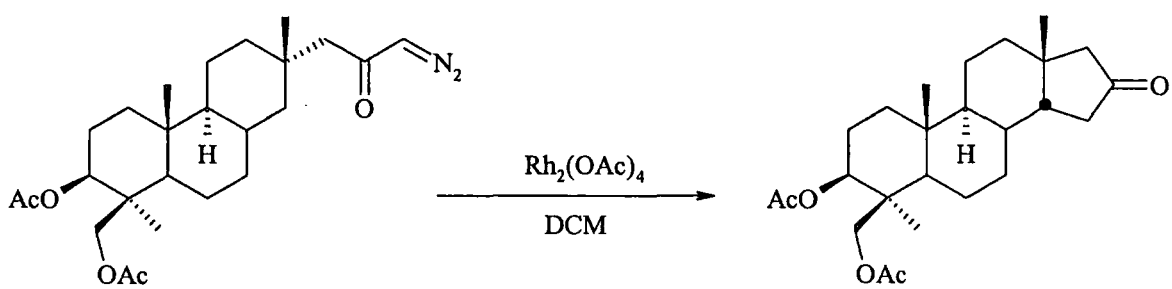
Initial observation of an intramolecular C-H insertion reaction was made when 21-diazo-5α-pregnan-20-one **(118)** was decomposed in refluxing toluene in the presence of copper (I) oxide (Scheme 1.60).[116]



(118) **(119)**

Scheme 1.60

In 1982, Wenkert[117] reported the superiority of rhodium catalysts compared to copper catalysis. Indeed, rhodium(II) acetate showed a good efficiency in the cyclization of **(120)** to the cyclopentanone **(121)** while the reaction under copper catalysis proceeded in poor yield (1%) (Scheme 1.61).



(120) **(121)**, 59%

Scheme 1.61

Since then, extensive studies mostly by Taber,[118] Doyle and Davies, have improved understanding of the selectivity, regiocontrol and enantioselectivity of this transformation. These studies revealed that selectivity and regiocontrol of the intramolecular C-H insertion of metallocarbenes derived from diazocarbonyl decomposition is governed by steric, conformational and electronic influence of the substituents of both catalyst and substrate. These aspects will be discussed in much more detail in the following sections.

1.3.3.1-Catalysts for C-H insertion :

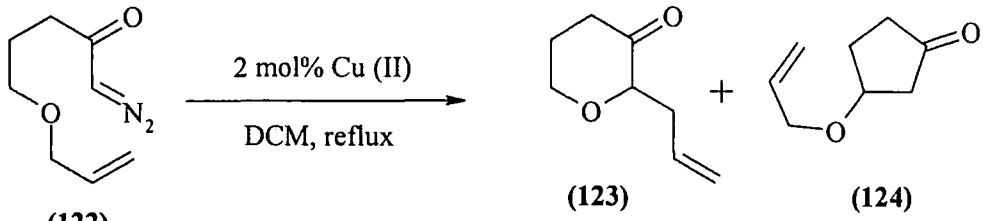
Reactivity towards diazodecomposition is a function of the Lewis acidity of the metal complex.[119] Electrophilic addition of the transition metal catalysts, MLn, to the diazocompound causes the loss of dinitrogen and the formation of a metal-stabilized carbene. Only "late" transition metals in the 3rd and 4th periods have proven to effectively catalyze decomposition of diazocarbonyl compounds, and among them, copper and rhodium are the most frequently used.

1.3.3.1.1-Copper catalysts :

Copper bronze and Cu(II) sulfate are the oldest of the copper catalysts employed for diazodecomposition. Early work in this area made use of insoluble copper catalysts (i.e. : Cu powder, Cu_2O, CuO, CuCl, CuBr). Although these catalysts are still employed today, their use has considererably decreased with the use of homogeneous copper catalysts such as Cu(I) triflate and $Cu(acac)_2$.[120]

Due to their stability, their general ease of preparation and handling, Cu(II) complexes have been favored over those of Cu(I). However, Cu(I) rather than Cu(II) was established as the active catalyst[121] with the diazo compound believed to reduce Cu(II) to Cu(I). Two bidentate ligands (i.e. acac) are bound to Cu(II), and one of these ligands is presumed to dissociate upon reduction by the diazo compound and only one remains bound to the active Cu(I) catalyst.

Copper catalysts have been mostly reported as useful for cyclopropanation,[122] X-H insertions[123] (X=N, O) and ylide formation.[124] Products from C-H insertion have been essentially reported as side products in moderate yield as shown in the following scheme (Scheme 1.62).[125]



(122)

	(123)	(124)
$Cu(acac)_2$	61%	12%
$Cu(tfacac)_2$	78%	/
$Cu(hfacac)_2$	83%	/

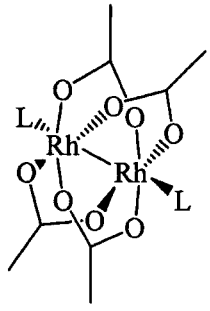
Scheme 1.62

Diazodecomposition of **(122)** using copper catalysts led to the formation of the major product **(123)** by oxonium ylide generation followed by [2,3]-sigmatropic rearrangement. The C-H insertion reaction yielding the product **(124)** is a competing reaction which did not occur when using copper catalysts with electron-withdrawing ligands such as $Cu(tfacac)_2$ and $Cu(hfacac)_2$. Copper catalysts tend to be highly electrophilic and so generate carbenoids too active to undergo selective C-H activation reactions.

1.3.3.1.2-Rhodium catalysts :

Originally based on the use of copper catalysts, the insertion of metallocarbenes into C-H bonds has undergone a renaissance with rhodium(II) carboxylate catalysts. Recognition of dirhodium(II) acetate as an alternative to copper catalysts occured in 1973[126] but it is only since the 1980s that Rh(II) catalysts begun to be described as enhancing the selectivity of these reactions.

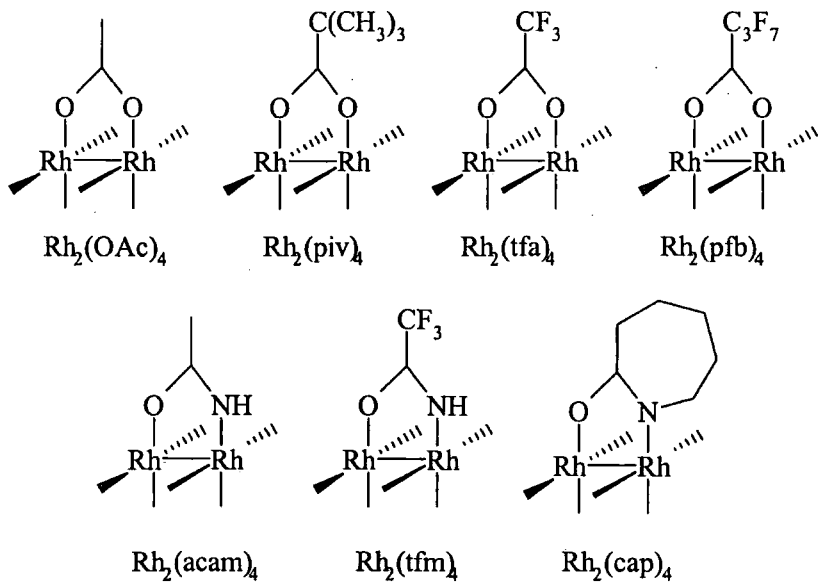
Rhodium acetate, the most common and best-studied Rh(II) catalyst, exists as a dimer where acetates are coordinating to both metal centres (Scheme 1.63).



Scheme 1.63

The axial ligands are absent when the dimers are used for catalytic processes and the axial position is believed to be the site of binding with the carbene center.

Replacement of the acetate ligands by other carboxylate or carboxamide ligands has made available a wealth of dirhodium(II) catalysts (Scheme 1.64).[127]



Scheme 1.64

Doyle[128] and Padwa[129] established that selectivity could be greatly influenced by the electronic properties of the Rh(II) ligands. The use of $Rh_2(pfb)_4$ (dirhodium perfluorobutyrate), whose ligands are strongly electron withdrawing, showed a high reactivity for diazo decomposition but gave low stereo- and regio-control.[130] In contrast, dirhodium(II) carboxamidates[130] like $Rh_2(acam)_4$ and $Rh_2(cap)_4$ showed lower reactivities but higher selectivities. Rhodium catalysts can be classified as follows (Scheme 1.65).

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

increased reactivity for diazodecomposition →

← increased stereo- and regioselectivity

Scheme 1.65

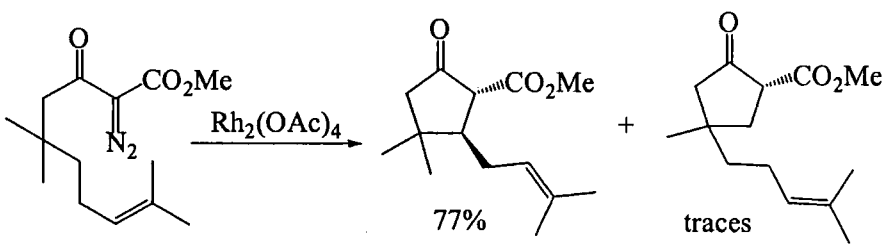
Examples illustrating the influence of the catalyst on the chemo- and regioselectivity of the C-H insertion will be given in the following section.

1.3.3.2-Regioselectivity :

1.3.3.2.1-Generality :

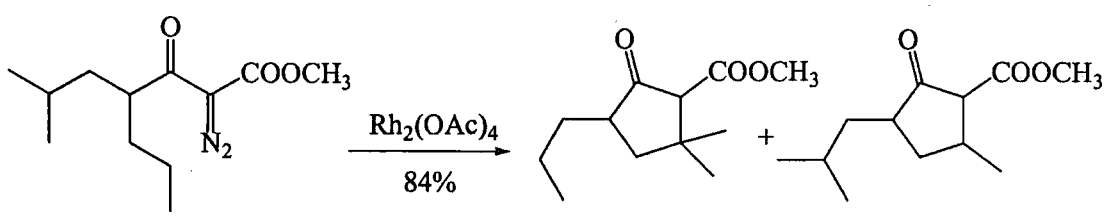
In cases where several non-equivalent C-H bonds are positioned equidistantly from the diazo moiety, the generation of isomeric products may be observed. But the regioselectivity appears to be dependant upon steric, conformational and electronic effects. The same year as Wenkert reported the first use of $Rh_2(OAc)_4$ for C-H insertion, Taber began a series of investigations on competitive intramolecular C-H insertion. Steric and electronic selectivity in the C-H insertion process have been studied in some detail by both groups.[118c,131]

When substrates that contained two competing sites for reaction were used, insertion into a methylene C-H bond was found to be significantly favored over insertion into a methyl C-H bond (Scheme 1.66).[118a]



Scheme 1.66

When α-diazoketoester **(124)** was treated with rhodium(II) acetate, a 4.6:1 mixture of cyclopentanones **(125)** and **(126)** was observed (Scheme 1.67).[131] This result indicates a preference for insertion into a methine C-H bond over a methylene C-H bond.

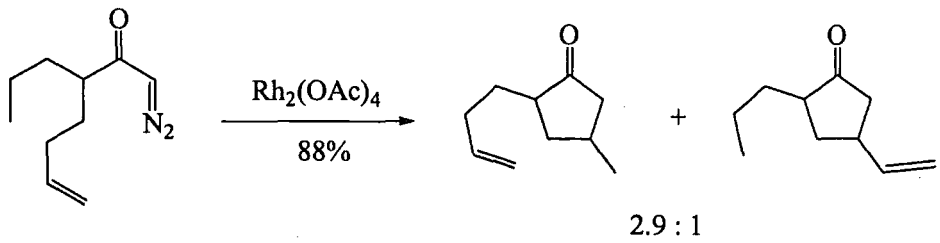


(124) **(125)** **(126)**

4.6 : 1

Scheme 1.67

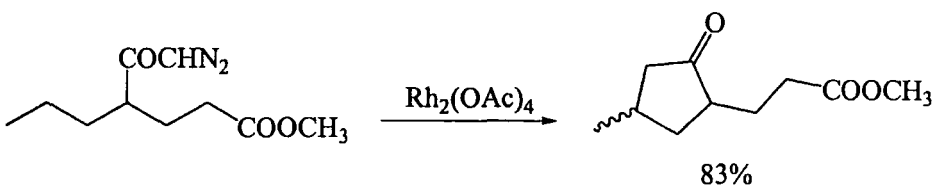
Therefore methine insertion is preferred over methylene insertion, which is preferred over methyl insertion. Therefore, the order of reactivity of the target C-H site is CH > CH_2 > CH_3. In addition, Taber showed that rhodium(II) acetate mediated insertion into allylic and benzylic methylene moieties are disfavoured compared to insertions into the C-H bond of an aliphatic methylene (Scheme 1.68).[131]



Scheme 1.68

This was rationalized by the relative ability of each substituent to donate electron density towards the reacting carbenoid center. Alkyl groups are inductively electron donating and so increase the electron density of the C-H bond making it more susceptible to the attack by the electrophilic rhodium-carbene species. Vinyl and phenyl groups are inductively electron withdrawing and so decrease the reactivity of the adjacent C-H bond.

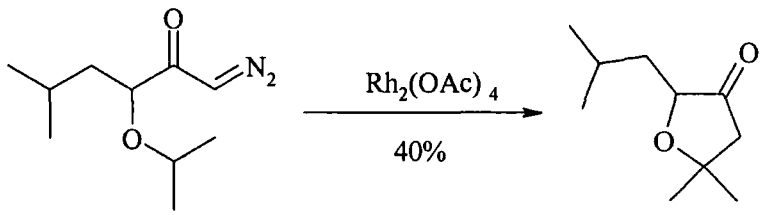
Stork and Nakatani[132] have discovered that an electron-withdrawing group such as an ester when attached to the α-diazoketone side chain influenced significantly the regiochemistry of the C-H insertion. The ester functionality directed the carbenoid insertion away from the adjacent methylene hydrogens (Scheme 1.69).



Scheme 1.69

The ester substituent deactivates both α- and β-methylene groups towards C-H insertion. If insertion adjacent to an ester is the only intramolecular pathway possible, only carbene dimers are formed.

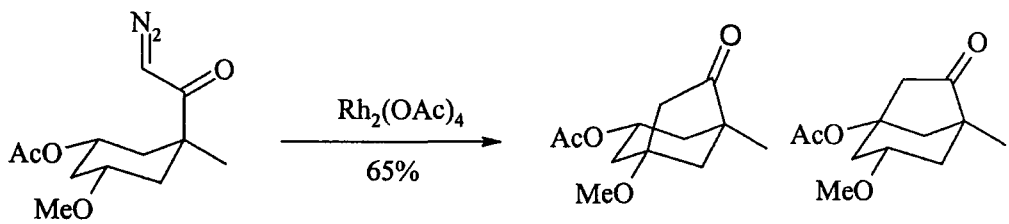
In contrast, Adams[133] showed that an electron-donating group activates the adjacent C-H bond. Thus, treatment of **(128)** with $Rh_2(OAc)_4$ led to the exclusive formation of 3-(2H)-furanone **(129)** (Scheme 1.70).



(128) **(129)**

Scheme 1.70

Another interesting example, also reported by Adams[134], is the cyclization of the pseudosymmetric diazoketone **(130)**, which generates exclusively cyclopentanone **(131)** (Scheme 1.71).



(130) **(131)** **(132)**

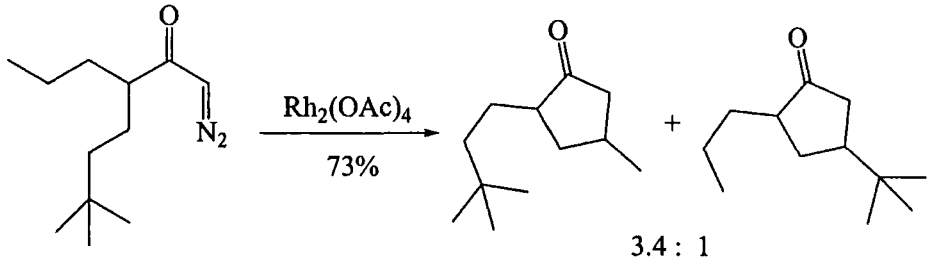
> 99 : 1

Scheme 1.71

The selective formation of **(131)** was attributed to the electron donating character of the ether group and the electron withdrawing character of the acetate group.

From these studies, the order of reactivity for XCH towards C-H insertion is therefore, $X = O > X = C_{aliph.} > X = C_{Ph.} \sim X = C_{vinyl.}$.

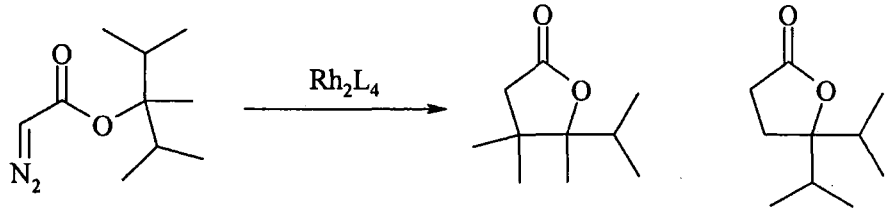
Steric effects can also direct the insertion process into a site as illustrated in the following scheme (Scheme 1.72).[131] The electronic effects are approximately equal but the steric effect of the *tert*-butyl group predominates causing insertion into the propyl side chain. Van der Waals interactions between the *tert*-butyl group and the ligands on the rhodium disfavored insertion.



Scheme 1.72

Both steric and electronic effects govern selectivity but regioselectivity is also catalyst dependent. It may be possible to modify the balance by modifying the electronic and steric bulk of the ligand on the catalyst.

Indeed, Doyle[135] examined C-H insertion reactions of diazoacetoacetates and diazoacetates and reported an exceptional dependence of regioselectivity upon the carboxylate or carboxamide ligands of the rhodium(II) catalyst (Scheme 1.73).



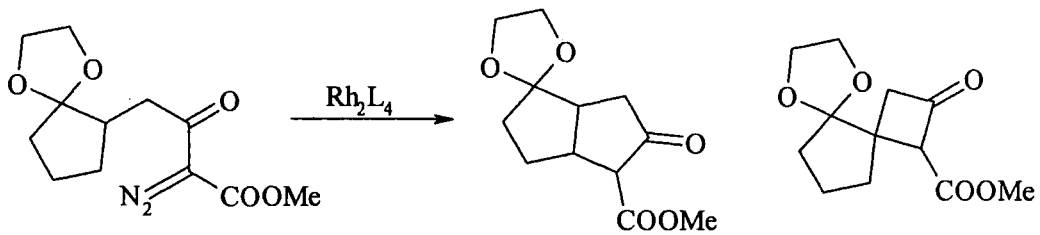
(133) **(134)** **(135)**

$Rh_2(pfb)_4$,	56%	32	68
$Rh_2(OAc)_4$,	81%	53	47
$Rh_2(acam)_4$,	96%	> 99	< 1

Scheme 1.73

The more electron-deficient carbenoid generated from $Rh_2(pfb)_4$ underwent C-H insertion in a non-selective manner, while the more electron rich carbenoid generated from $Rh_2(acam)_4$ provided excellent selectivity for insertion into the methine C-H.

Ikegami[136] has reported that dirhodium(II) tetra(triphenylacetate) ($Rh_2(tpa)_4$) provides a high degree of regiocontrol for C-H insertions for steric reasons (Scheme 1.74).

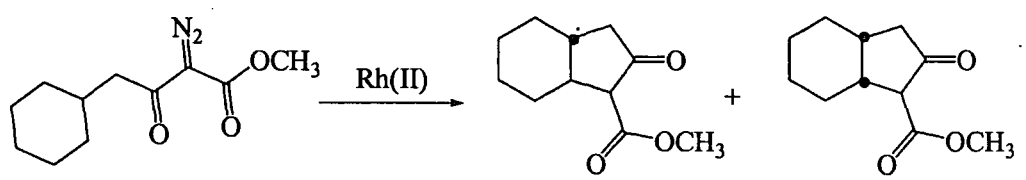


(136) **(137)** **(138)**

$Rh_2(tfa)_4$	56	44
$Rh_2(OAc)_4$	37	63
$Rh_2(tpa)_4$	96	4
$Rh_2(acam)_4$	14	86

Scheme 1.74

Steric factors of the ligands also play an important role in determining the ratio of potential insertion products. Thus, the intramolecular C-H insertion of the cyclohexane analogue **(139)** led to a mixture of *trans/cis* products and the observed ratio depended on the nature of the catalyst (Scheme 1.75).



(139) **(140)** **(141)**

$Rh_2(OAc)_4$	3 : 1
$Rh_2(oct)_4$	5 : 1
Rh(tpp)Cl	15 : 1

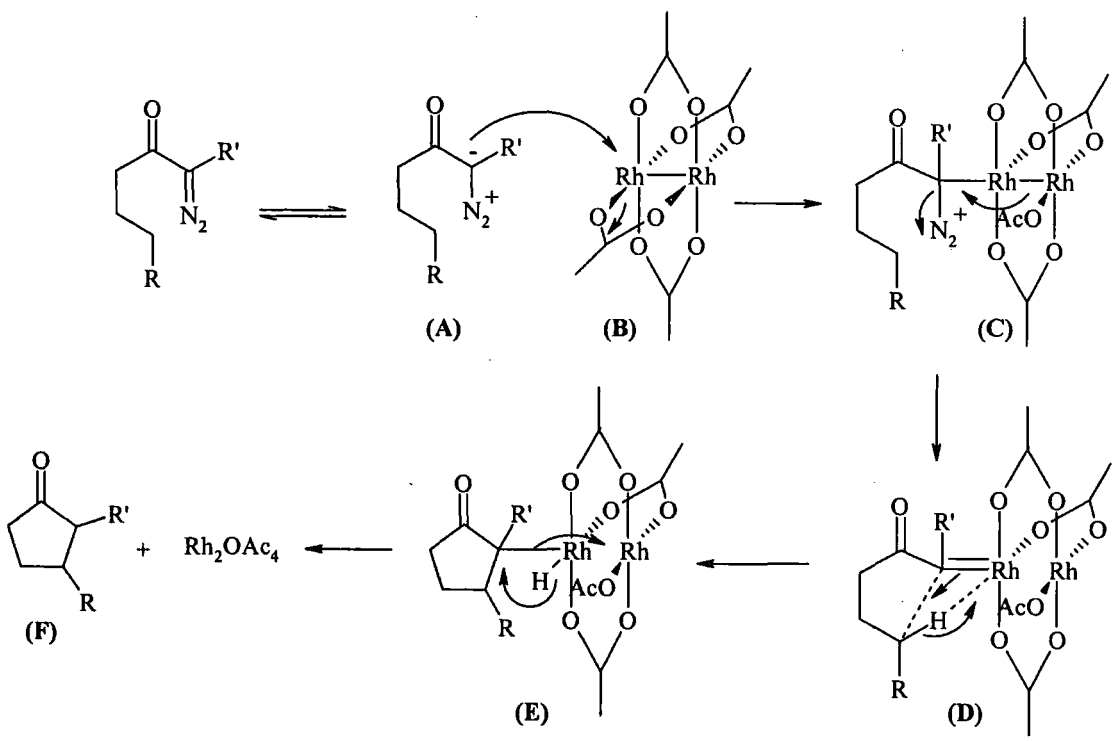
Scheme 1.75

Treatment of the diazoketone **(139)** with Rh(II) acetate led to a 3:1 mixture of the *trans/cis* adducts **(140/141)**. Changing the catalyst to Rh(II) octanoate increased the ratio to 5:1 and with the even larger tetraphenylporphyrin rhodium chloride, the ratio increased to 15:1 in favor of the *trans* product.

1.3.3.2.2-Ring size formation :

The regioselectivity, which leads to the control of the ring size, depends upon the type of diazo function, the degree of substitution of the carbon where insertion takes place, steric and electronic factors. In general, five-membered ring formation is the favored process.[137]

Taber proposed a mechanism that accounts for preferential 5-membered ring formation (Scheme 1.76).



Scheme 1.76

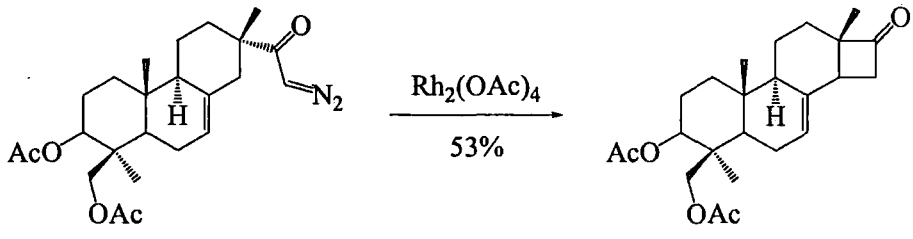
Initial attack of the α-diazocarbonyl compound (**A**) at the axial position of the rhodium dimer (**B**) gives the intermediate (**C**). This is followed by cleavage of the Rh-Rh bond with concomitant loss of nitrogen to generate (**D**). Electronic reorganisation results in C-C bond formation (**E**). A final step requires β-hydride transfer from the metal to regenerate

the catalyst and offer the product (**F**). The insertion occurs into a C-H bond placed in proximity to the carbene center with regeneration of the catalyst.

However, the construction of other rings sizes (in general four- and six-membered rings) by carbene C-H insertion is also observed in competition with 5-membered ring formation.

➢ **Four-membered ring formation :**

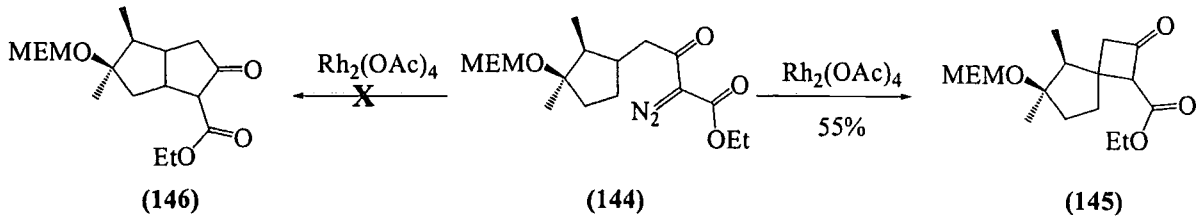
There are few examples of 4-membered carbocycle formation *via* intramolecular C-H insertion.[138] It is usually observed as a low yield by-product with the 5-membered ring product. However with suitable substrates, cyclobutanone products can be obtained. Ceccherelli and co-workers have reported the formation of the D-norsteroid system **(143)** (Scheme 1.77).[139]



(142) **(143)**

Scheme 1.77

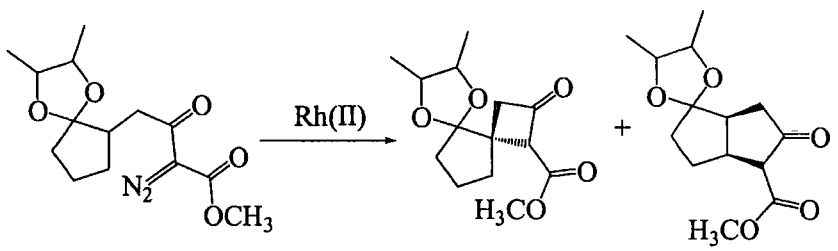
Cane and co-workers have reported that the catalytic decomposition of the diazo ester **(144)** resulted in spirocyclo-butanone **(145)** with no trace of 5-membered ring product **(146)**. The 1,3-interactions of the MEM ether and the secondary methyl group may have hindered the approach of the carbenoid to the secondary C-H bond directing the attack to the opposite face of the cyclopentane ring, on which only the tertiary atom is accessible leading to **(145)** (Scheme 1.78).[140]



(146) (144) (145)

Scheme 1.78

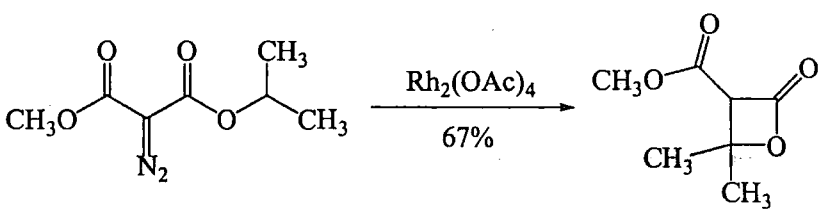
The nature of the transition-metal ligands can also influence the 4-membered carbocycle formation. It has been observed, for example, that the catalytic decomposition of α-diazo-β-ketoester **(147)** by rhodium(II) acetamidate leads to the 4-membered product **(148)** whereas rhodium(II) triphenyl acetate favors formation of cyclopentanone **(149)** (Scheme 1.79).[141]



(147)	(148)		(149)
Rh(II) acetamidate	100	:	0
Rh(II) triphenyl acetate	0	:	100

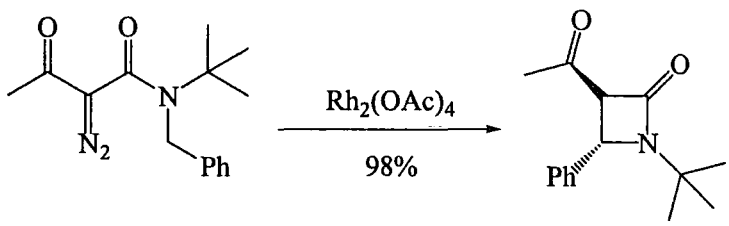
Scheme 1.79

There are few examples of 4-membered carbocycles but in contrast, a wide range of 4-membered heterocycles is accessible by the C-H insertion process. For example, β-lactones can be obtained (Scheme 1.80).[142] The preference for 4-membered ring formation is due to the activation by the adjacent oxygen atom.



Scheme 1.80

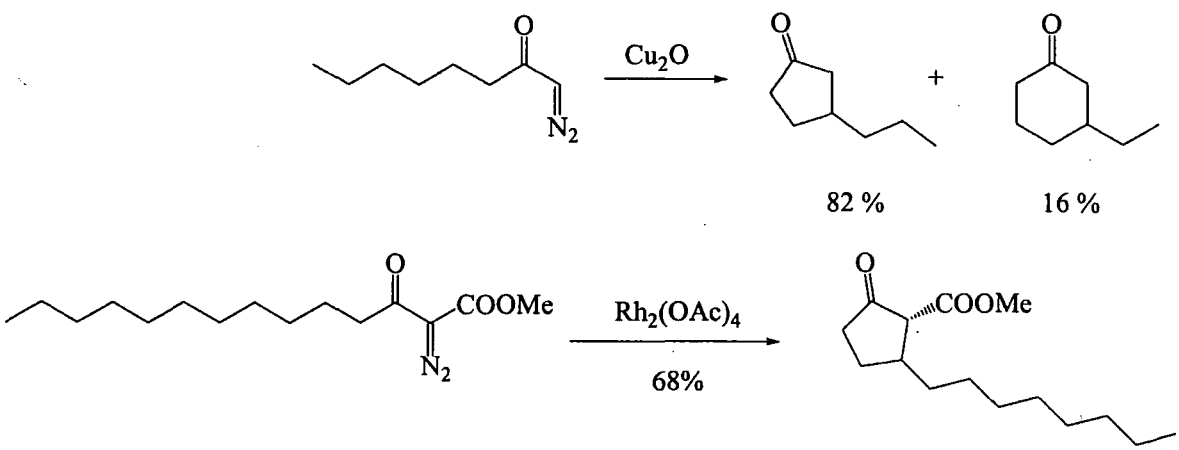
The reaction has attracted attention as a versatile procedure for the construction of the β-lactam ring.[143] A number of examples of β-lactam formation have been reported *via* catalytic decomposition of diazoamides.[144] Doyle and co-workers[145] have demonstrated that the use of rhodium(II) carboxylates as catalysts gives rise to high yields and exceptional selectivity (Scheme 1.81).



Scheme 1.81

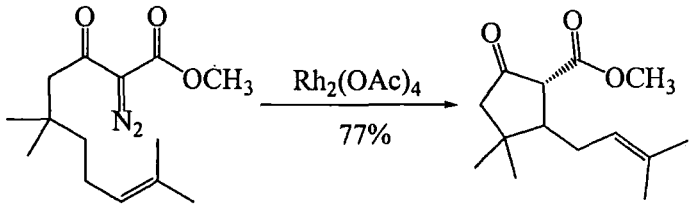
➢ **Five-membered ring formation :**

Cyclopentanes are important structural units of natural products. This area represents one of the most useful applications of intramolecular diazocarbonyl insertion reactions. The ligand on the transition metal, electronic effects and steric factors play an important role in governing selectivity. Indeed, it was found that copper catalysis gave a mixture of 5- and 6-membered ring products[146] whereas the use of rhodium(II) acetate showed significant electronic selectivity and produced exclusively the 5-membered ring product (Scheme 1.82).[118a]



Scheme 1.82

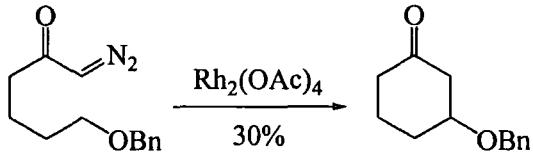
A full study by Taber and co-workers of rhodium(II) acetate catalyzed intramolecular C-H insertion of α-diazo-β-keto esters into freely rotating aliphatic side chains showed significant electronic selectivity towards the 5-membered ring formation (Scheme 1.83).[118a]



Scheme 1.83

➢ **Six-membered ring formation :**

Intramolecular C-H insertion of α-diazocarbonyl compounds into freely rotating aliphatic chain forms generally 5-membered rings, however when a δ-C-H bond is activated by an adjacent heteroatom, the C-H insertion results in a 6-membered ring (Scheme 1.84).[147]

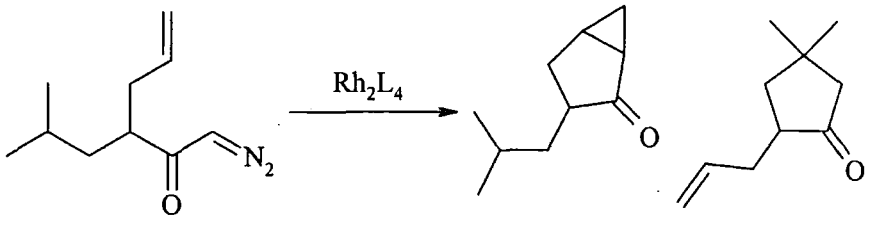


Scheme 1.84

In conclusion, the regioselectivity, which leads to the control of the ring size formation, depends upon the type of diazo function, the degree of substitution of the carbon where insertion takes place, steric and electronic factors. So, in certain circumstances 4- or 6-membered ring formation can compete with 5-membered ring formation.

1.3.3.3-Chemoselectivity :

Competitive intramolecular transformations of dirhodium(II) carbenes have been reported. Padwa was one of the first to study the influence of the catalyst and its ligands on the chemoselectivity.[148] It can effectively, and sometimes completely, switch reaction preference as illustrated on the following scheme (Scheme 1.85).



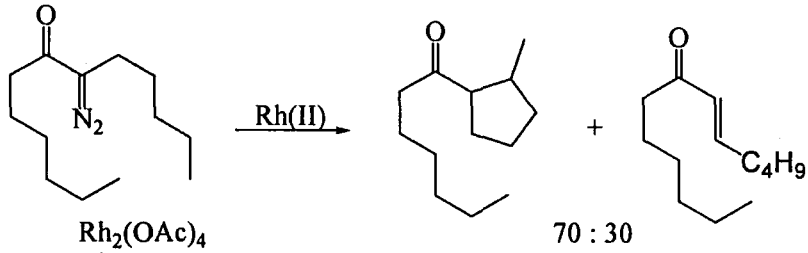
(150) (151) (152)

$Rh_2(OAc)_4$	44	56
$Rh_2(pfb)_4$	0	100
$Rh_2(cap)_4$	100	0

Scheme 1.85

In competitive insertion/cyclopropanation, the use of $Rh_2(pfb)_4$ produced the insertion product **(152)** exclusively, whereas $Rh_2(cap)_4$ produces the cyclopropanation product **(151)** exclusively. Thus, strongly electron-withdrawing ligands favour cyclopropanation while C-H insertion is favoured by electron donating ligand.

Taber's group has also noted and reported the importance of the ligand in the C-H insertion process.[149] They observed that strongly electron withdrawing ligands favour β-hydride elimination while the C-H insertion is favoured by electron donating ligands (Scheme 1.86). The more reactive rhodium carbenoid derived from the trifluoroacetate catalyst favors the entropically less demanding pathway : β-hydride elimination.

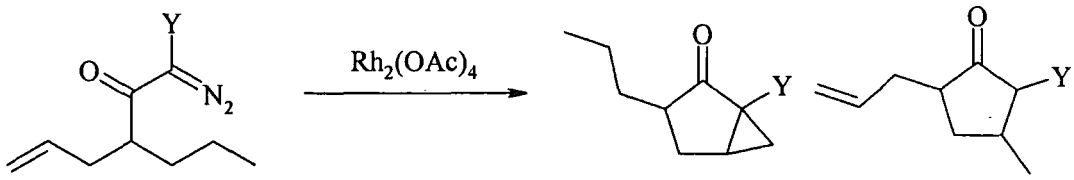


$Rh_2(OAc)_4$	70 : 30
$Rh_2(OBz)_4$	60 : 40
$Rh_2(tfa)_4$	38 : 62

Scheme 1.86

But it is worth noting that carbene substituents also influence chemoselectivity. In the following competitive insertion/cyclopropanation reactions (Scheme 1.87),[118c,150] an α-

diazo-β-ketoester undergoes preferential insertion, whereas the α-diazoketone undergoes preferential cyclopropanation.



		(155)	(156)
(153)	Y=COOEt, 78%	28	72
(154)	Y=H, 61%	92	8

Scheme 1.87

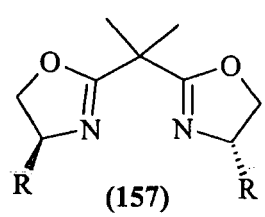
Therefore, both catalyst and diazocompound have an influence on the chemoselectivity.

The last aspect that needs to be mentioned in this introduction is the enantiocontrol in intramolecular C-H insertion. However, it is not the object of this work and therefore will just be discussed briefly in the following section.

1.3.3.4-Enantioselectivity :

Enantiocontrol in intramolecular C-H insertion using chiral catalysts is recent, but major advances have been made in the past few years.

As mentioned earlier, copper catalysts were essentially efficient in cyclopropanation and impressive efforts have been made towards the design of chiral catalysts to induce high enantiocontrol. Few isolated cases have been reported of impressive asymmetric induction in C-H insertion reactions.[151] The most effective chiral copper catalysts are the C2 symmetric bisoxazoline complexes **(157)** formed *in situ* by reaction of the ligands with copper triflate (Scheme 1.88).

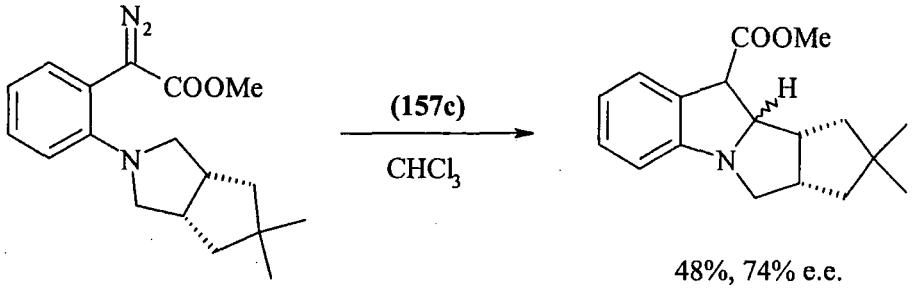


(157)

a : R=iPr
b : R=Bn
c : R=tBu

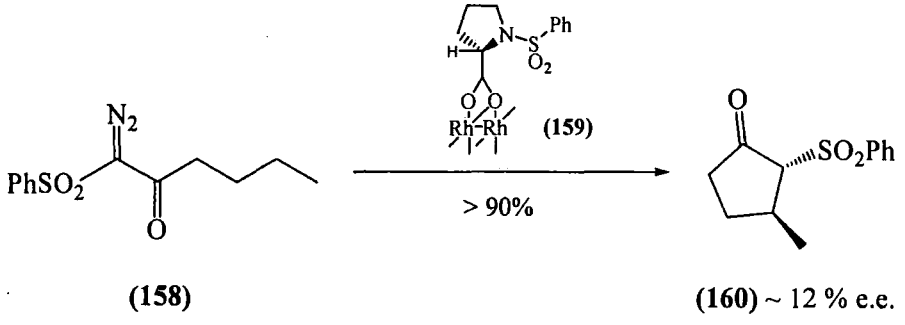
Scheme 1.88

The ligand with ^{t}butyl substituent gives best results with enantio-induction up to 74% e.e. in intramolecular C-H activation (Scheme 1.89).[128]



Scheme 1.89

Asymmetric induction in C-H insertion using a chiral rhodium catalyst was first reported by McKervey (Scheme 1.90).[152]

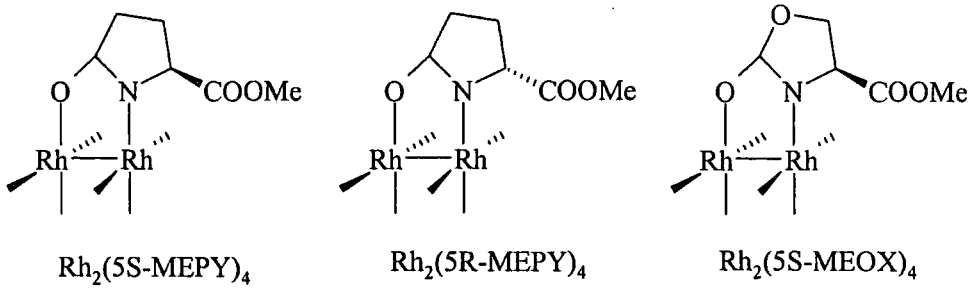


(158) **(160)** ~ 12 % e.e.

Scheme 1.90

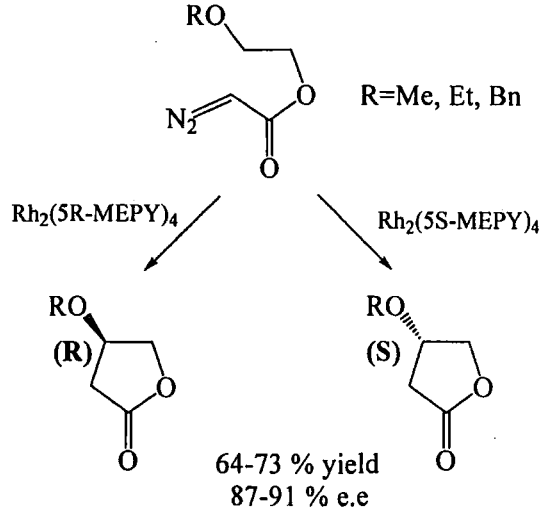
The reaction of α-diazo-β-ketosulfone **(158)** with the N-protected L-proline rhodium **(159)** led to the formation of cyclopentanone **(160)** in good yield but low e.e.

Doyle and co-workers have developed a class of rhodium (II) compounds that possess chiral amide ligands of which, dirhodium tetrakis[methyl-2-pyrrolidone-5(S)-carboxylate] $Rh_2[5S\text{-}MEPY]_4$ and its enantiomeric form $Rh_2[5R\text{-}MEPY]_4$ are representative (Scheme 1.91).



Scheme 1.91

High enantiocontrol in C-H insertion reactions has been achieved with the use of these catalysts (Scheme 1.92).[153]



Scheme 1.92

The S-ligand catalyst formed the S-enantiomer whereas the R-ligand catalyst formed the R-enantiomer with good enantiomeric excess. These sterically encumbered catalysts proved to be exceptional catalysts for asymmetric induction in intramolecular C-H insertion reactions especially for the reaction of diazoacetates and diazoacetamides.[154]

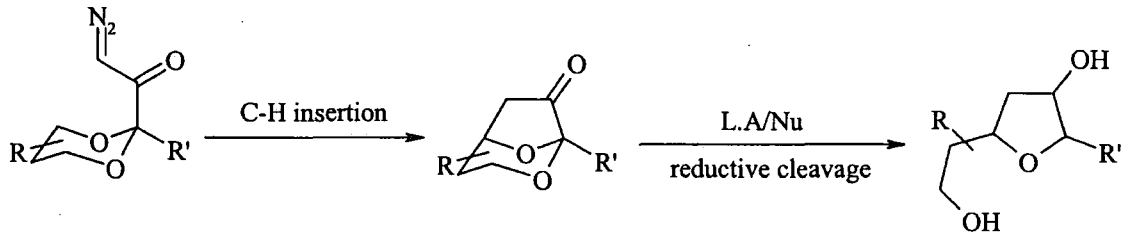
Thanks to extensive systematic investigations of both steric and electronic effects of both substrate and catalyst, the intramolecular insertion of metallocarbenes in C-H bonds has been found to be very general and predictable. The reaction has proved its real synthetic value for the synthesis of complex carbocyclic and heterocyclic natural products.[155]

Considerable progress has been made in the development of chiral catalysts and in their application in intramolecular C-H insertion reactions for the asymmetric construction of both carbocylic and heterocyclic ring systems.[156]

1.4-Proposed work :

This introduction chapter has provided an overview of the typical transformations of metallocarbenes and has illustrated the potential of these compounds as used in organic synthesis. In accord with the present research, most emphasis was placed on intramolecular C-H insertion reactions. The intramolecular carbene insertion into C-H bonds has assumed strategic importance in organic synthesis providing a convenient and valuable method for the synthesis of carbocyclic and heterocyclic systems.

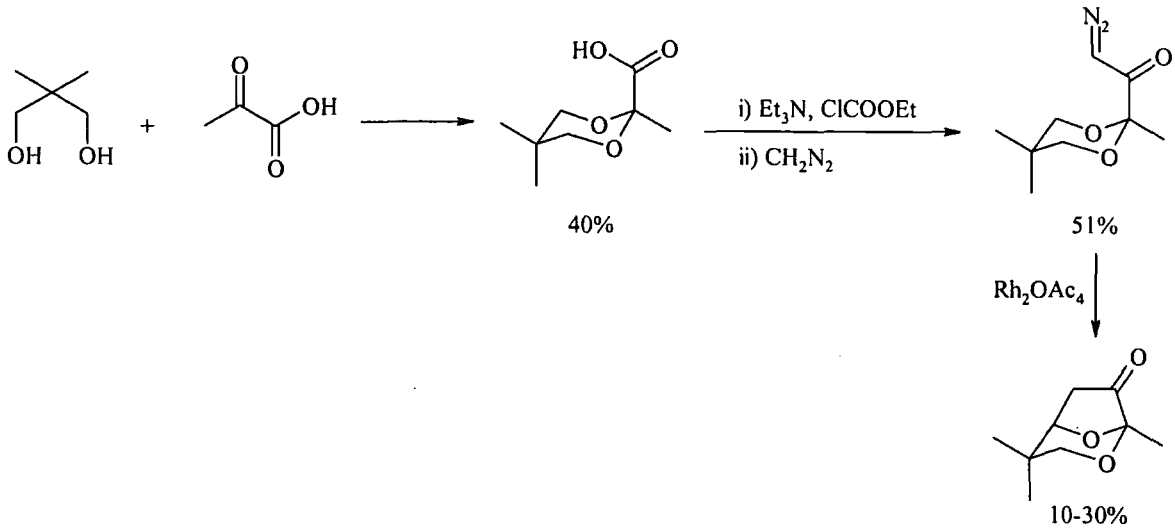
As mentioned at the beginning of this introduction, the aim of this project was to develop a method to access highly functionalised tetrahydrofurans. The strategy adopted is a tandem methodology, which involves an intramolecular C-H insertion of diazoketone acetal templates **(I)**, as a key step, followed by a Lewis acid-mediated reductive cleavage of the bicyclic acetals formed **(II)** (Scheme 1.93).



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

Scheme 1.93

Preliminary work in the group[157] showed that rhodium acetate treatment of the diazoketones **(I)** generates the bicyclic core **(II)**. However, the diazoketones synthesized from the corresponding acid acetals, prepared by ketalisation of simple diols with pyruvic acid, were obtained in low yields (Scheme 1.94).



Scheme 1.94

Therefore, the first objective of this work was to optimise the preparation of the diazoketones and explores their intramolecular insertion reactions upon treatment with rhodium catalysts.

The first results and discussion chapter will describe work on two synthetic routes to the acid acetals, the synthesis of the diazoketones and the associated insertion experiments. As mentioned in the general introduction, the bicyclic acetals are key intermediates in our strategy, but the bicyclic core is also found in many biologically active natural compounds and so becomes a target for total synthesis. Sordidin is an example and attempts to synthesis this compound will be reported.

Problems of isolation of the C-H insertion products, possibly due to their volatility and lack of chromophores, were encountered which prompted us to study modified substrates. To that aim, preparation of 2-substituted-1,3-propanediols was necessary and will be described and their use for the synthesis of new bicyclic ketones. This chapter will also report the optimisation studies of the C-H insertion reaction, realised by varying several parameters of the reaction such as concentration of the reagents, rate of addition, temperature and catalyst (metal, ligands).

The last results and discussion chapter will describe the Lewis-acid-mediated reductive cleavage of the bicyclic ketones to obtain highly functionalised tetrahydrofurans.

Finally, the last section of this thesis will detail the experimental procedures and analysis of the products synthesized.

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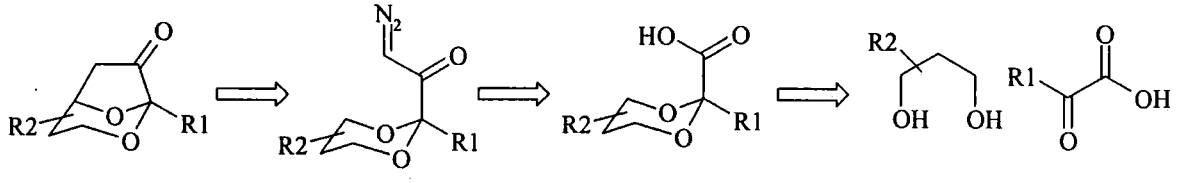
CHAPTER II: SYNTHESIS OF BICYCLIC KETONES

2.1-Introduction :

The first objective of the project was to explore the intramolecular insertion reaction of diazoketone templates for the formation of O,O-bicyclic acetal cores. The retrosynthetic disconnections, which form the basis of the strategy, are illustrated in the following scheme (Scheme 2.1).



Scheme 2.1

A short preliminary study in the group[1] has shown that the rhodium acetate treatment of diazoketones **(II)** generated the bicyclic core **(I)**. The diazoketones were obtained from the corresponding acid acetals **(III)**, which can be obtained by ketalisation of diols **(IV)** with pyruvic acid **(V)**.

This chapter will describe two synthetic routes to the acid acetals, the subsequent diazoketone synthesis and the associated insertion experiments. Finally, the attempt to apply the insertion strategy to the construction of the bicyclic acetal core of sordidin will be reported.

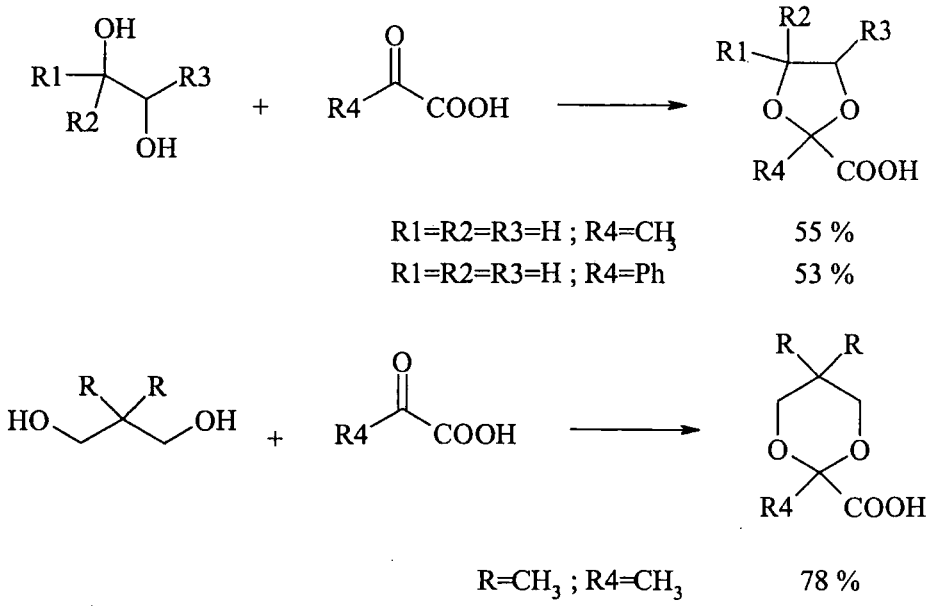
2.2-Acid acetal synthesis :

Initial studies were directed towards the preparation of acid acetals. As mentioned above, two routes were explored.

2.2.1-Ketalisation of diols with pyruvic acid (method A) :

2.2.1.1-Propanediol and 2,2-dimethylpropane-1,3-diol :

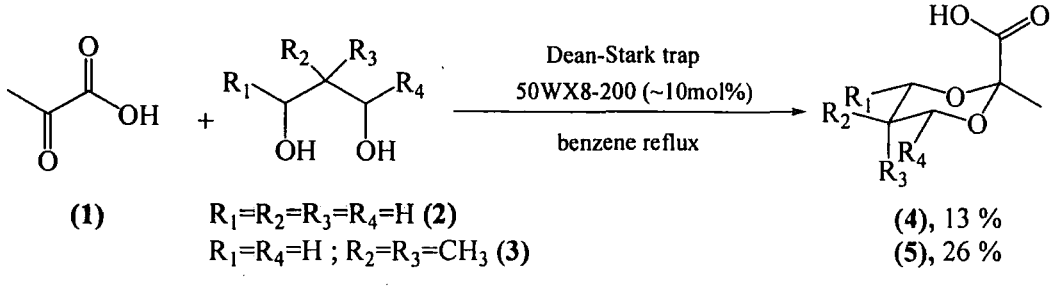
In 1973 Newman and Chen[2] reported the synthesis of a series of 2-carboxy-1,3-dioxolanes and 1,3-dioxanes from diols and pyruvic acid under acidic catalysis (Scheme 2.2).



Scheme 2.2

In this procedure, a mixture of pyruvic acid, an excess of diol (1.5eq.) and an acidic ion exchange resin (Amberlite IR-120, ~10 mol %) were heated to reflux in benzene. A Dean-Stark trap was used to remove the water and displace the equilibrium in favour of the formation of the cyclic acetals. During the work up, an alkaline treatment [3M aqueous NaOH, 2h reflux] was needed to hydrolyse any ester by-products formed during the reaction.

Following this precedent, acetals of pyruvic acid **(1)** were generated with propanediol **(2)** and 2,2-dimethyl-1,3-propanediol **(3)** using Dowex 50WX8-200, a strong cation exchanger, as the acid catalyst (Scheme 2.3).



Scheme 2.3

Evidence for the formation of the acetals was found in the ^{13}C NMR spectroscopy. The acetals were formed as a single product, as ascertained by ^{13}C NMR, with a single quaternary C-2 signal observed for each acetal (**4** and **5**) at 98.1 ppm and 97.8 ppm respectively. The C-2 carboxylate group was believed to adopt an axial position favoured by the thermodynamically controlled conditions. Preference for axial position over equatorial in 2-carboethoxy-2,4-dimethyl-1,3-dioxanes, due to a strong anomeric effect of about 3 to 4 kcal/mol, was reported by Bailey[3] in 1974 but also observed and defined before by Anderson[4] and Eliel.[5]

Despite the simple procedure, the yields after recrystallisation from petrol were disappointingly poor (13 % and 26 %). The low yields were attributed to the acid-base treatment performed during the work-up. The acidic extraction procedure which required a careful neutralisation with cold 1M aqueous HCl followed by acidification to pH 1 with 6M aqueous H_3PO_4 may have caused the ring opening of the acetals. Consequently, alternative work-up procedures were explored. The best results were obtained when the alkaline treatment was followed by several careful acidifications with cold 5M aqueous HCl followed each time by quick extractions with EtOAc. The acetals **(4)** and **(5)** were obtained in 35 % and 38 % yields. Alternative experiments, modifying both the solvent (benzene and the less toxic toluene) and the acid catalyst (p-TsOH, Amberlyst), were performed but no further enhancement could be obtained.

2.2.1.2-*meso*-2,4-Pentanediol (6) :

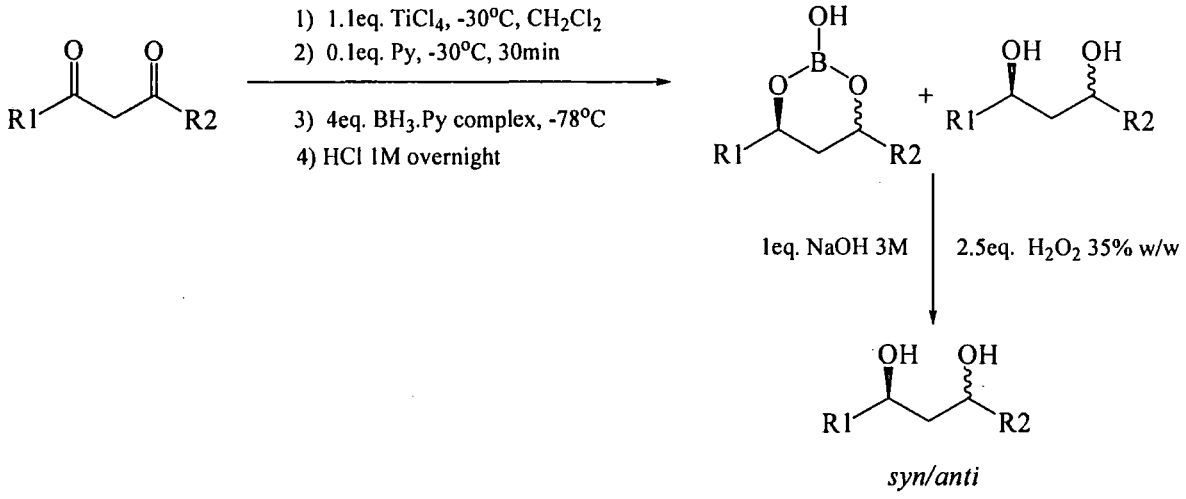
For the synthesis of sordidin, the use of *meso*-2,4-pentanediol to form the acid acetal was needed as starting material. Unfortunately, while this *meso* diol is commercially available, it is expensive (£70.0/500mg, Aldrich). Therefore, methods for its preparation were explored.

Various procedures have been reported for preparing syn-1,3-diols, either by stereoselective reduction of the corresponding β-hydroxyketones[6] or by reduction of the corresponding diketones.[7]

2.2.1.2.1-Diastereoselective reduction of pentan-2,4-dione :

In a recent protocol, Bartoli *et al*[8] reported the diastereoselective formation of a series of *syn*-1,3-diols by reduction of the corresponding 1,3-diketones using a BH_3-pyridine complex in the presence of $TiCl_4$ and pyridine. This reduction gave a mixture of diols and

the cyclic boron derivatives,[9] the latter being converted into the diols by treatment with basic hydrogen peroxide. Results of their study are summarized in the following scheme and table (Scheme 2.4, Table 2.1).



Entry	Substituents	Yield (%)	Ratio *syn/anti*
1	R1=Ph ; R2=Me	86	97/3
2	R1=*i*Bu ; R2=Me	83	96/4
3	R1=CH_2Ph ; R2=Me	86	95/5
4	R1=R2=*t*Bu	80	98/2
5	R1=R2=Ph	45	>99/1

Scheme 2.4, Table 2.1

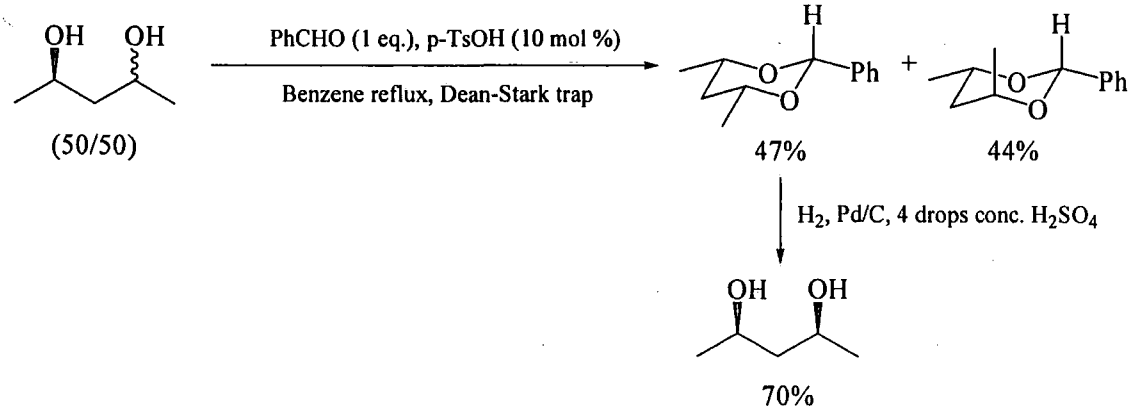
In all cases, the reaction proceeded with excellent diastereoselectivity and the *syn*-diols were obtained in good yields, except when R_1=R_2=Ph (entry 5) where the *meso*-diol was obtained in 45 % yield only, together with 37 % of recovered starting material. It was postulated that it could be due to resonance between the carbonyl and the aromatic ring, which decreases the reactivity of the carbonyl. The presence of $TiCl_4$ is essential to the reaction, no reaction has been observed in absence of the Lewis acid. A non-polar solvent is necessary to achieve high yield and high diastereoselectivity, CH_2Cl_2 giving the best results. Among a variety of BH_3-amine complexes screened, BH_3-pyridine appeared to be the best. Finally, better yield and diastereoselectivity were achieved by adding 0.1 equivalents of pyridine to the substrate and $TiCl_4$ prior to the treatment with BH_3-pyridine complex.

Initial attempts to reduce 2,4-pentanedione (R_1=R_2=Me) following this precedent gave poor diastereoselectivity and low yields. The first problem was solved by rigorous control of the reaction temperature. Thus, the BH_3-pyridine complex was diluted in CH_2Cl_2, cooled to -78°C, and slowly added *via* a cannula to the reaction mixture maintained at the same temperature. Although this afforded the product with high diastereoselectivity (~100 % as ascertained by NMR), the yield remained low (~30 %). Evidence for the specific formation of the *meso*-diol **(6)** was ascertained by ^1H and ^{13}C NMR spectroscopy. The ^1H spectrum, showing only four signals and in particular the doublet at δ=1.16 ppm which integrated for 6 H, proved that the two CH_3 groups are equivalent and the molecule symmetric. The ^{13}C spectrum confirmed this by its simplicity showing only 3 signals at δ=69.3, 46.6 and 24.4 ppm. The low yields observed were attributed to isolation technique problems, and much experimentation was undertaken to enhance this process. However, despite the use of several continuous liquid/liquid extraction techniques, no significant increase in the yield was achieved.

Given these problems, this approach to *meso*-2,4-pentanediol **(6)** synthesis was abandoned and others methods were explored.

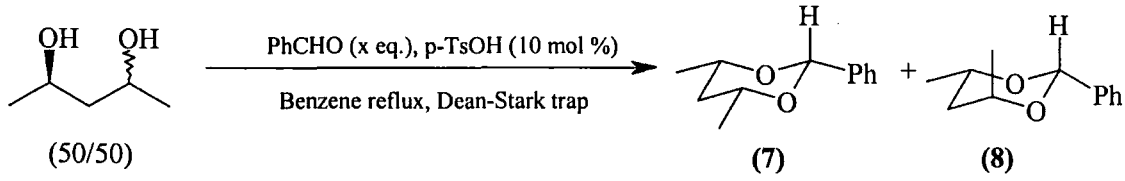
2.2.1.2.2-Separation from a diastereoisomeric mixture :

In 1991, Denmark[10] reported an easy method for the separation of the *meso*- and *d,l*-diol isomers from a diastereoisomeric mixture using standard acetalization with benzaldehyde followed by separation of the corresponding benzylidene acetals by chromatography. The pure *meso*-diol was simply regenerated by hydrogenation [H_2, 5 % Pd/C] (Scheme 2.5).[11]



Scheme 2.5

Following this precedent, the reaction of the commercially available *meso/d,l-* 2,4-pentanediol mixture (£69.20/50g, Aldrich) with benzaldehyde and p-TsOH, varying the number of equivalents of benzaldehyde, was investigated. Results of the study are summarised in the following table (Scheme 2.6, Table 2.2).



(50/50) **(7)** **(8)**

Entry	Number of equivalent of PhCHO	Yield (%)	Ratio **(7/8)**
1	1	45	50/50
2	0.6	40	80/20
3	0.5	42	90/10
4	0.45	40	95/5

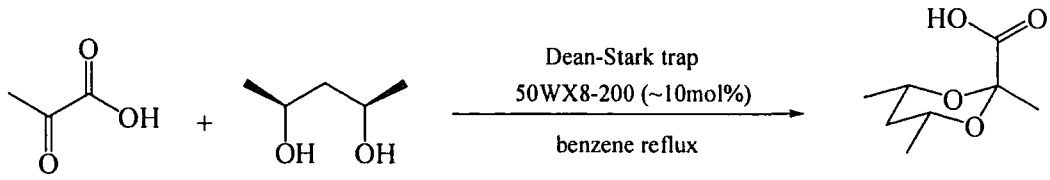
Scheme 2.6, Table 2.2

The use of 0.45eq of benzaldehyde resulted in a highly enriched mixture of **(7)**. The major isomer **(7)** was easily separated by silica gel chromatography from the compound **(8)**, the latter has not been isolated. Further purification by kugelrohr distillation gave **(7)** as a colourless oil in 40 % yield. The structure and stereochemistry of the product **(7)** was established by 1D and 2D NMR experiments (^1H, ^{13}C, COSY and NOESY) together with comparison with literature data.[16] The ^1H NMR spectrum showed a qdd at 3.95 ppm, integrating for 2H with the coupling constants $Jd_{ax\text{-}ax}$=12.4 Hz, $Jd_{ax\text{-}eq}$=2.5 Hz and Jq= 7.2 Hz, attributed to 4-H and 6-H. These protons are therefore equivalent and in the axial position. The nOe between 4-H and 2-H on one hand, and 6-H and 2-H on the other hand, showed that the phenyl group preferentially adopted the equatorial position.

Subsequent hydrogenation of **(7)** in the presence of catalytic Pd/C (5 mol%) and few drops of concentrated H_2SO_4, at room temperature overnight, led to the *meso*-diol **(6)** as a colourless oil in quantitative yield.

2.2.1.2.3-Ketalisation of *meso*-2,4-pentanediol (6) :

With *meso*-2,4-pentanediol **(6)** in hand, attention turned to the formation of the acid acetals.



(1) **(6)** **(9)**, 25%

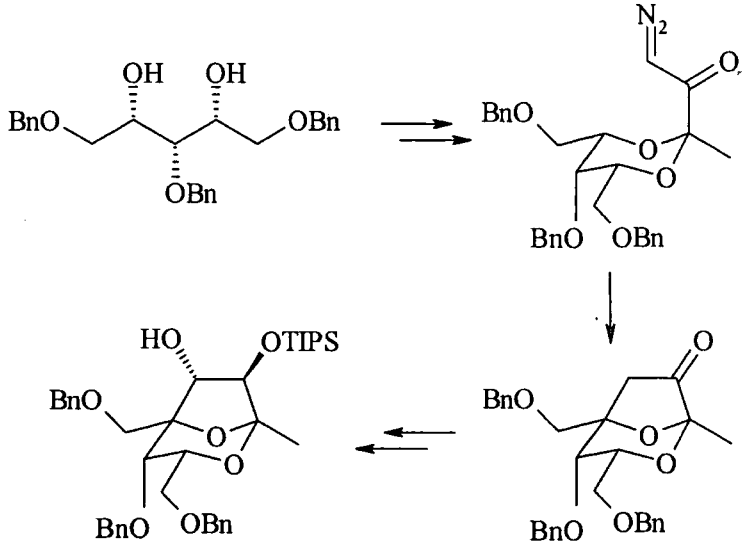
Scheme 2.7

Following the Newman and Chen procedure,[9] the derived acetal **(9)** was obtained in a 25 % yield (Scheme 2.7). Modification of the work-up procedure, as described in section (2.2.1.1) afforded an enhanced yield of 32 %. Evidence for the formation of the derived acetal was found in ^{13}C NMR spectrum with the C-2 signal at 98.4 ppm and again, the acetal was formed as a single stereoisomer. The preferential formation of the axial-2-carboxylate is consistent with the thermodynamically controlled reaction.

Unfortunately, despite much effort made to enhance yields, the Newman and Chen approach to the acid acetals formation was not satisfying and other methods were explored.

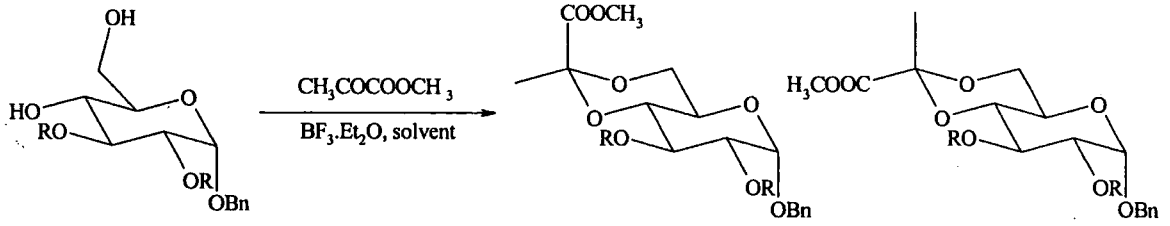
2.2.2-Wardrop method :

Concurrently with our study and efforts, Wardrop[12] reported the preparation of the bicyclic core of zaragozic acid via a dirhodium(II)-catalyzed intramolecular C-H insertion of 2-diazoacetyl-1,3-dioxane (Scheme 2.8).



Scheme 2.8

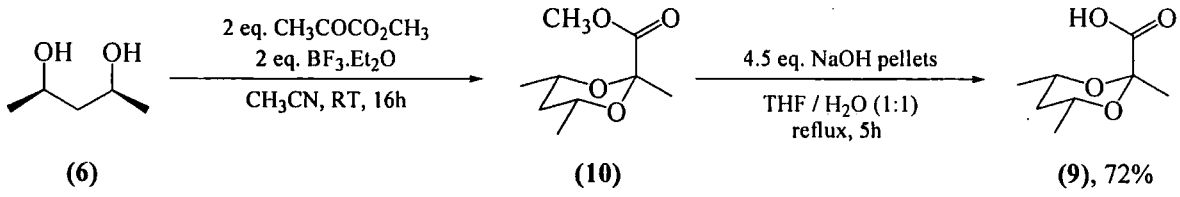
He developed a method, which involved the formation of acid acetals by hydrolysis of the corresponding pyruvate ester acetals made following a protocol reported by Ziegler.[13] Ziegler showed that condensation of partially protected D-glucosides with methyl pyruvate in the cation-stabilising solvent acetonitrile, led to preferential formation of the thermodynamically favoured diastereoisomer having an axial-oriented methoxycarbonyl group (Scheme 2.9). Similar observations had been described before for pyruvate acetals of aliphatic diols.[10,14]



R=Piv, CH_3CN	69%	traces
methyl pyruvate	11%	33%
R=Bz, CH_3CN	86%	-
methyl pyruvate	29%	34%

Scheme 2.9

Following this precedent, *meso*-2,4-pentanediol **(6)** was reacted with methyl pyruvate in the presence of $BF_3.Et_2O$ and after purification, the ester acetal **(10)** was hydrolyzed to the corresponding acid acetal **(9)** (Scheme 2.10).



(6) **(10)** **(9)**, 72%

Scheme 2.10

Key evidence for the formation of the ester acetal **(10)** was found in the ^{13}C NMR spectrum where a single quaternary C-2 signal was observed at 98.8 ppm and the ester carbonyl signal at 171.8 ppm together with the ^{1}H NMR signal of the methoxy group at 3.77 ppm. Subsequent hydrolysis of the ester acetal led to the corresponding acid acetal **(9)**. Evidence for the formation of **(9)** was found in the ^{1}H NMR spectrum with the disappearance of the methyl ester signal at 3.77 ppm and the appearance of the acid OH signal at 8.2 ppm together with the carbonyl acid signal observed in the ^{13}C NMR spectrum at 175.7 ppm. Encouragingly, 2-carboxy-2,4,6-trimethyl-1,3-dioxane **(9)** was obtained in a 72 % yield (after two steps) in contrast to the 32 % yield obtained using Newman and Chen procedure. Importantly, as before, the acetalisation provided a single diastereoisomer in which the carboxylate group was found to be in the axial orientation as ascertained by nOesy experiments.

In conclusion, it was shown that the isolation of *meso*-2,4-pentanediol was viable and the *meso* diol was obtained in good yield although with two additional steps added to the strategy. The previous attempt to form the diol by reduction of the corresponding diketone was not efficient (30 % yield) although giving ~100 % diastereoselectivity. Following the Wardrop procedure, the route to the acid acetals is multistep but with good yields, whereas a one-pot process involving treatment of diols with pyruvic acid provided the acid acetals in low yields (30-40 %).

With routes to acid acetals now established, attention turned to the formation of the corresponding diazoketones.

2.3-Synthesis of the diazoketones :

There are various routes available for converting a carboxylic acid to an α-diazoketone. As seen in the introduction chapter (section 1.3.2.2, p.11), a useful strategy is the acylation of diazomethane with an acyl chloride[15] or less commonly with an anhydride.[16]

2.3.1-Arndt-Eistert and Bradley's procedure :

According to Arndt-Eistert and Bradley,[15] the use of an excess of diazomethane is essential to the method. Indeed, the diazoketones formed can further react with HCl leading to halogenomethylketones **(Eq 2)**. An excess of diazomethane is needed to trap HCl by forming methylchloride **(Eq 3)**. The overall reaction is summarized in the following scheme (Scheme 2.11).

$$RCOCl + CH_2N_2 \rightarrow RCOCHN_2 + HCl \qquad \textbf{(Eq 1)}$$

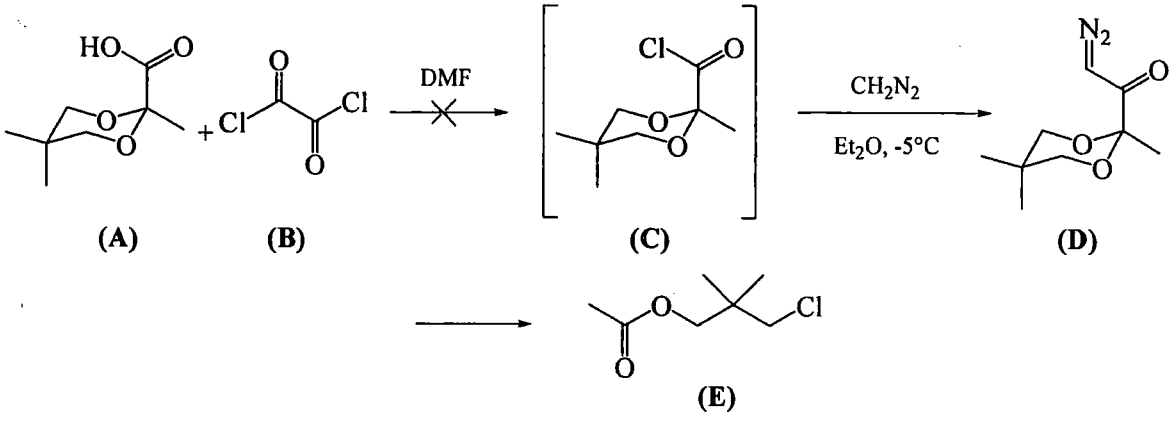
$$RCOCHN_2 + HCl \rightarrow RCOCH_2Cl + N_2 \qquad \textbf{(Eq 2)}$$

$$CH_2N_2 + HCl \rightarrow CH_3Cl + N_2 \qquad \textbf{(Eq 3)}$$

$$RCOCl + 2\ CH_2N_2 \rightarrow RCOCHN_2 + CH_3Cl + N_2$$

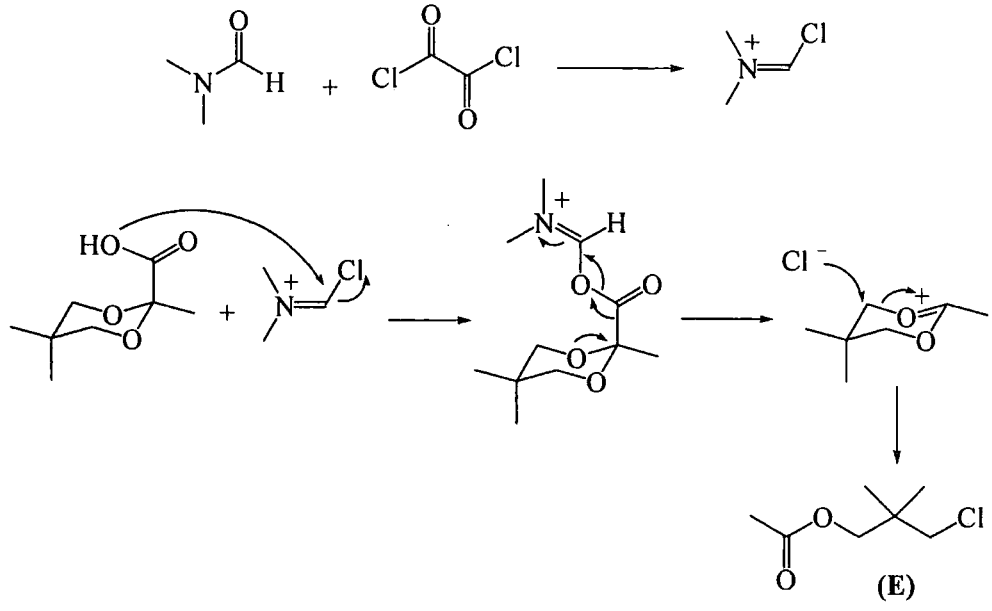
Scheme 2.11

Previous attempts in the group to follow the Arndt-Eistert procedure,[15a] by activating the ketal acid **(A)** to the acyl chloride **(C)**, produced the acyclic compound **(E)** instead of the desired diazoketone **(D)** (Scheme 2.12).



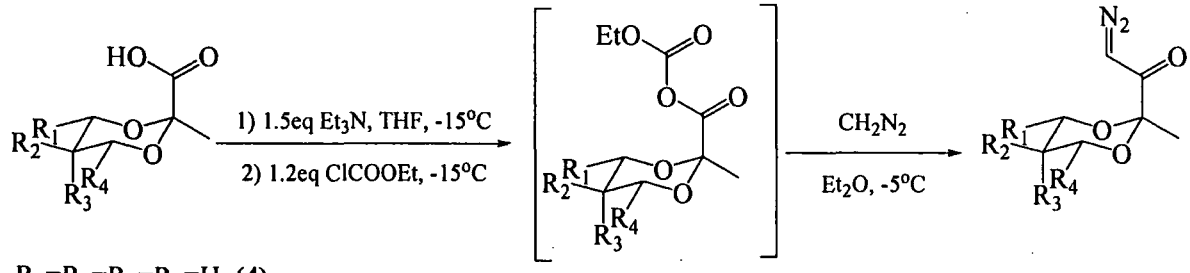
Scheme 2.12

A possible explanation was postulated through a mechanism which goes *via* a DMF intermediate followed by a ring opening of the acetal core leading to the compound **(E)** (Scheme 2.13).



Scheme 2.13

Consequently, alternative routes for the activation of the acid were explored. Bradley and Robinson have shown that anhydrides are also suitable acylating agents for diazomethane.[15] A convenient *in situ* procedure to form mixed anhydrides involves treatment of the acid acetals with chloroformate esters. This strategy was adopted for the synthesis of the diazoketones (Scheme 2.14).[17]

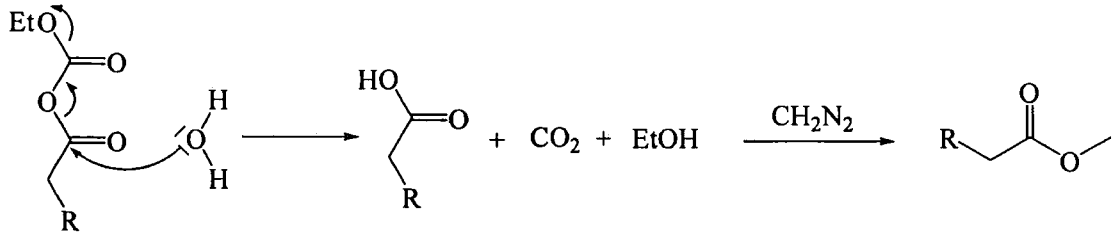


$R_1=R_2=R_3=R_4=H$ **(4)**
$R_1=R_4=H$; $R_2=R_3=CH_3$ **(5)**
$R_1=R_4=CH_3$; $R_2=R_3=H$ **(9)**

(11), 75%
(12), 79%
(13), 62%

Scheme 2.14

Treatment of the acid acetals **(4,5,9)** with Et_3N and ethyl chloroformate generated the corresponding mixed anhydrides, which were not isolated. Complete consumption of the acid was established by TLC, and the reaction mixture was then treated with an ethereal solution of diazomethane. Diazomethane was prepared from the commercially available precursor : Diazald® following DeBoer and Backer procedure.[18] In this procedure, a solution of Diazald® in Et_2O was added to a mixture of KOH (1.1eq) in di(ethyleneglycol) methyl ether (3eq), Et_2O (1eq) and H_2O (5.5eq) at 60°C. The α-diazoketones **(11-13)** were obtained in 75, 79 and 62 % yield respectively. Evidence for the formation of the diazoketones was found in IR and ^1H NMR spectra with the band at ~2100 cm^{-1} and the NMR shift at ~5.7 ppm attributed to the (***CH***N_2) functionality. It is worth noting that the IR spectra of the crude diazoketones also showed a small band ~1822 cm^{-1} which has been attributed to the unreacted mixed anhydride and another band at ~1740 cm^{-1} which has been attributed to the methyl ester by-product of the reaction. Methyl ester formation was previously observed by Cassal *et al*[19] and Plucinska *et al.*[20] The latter explained its formation by the reaction of the mixed anhydride with H_2O, which competed with the reaction of diazomethane as a nucleophilic reagent. Subsequent methylation of the resulting acid formed with CH_2N_2 led to the methyl ester (Scheme 2.15).



Scheme 2.15

However, this by-product was generally only observed when using ethanol or H_2O as solvent. The preparation of a non-ethanolic solution of diazomethane using a higher boiling solvent, di(ethyleneglycol)methyl ether, limitated the formation of the methyl ester.

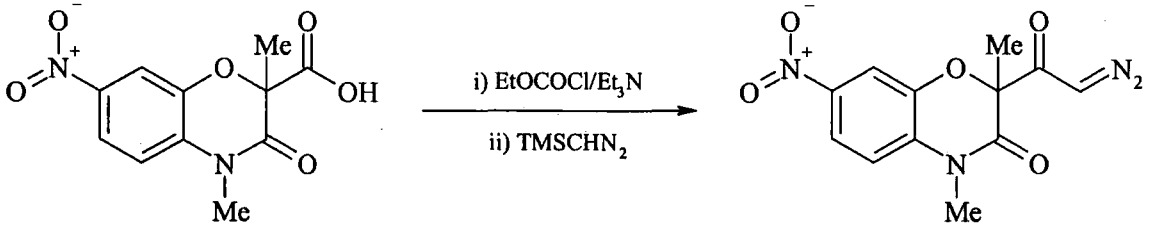
It is worth noting that, following the Wardrop procedure,[12] treatment of acid acetal **(9)** with isobutyl chloroformate, instead of ethyl chloroformate, led to **(13)** with an enhanced yield of 84%. It has been postulated that the larger isobutyl group could possibly protect

the α-carbonyl group leading to the preferential attack by the diazomethane on the other carbonyl.

The synthesis of diazoketones was achieved in good yield but one of the major problems, or disadvantages, of this method was the use of diazomethane. Diazomethane is not only highly toxic but also presents some risk of explosion and hence, should be carefully handled (its synthesis required the use of special glassware without sharp edges and glass joints). Therefore, it was decided to investigate the use of a less hazardous substitute.

2.3.2-Use of TMS diazomethane :

An initial review of the literature showed that TMS-diazomethane has been successfully used as a stable and safe substitute in reactions previously dominated by diazomethane, particularly in the Arndt-Eistert synthesis[21] and in the formation of alkylidene carbenes from ketones.[22] Recently, a group from Slovenia[23] successfully used TMS-diazomethane for the formation of a diazoketone starting from a mixed anhydride as shown on the following sheme (Scheme 2.16).



Scheme 2.16

Following this precedent, acid acetal **(9)** in solution in THF was treated successively by Et_3N (1.1eq) and EtOCOCl (1.1eq) at -15°C and the reaction mixture subsequently stirred for 30 minutes at -5°C. After filtration of the $Et_3NH^+Cl^-$ precipitate, the residue in solution in CH_3CN was treated with commercially available TMS-diazomethane (2.0 M solution in hexane, 2eq) and the reaction mixture stirred for 24h at +4°C. After work-up, TLC showed a complex mixture of products and the NMR of the crude mixture showed the formation of only a small amount of the desired diazoketone. Evidence for the formation of the diazoketone **(13)** was found in the IR and ^1H NMR spectra with the IR

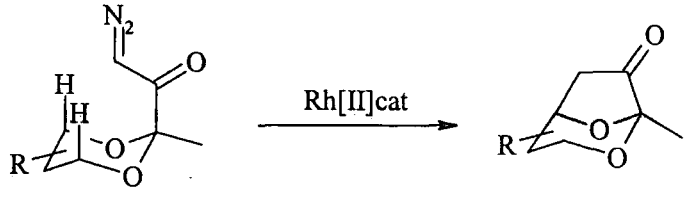
band at ~2100 cm^{-1} attributed to the (CHN_2) group together with the ^1H NMR shift at ~5.6 ppm (***CH***N_2). After purification by column chromatography on silica gel, the diazoketone **(13)** was isolated as a yellow solid in only 13% yield. The major product isolated in 85% yield appeared to be the free *meso*-2,4-pentanediol as confirmed by the ^1H NMR spectrum showing a characteristic doublet at 1.18 ppm which integrated for 6H. It is likely that the use of formic acid in the work up caused the ring opening of the acid acetal **(9)**. Due to this disappointing result, the use of TMS-diazomethane was not further investigated at this time. Attention turned to the study of the insertion process, which would lead to the formation of the bicyclic acetals.

2.4-Rhodium-mediated C-H insertion :

2.4.1- Introduction :

As seen in the introduction chapter, rhodium (II) carboxylates are useful catalysts for the catalytic decomposition of α-diazocarbonyl compounds leading to transition-metal carbenoids, reactive intermediates, able to insert into a C-H bond. Extensive efforts by a number of groups have enabled the identification of the factors controlling the site-selectivity of intramolecular C-H insertion reactions. Independent work carried out by Taber[24], Doyle[25] and Wenkert[26] has shown that the cyclization of these carbenoids preferentially formed 5-membered rings and cyclization of heteroatomic compounds proceeded with a preference for insertion into a C-H bond α to the heteroatom.

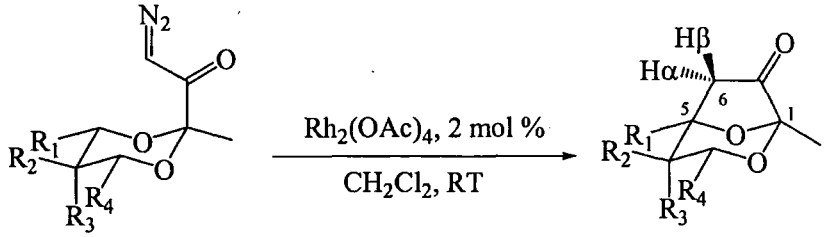
As seen previously (section 2.2.1.1), 2-carboxy-1,3-dioxanes display a pronounced preference (~3 to 4 kcal/mol) for the axial-oriented 2-carboxylate group. Thus, the C-2-diazoacetyl group is positioned in a coplanar arrangement with the activated C-4/6 C-H bonds (α to an oxygen) providing the ideal situation for a rhodium-mediated C-H insertion to take place, which will lead to the formation of 2,8-dioxabicyclo[3.2.1]octanones (Scheme 2.17).



Scheme 2.17

2.4.2-Formation of the bicyclic ketones :

In the initial attempts, the diazoketones **(11-13)** were subjected to rhodium(II) acetate treatment following the conditions developed during preliminary studies in the group.[1] In a typical reaction, a solution of the diazoketone in CH_2Cl_2 was added dropwise to a stirred solution of rhodium diacetate dimer, $Rh_2(OAc)_4$, in CH_2Cl_2 (Scheme 2.18).



$R_1=R_2=R_3=R_4=H$, **(11)** **(14)**
$R_1=R_4=H;R_2=R_3=CH_3$, **(12)** **(15)**
$R_1=R_4=CH_3$; $R_2=R_3=H$, **(13)** **(16)**

Scheme 2.18

Evidence for the formation of the bicyclic ketals was found in the ^{13}C NMR data where tertiary C-5 signals were observed at δ=71.5, 80.1 and 77.2 ppm and the carbonyl signals observed at δ=211.0, 211.2 and 212.2 ppm for the bicyclic ketones **(14)**, **(15)** and **(16)** respectively. In the case of **(15)**, a *dd* integrating for 2H was expected for both diastereotopic 6-H_α and 6-H_β due to the *gem*-coupling and the coupling with 5-H. Instead, only one *dd* was observed at 2.5 ppm which integrated for 1 H with coupling constants of $J_{5\text{-H}/6\text{-H}}$=7.5 Hz and $J_{6\text{-H}\alpha/6\text{-H}\beta}$=18.3 Hz together with a *d* at 2.35 ppm which also integrated for 1 H with a coupling constant of $J_{6\text{-H}\alpha/6\text{-H}\beta}$=18.3 Hz. This suggested that the conformation of the molecule was such that 6-H_β and 5-H were at ~90° to each other and so had a coupling constant of 0 Hz. This was confirmed by the signal observed for 5-H, a *d* due to the coupling with 6-H_α with a coupling constant of $J_{5\text{-H}/6\text{-H}\alpha}$=7.5 Hz.

In all cases studied, the C-H insertion process led to the formation of only one cyclo adduct showing that the insertion was stereospecific and occurred into the C-H bond α to the heteroatom. Disappointingly, after having successfully prepared the bicyclic acetals **(14-16)**, their purification proved to be problematic. Indeed the isolated yields after purification were poor as **(14)**, **(15)** and **(16)** were obtained in 2, 5 and 9 % respectively. This could be attributed to the possible instability of the bicyclic compounds to silica gel

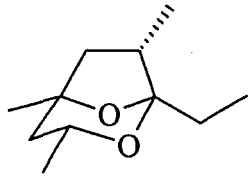
chromatography, in addition to their volatility. Alternative purification procedures were then explored, and enhanced isolated yields of 28, 37 and 38 % were obtained after purification by flash chromatography on alumina.

With a synthetic strategy for the formation of bicyclic cores now established, demonstration of its versatility through the synthesis of naturally occuring bioactive molecules was sought.

2.5-Attempts to synthesise sordidin :

2.5.1-Introduction :

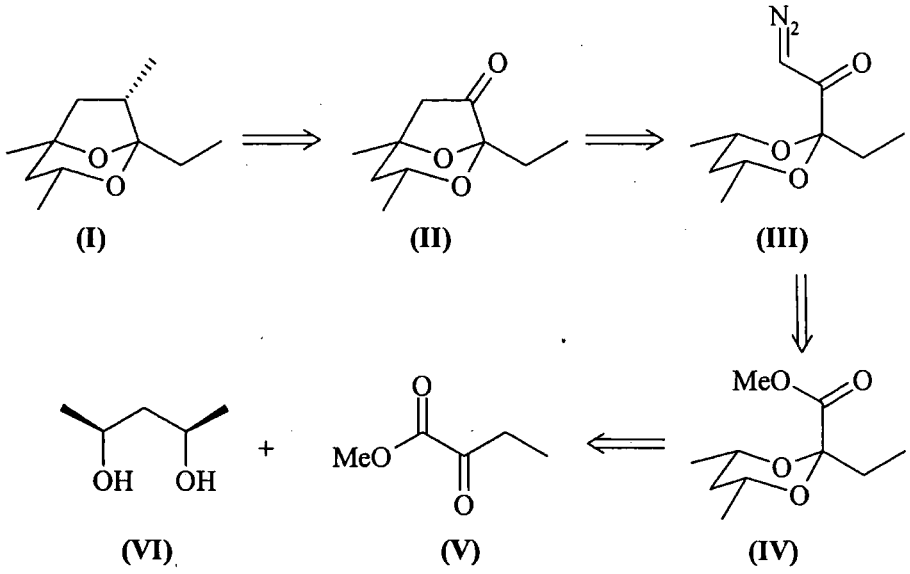
Sordidin,[27] a volatile aggregation pheromone released by male *C.sordidus* banana weevils was chosen as a target molecule to demonstrate the utility of our synthetic route (Scheme 2.19).



Scheme 2.19

It has been shown that sordidin lures in field traps led to a significant capture rate of adult *C.sordidus*.[28] The mass trapping could overcome their reproductive capacity and limit the destruction of banana trees. Therefore, synthetic methods for the synthesis of sordidin are of considerable interest.

The retrosynthetic disconnections, which form the basis of the strategy for the synthesis of sordidin are illustrated in the following scheme (Scheme 2.20).

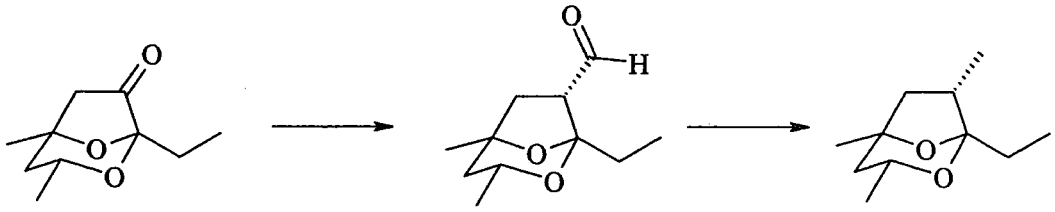


(I) (II) (III)

(VI) (V) (IV)

Scheme 2.20

The bicyclic ketone **(II)**, our key intermediate, should be obtained in three steps from *meso*-2,4-pentanediol **(VI)** and ethyl pyruvate **(V)** using the synthetic strategy established. The strategic route chosen for the formation of the sordidin **(I)** from the bicyclic ketone **(II)** is illustrated in the following scheme (Scheme 2.21). The bicyclic ketone **(II)** would be converted to the aldehyde **(VII)** whose subsequent Clemmensen or Wolff-Kishner reduction will lead to the target compound **(I)**.



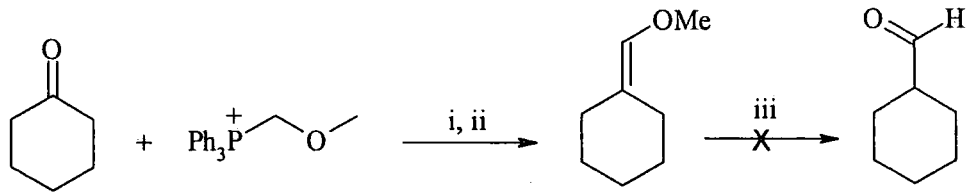
(II) (VII) (I)

Scheme 2.21

Initial investigation focused on the synthesis of the aldehyde **(VII)**. Due to the volatility of the bicyclic ketones, and therefore the difficulty in obtaining sufficient quantities to test the reactions, cyclohexanone, a heavy cyclic ketone, was used as a model system

2.5.2-Wittig reaction :

The first attempt to convert the cyclohexanone to the aldehyde system was made using a Wittig reaction[29] followed by treatment with acid (Scheme 2.22).



(17), 65% **(18)**

Reagents and conditions :
i) phosphonium salt + nBuLi, THF, 0°C, 2h; ii) ketone, THF, 0°C to rt, overnig
iii) pTsOH, THF/H_2O (1:1), rt or HCl 1M, THF, rt

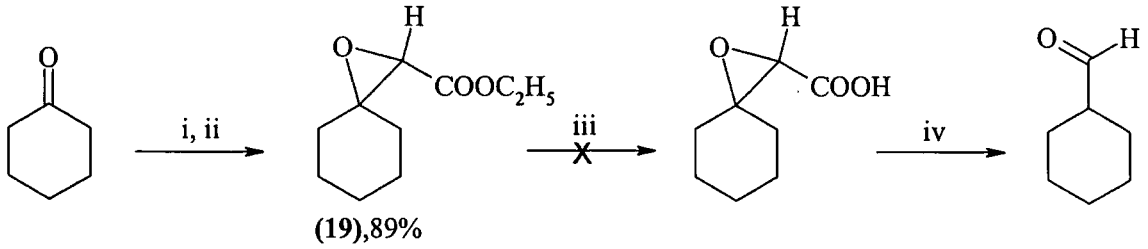
Scheme 2.22

To a solution of methoxymethyl triphenyl phosphonium chloride (1.5eq) in THF, nBuLi (1.5eq) was added at 0°C and the reaction was stirred at that temperature for 2 hours. The cylohexanone (1eq) in solution in THF was then added, the reaction was allowed to warm to room temperature and stirred overnight. After work up and purification by flash chromatography, the methoxymethylene cyclohexane **(17)** was obtained in 65 % yield. Evidence for the formation of the compound **(17)** was found in the ^1H NMR spectrum with a singlet for the methoxy at 3.50 ppm and a singlet at 5.7 ppm for the ethylene proton. Attempts to convert the methoxymethylene cyclohexane **(17)** into the aldehyde **(18)** by treatment with pTsOH (10 mol%) or aqueous HCl (1M, 1 and 2eq) were unsuccessful with no aldehyde obtained and no recovery of the starting methoxymethylene cyclohexane.

In addition, the application of the Wittig conditions to the bicyclic ketone **(16)** led to the recovery of the starting ketone. A complex reaction mixture was obtained when 5 equivalents of both phosphonium salt and nBuLi were used. The instability of the methoxymethylene derivative was first blamed and a subsequent treatment with dilute HCl, without prior isolation of the methoxy methylene derivative, was attempted but no aldehyde was isolated. No further investigations were made and this strategy was abandoned.

2.5.3-Darzens condensation :

An alternative strategy using a Darzens condensation[30] followed by hydrolysis and decarboxylation was devised (Scheme 2.23).



Reagents and conditions :
i) EtONa, $BrCH_2COOEt$, DCM, -78°C, 3h, ii) cyclohexanone, -78°C to 0°C, overnight
iii) hydrolysis ($LiOH.H_2O$, $MeOH/H_2O$ (3:1) or aq.NaOH (3M), THF/H_2O (1:1), rt, overnight)
iv) pyridine, Δ : decarboxylation

Scheme 2.23

To a solution of sodium ethoxide (1.2eq) in DCM at -78°C, ethyl bromoacetate (1eq) was added, and the reaction mixture was stirred at -78°C for 3 hours. The cyclohexanone (1.5eq) in solution in DCM was then added and the reaction mixture slowly warmed up from -78°C to 0°C and stirred at 0°C overnight. After work up and purification by flash chromatography, the oxa-spiro-octane derivative **(19)** was obtained in 89 % yield. Evidence for its formation was found in the ^1H NMR spectrum with a singlet at 3.30 ppm integrating for 1 H corresponding to the proton of the epoxide, a triplet at 1.27 ppm (3H) for the methyl of the ethoxy group and a quadruplet at 4.22 ppm for the methylene of the ethoxy group. Subsequent hydrolysis of the ester functionality into the acid using $LiOH.H_2O$ (1.65eq) in a $MeOH/H_2O$ mixed-solvent or using aqueous NaOH (3M,1.5eq), at room temperature and at reflux, led to a complicated reaction mixture with no trace of the desired product.

Concurrent to our efforts, Wardrop published a synthesis of episordidin,[31] the epimer of sordidin, using a similar strategy and therefore, no further experiments were conducted and the synthesis of sordidin abandonned.

2.6-Conclusion :

The first aim of the project was to form bicyclic ketones, which are key intermediates for the formation of tetrahydrofuran rings by reductive cleavage, but also make up the bicyclic core of such molecules as sordidin, our target natural product.
Despite much effort, several problems have arisen during this study :

§ Methods for the preparation of *meso*-2,4-pentanediol **(6)**, which was required as starting material for the synthesis of sordidin, were explored due to its high cost. Isolation from a commercially available diastereoisomeric mixture was viable although it added two steps to the strategy. However, the alternative diastereoselective reduction of the corresponding diketone using the Bartoli procedure was not efficient, affording the *meso*-diol **(6)** in poor yield (30 %) although with a good diastereoselectivity.

§ The one-pot process for the preparation of acid acetals involving treatment of the diols with pyruvic acid was successful. Disappointingly, the overall yields were low (30-40%) despite much effort to enhance them. Alternatively, good yields were obtained when, following the Wardrop strategy, the acid acetals were formed by hydrolysis of the corresponding ester acetals.

§ Due to the lack of chromophores and their volatility, the C-H insertion products were difficult to detect, which consequently made the reactions difficult to follow by TLC.

§ Finally, concurrently to our study and efforts, Wardrop published a synthesis of episordidin (epimer of sordidin) using a similar synthetic strategy.

Owing to these issues, we decided to focus our efforts on the investigation of the synthetic methodology towards the stereoselective synthesis of highly functionalised THF rings.
To overcome the problems of volatility and the difficulties of following the reactions by TLC, it was decided to introduce heavy substituents, which also possessed chromophoric groups. The phenyl, benzyl, *p*-nitrophenyl and *p*-aminophenyl groups were chosen. This would also permit the study of the effect of electronegativity on the C-H insertion process and on the reductive cleavage.

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CHAPTER III: SYNTHESIS OF NEW BICYCLIC KETONES

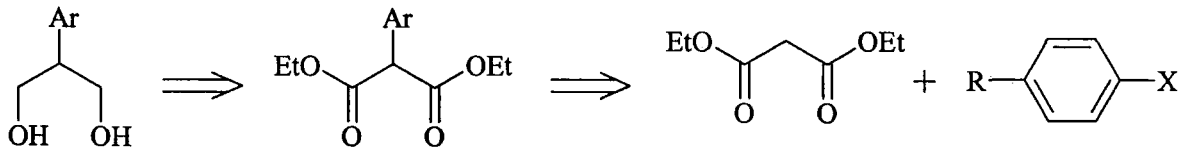
3.1-Introduction :

As explained in the conclusion of the preceding chapter, the synthesis of new bicyclic ketones possessing a phenyl, a benzyl, a *p*-nitrophenyl and *p*-aminophenyl group at C-4 was targeted.

Although 2-phenylpropane-1,3-diol is commercially available, few other 2-substituted-propane-1,3-diols are. Therefore, methods for the necessary preparation of 2-benzyl, 2-*p*-nitrophenyl and 2-*p*-aminophenyl diols were explored. This chapter will describe the synthesis of these diols and their conversion to bicyclic ketones following the strategy previously established.

3.2-Preparation of 2-aryl-propane-1,3-diols :

The retrosynthetic disconnections, which form the basis of our synthetic strategy for the preparation of 2-aryl-propane-1,3-diols, are illustrated in the following scheme (Scheme 3.1).



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

R=alkyl, NO_2, NH_2, OMe, CF_3
X=Cl, Br, I, F

Scheme 3.1

The 2-arylpropane-1,3-diols **(I)** may be obtained by reduction of the corresponding aryldiethylmalonates **(II)** prepared by arylation of diethylmalonate **(III)**.

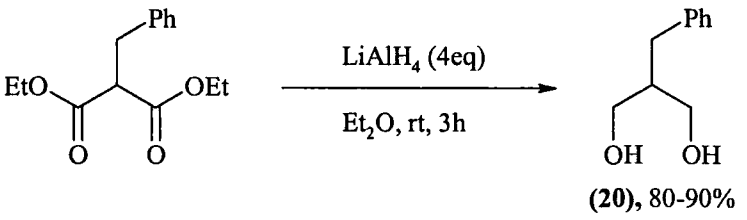
3.2.1-2-Benzyl-propane-1,3-diol :

2-Benzylpropane-1,3-diol is not commercially available. However, the corresponding diethylmalonate is and therefore, procedures for its reduction were explored.

$NaBH_4$ is a safe and easy to handle reducing agent, but reduces esters slowly. Therefore, $LiAlH_4$ is usually used although reactions maybe more dangerous, as it reacts violently

with water and presents risks of explosive decomposition if heated above 120°C. Despite these drawbacks, it remains a valuable reagent widely used but with precautions.

Thus, a cooled solution of $LiAlH_4$ (4eq) in Et_2O at 0°C was treated dropwise with a solution of benzyl diethylmalonate and the reaction mixture stirred for 3 hours at room temperature (Scheme 3.2).[1]



(20), 80-90%

Scheme 3.2

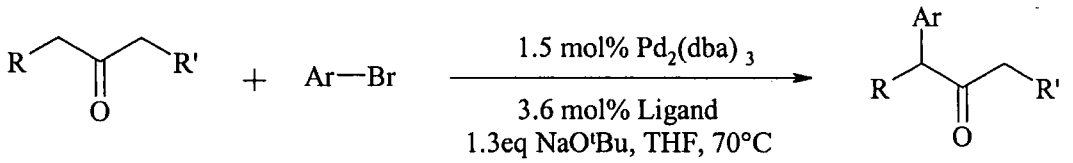
After work-up, the residue was purified by flash chromatography on silica gel and further recrystallised from cyclohexane. The diol **(20)** was obtained in good yield (80-90%) as a white solid. Evidence for the formation of the diol was found in the IR and ^1H NMR spectra. The study and comparison of the IR spectra of the starting material and the product showed the appearance of the broad IR band characteristic of alcohols at ~3440-2980 cm^{-1} and the disappearance of the ester signal at 1740 cm^{-1}. The ^1H NMR spectrum, by its simplicity, confirmed the diol formation by showing two signals at 3.87 ppm (2H, dd, J= 10.5, 3.5 Hz, 1-Ha, 3-Ha) and at 3.75 ppm (2H, dd, J= 10.5, 6.8 Hz, 1-Hb, 3-Hb) attributed to 1-CH_2 and 3-CH_2, together with a signal at 2.15 ppm (1H, m, 2-H) attributed to 2-CH. The absence of any carbonyl signal in the ^{13}C spectrum proved the total reduction of the ester groups to give the diol.

3.2.2- 2-(*p*-nitrophenyl)propan-1,3-diol and 2-(*p*-aminophenyl)propan-1,3-diol :

3.2.2.1-Arylation of diethylmalonate :

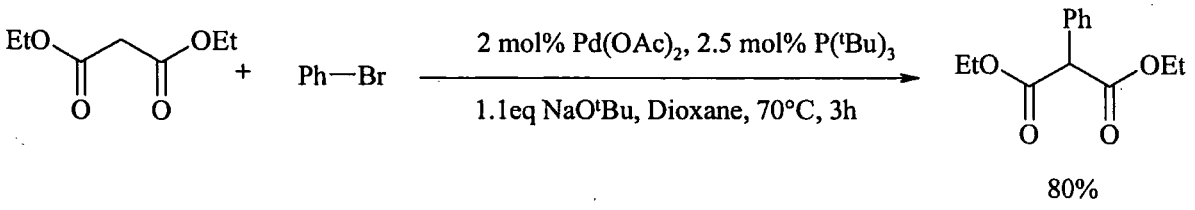
After a comprehensive literature survey, it appeared that cross-coupling reactions involving ketone enolates as nucleophiles were limited and occurred in modest yield. Reactions between aryl halides and enolates derived from dialkyl malonates or cyanoesters were typically conducted using stoichiometric amounts of copper(I) salts,[2] unless the halides were activated by an *o*-carboxylate group.[3] However, in 1993, the arylation of malonates and cyanoesters was achieved using a catalytic loading of copper

(CuI, 10 mol%) in the presence of K_2CO_3 (4eq) but the reaction required the use of aryl iodides and high temperature.[4] In 1997, Buchwald and Palucki[5] were the first to publish a novel Pd-catalyzed method for the direct cross-coupling of aryl bromides with ketones (Scheme 3.3).



Scheme 3.3

They found that the combination of $Pd_2(dba)_3$ and Tol-BINAP or BINAP in the presence of NaO^tBu effectively catalyzed the desired coupling reaction. In 1999, Hartwig *et al.*[6] reported the α-arylation of a series of ketones and malonates (di-*tert*-butyl and diethyl-malonate) with aryl bromides and chlorides using a combination of $Pd_2(dba)_3$ and D^tBPF, a bisphosphine ligand. While the reaction of phenyl chloride with di-*tert*-butylmalonate in the presence of D^tBPF and $Pd_2(dba)_3$ as catalyst led to the formation of the aryl malonate in 78% yield, the reaction of diethylmalonate with this catalyst system did not produce the desired aryl malonate product in good yield. However, the use of $Pd(OAc)_2$ and $P(^tBu)_3$ as catalyst did produce the desired aryl malonate in 80% yield (Scheme 3.4).



Scheme 3.4

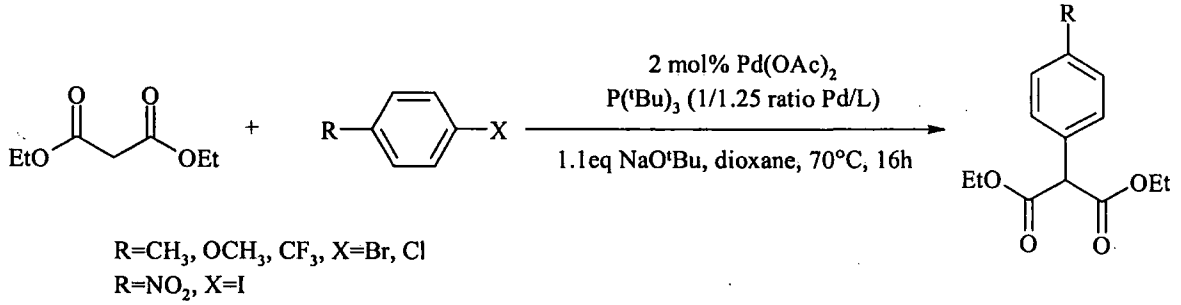
After this literature survey, it clearly appeared that successful arylation of malonates with aryl halides is rare. The failures were postulated to be due to the high stability of the complex, formed by the anion of the β-dicarbonyl compound during the catalytic cycle, towards reductive cleavage. Hartwig found that complexes containing t-butyl phosphine ligands were more reactive than expected and so ligands electronically rich and sterically

encumbered might promote both oxidative addition and reductive elimination steps of the catalytic cycle.[7]

Considering these published results, a series of experiments was designed varying catalyst, base, solvent and aryl halide. The first set of reactions was carried out at 70°C under argon atmosphere, using 2 mol% $Pd(PPh_3)_4$, 1eq bromotoluene and 1.1eq diethylmalonate, but varying the base (1.2eq, KO^tBu or NaO^tBu) and the solvent of the reaction (THF, dioxane). The crude reaction mixtures were submitted to GC/MS analysis, but in all the cases, no arylation product was detected.

Consequently, it was decided to use a $Pd(OAc)_2/P(^tBu)_3$ system following the Hartwig conditions.[6] $Pd(OAc)_2$ (2 mol%), $P(^tBu)_3$ (1/1.25 ratio Pd/L) and 1.1eq of base were suspended in dioxane, followed by the dropwise addition of bromotoluene and diethylmalonate. The reaction mixture was then heated at 70°C and monitored by GC analysis. A series of bases was screened : KO^tBu, NaO^tBu, LiO^tBu, NaH and K_3PO_4. All reactions led to complicated reaction mixtures with little aryl malonate product formed according to GC/MS analysis.

It was finally decided to vary the aryl halides to see if there would be any difference of reactivity by varying the halogen atom (X=Br, Cl, I) or by varying the substituents on the phenyl ring (EWG, EDG). So another set of reactions was conducted and is summarised in the following scheme (Scheme 3.5).



Scheme 3.5

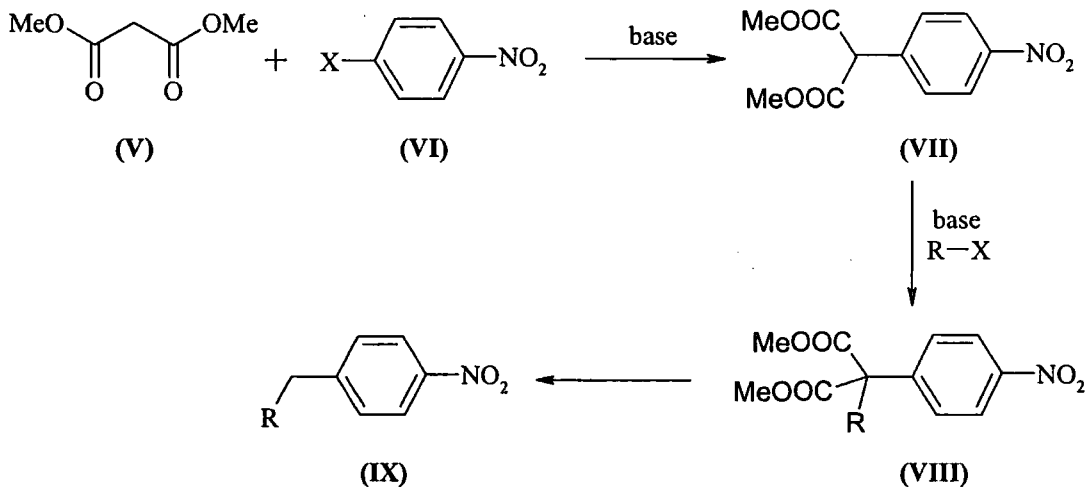
Once again, the reactions were analysed by GC and after 16h submitted to GC/MS. All reactions led to complicated mixtures with little aryl malonate products formed according to GC/MS analysis even with the more active aryl halide ($R=NO_2$, X=I). An attempt with

the latter using 5 mol% of catalyst was also unsuccessful and therefore, this strategy was abandoned.

The air sensitivity of the phosphine, $P(tBu)_3$, was possibly responsible for the failure of these reactions and the use of a glove box would probably be necessary for the success of this strategy.

3.2.2.2-Nucleophilic aromatic substitution :

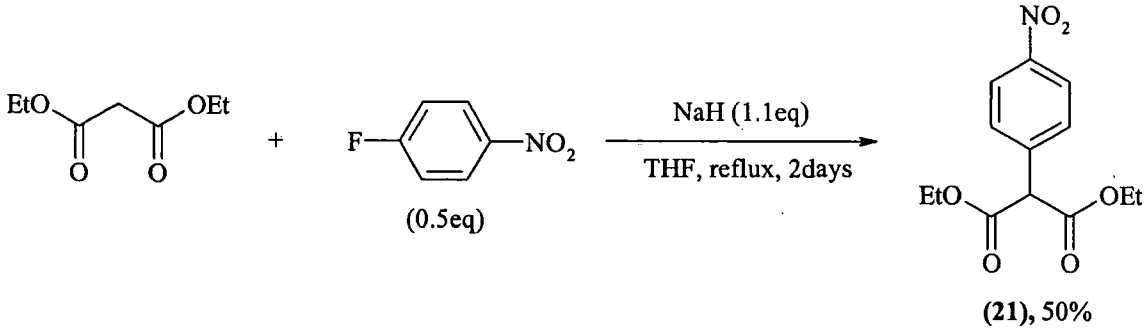
Nucleophilic aromatic substitution occurs only if the aromatic ring has an electron withdrawing substituent in an ortho or para position to the leaving group and a nitro group with strong inductive and resonance effects is the ideal substituent. In 2001, a group from India used dimethylmalonate as a linking agent for attaching a variety of substituents possessing different functionalities (such as ester, nitrile, olefin or ketone) to aromatic nitro compounds (Scheme 3.6).[8]



Scheme 3.6

Dimethyl malonate **(V)** was reacted with an aromatic compound **(VI)** under basic conditions leading to compound **(VII)** which was then alkylated to give product **(VIII)** and both ester functionalities were removed under Kraphcho's decarboxylation conditions[9] leading to the alkylated compound **(IX)**. The treatment of 3,4-dichloronitrobenzene or 4-fluoronitrobenzene under basic conditions afforded the corresponding diesters in good yield (75% and 65% respectively).

Following this approach, diethyl malonate was added dropwise to a suspension of NaH (1.1eq) in dry THF under ice cooling over a period of 10 mins. 1-Iodo-4-nitrobenzene (0.5eq) was then added, and the reaction mixture was stirred at room temperature and followed by GC. After 16h, the crude reaction mixture was submitted to GC/MS and only traces of the desired product were detected. Therefore, the reaction was heated to 70°C overnight but once more, the GC/MS of the crude reaction showed only traces of the desired product. Even a prior recrystallisation of 1-iodo-4-nitrobenzene did not enhance the yield. The same procedure was applied using the more reactive aryl halide, 1-fluoro-4-nitrobenzene. When the reaction was stirred at room temperature, the GC/MS of the crude mixture showed only traces of the desired product. However, when heated in THF at reflux, the reaction went to completion in a clean fashion, with only product and unreacted diethyl malonate in a 3:1 ratio. After unsuccessful separation by flash chromatography, the mixture was submitted to a Kugelrhor distillation and the desired diethyl (2-*p*-nitrophenyl)malonate **(21)** was obtained in 30% yield. An enhanced yield of 50% was obtained after refluxing the reaction mixture for two days (Scheme 3.7).



Scheme 3.7

Evidence for the formation of the diester was found in the IR and ^{13}C spectra with a carbonyl band at ~1740 cm^{-1}, a nitro band at ~1350 cm^{-1} and a carbonyl signal at 167 ppm and also confirmed by elemental analysis. Because of time constraints, the yield of this reaction was not optimised and conditions for the selective reduction of the diester were then explored.

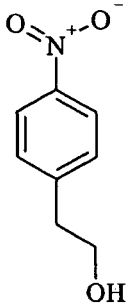
3.2.2.2(bis)-Reduction of 2-*p*-nitrophenyl diethyl malonate (21) :

Although $NaBH_4$ has proven to be a very useful reagent for the selective reduction of aldehydes and ketones in presence of other reducible groups, it has generally not been possible to use $NaBH_4$ for the reduction of esters. In 1982, an American group from Indiana has studied the effect of cations and solvent on the reactivity of Li, Na and Ca borohydrides towards the reduction of esters.[10] From their study, it appeared that $LiBH_4$ in Et_2O was the best system.

Following this precedent, the diester **(21)** in solution in Et_2O was added to a suspension of $LiBH_4$ (1.1eq) in Et_2O, the reaction mixture was stirred at room temperature and followed by GC. After 16h, the reaction mixture was submitted to GC/MS but no product was detected. Refluxing the medium or increasing the proportion of $LiBH_4$ to 4 eq did not yield the product.

Soai and Ookawa[11] reported that the addition of MeOH to a refluxing mixture of $NaBH_4$ and esters in ^{t}BuOH or THF enabled the reduction of the esters into the corresponding diols in high yields, and the combination of THF and MeOH was found to be the most effective.

Following this method, $NaBH_4$ (5eq) was added dropwise to a solution of the diethyl malonate derivative **(21)** in THF (4 ml/mmol of ester). MeOH (1/5 volume of THF) was slowly added to the refluxing mixture and the reaction followed by GC analysis. After completion, the reaction mixture was quenched, purified by flash chromatography and a compound, which was neither the starting diester nor the desired diol, was isolated in 51% yield. The study and assignment of the ^{1}H and ^{13}C NMR spectra permitted the determination of the structure of the by-product (**22**, Scheme 3.8, Table 3.1).



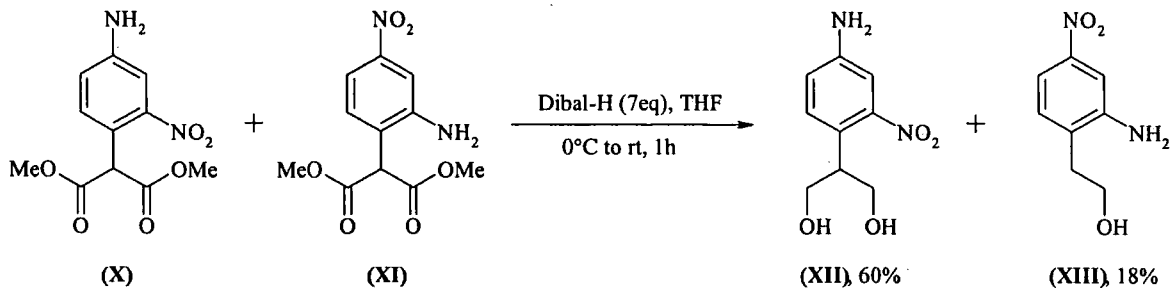
(22), 51%

Scheme 3.8

^{1}H NMR (δ in ppm)	^{13}C NMR (δ in ppm)	IR (in cm^{-1})
3.95 (2H, t, J=6.5Hz, 1-H)	62.8 (C-1)	/
3.00 (2H, t, J=6.5Hz, 2-H)	39.0 (C-2)	/
1.62 (1H, bs, OH)	/	3596-3146 (broad OH)

Table 3.1

The formation of similar by-products has been observed and reported by Tercel and Denny[12] in their attempts at synthesizing nitrogen and sulfur analogues of the seco-CI alkylating agent (CI=1a,2,3,5-tetrahydro-1H-cycloprop[1,2-c]indol-5-one) (Scheme 3.9).



Scheme 3.9

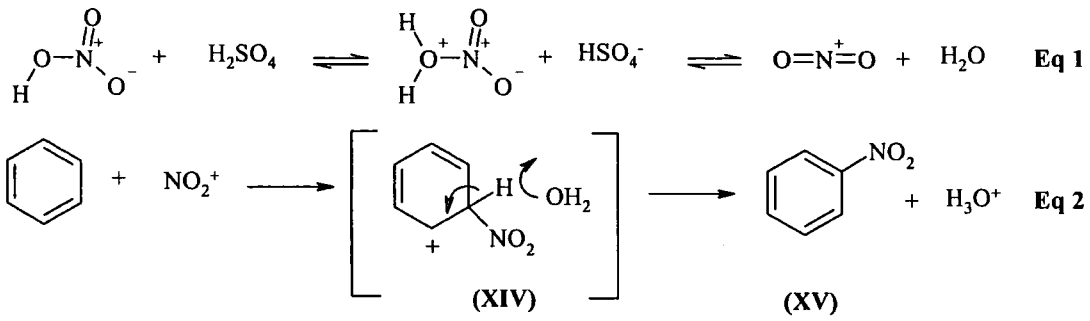
They also encountered difficulties in reducing either the ester or the nitro functional groups. Using Dibal-H, the compound **(XI)** with the nitro in the *para* position underwent decarbonylation followed by the reduction of the remaining ester group leading to the compound **(XIII).**

A further attempt was made using $LiAlH_4$ (4eq)[13] as reducing agent but as expected, because of its excessive reducing power, the reaction was not clean leading to a complex mixture.

As a result of the difficulties encountered for the selective reduction of the 2-*p*-nitrophenyl diethyl malonate **(21)** into the corresponding diol, other routes to the diol were explored.

3.2.2.3-Aromatic nitration :

It was decided to try a direct nitration of the commercially available 2-phenylpropan-1,3-diol. Aromatic rings can be nitrated by reaction with a mixture of concentrated nitric and sulfuric acids. The electrophile in this reaction is the nitronium ion, NO_2^+, which is generated from HNO_3 by protonation followed by loss of water (**Eq 1**, Scheme 3.10). The nitronium ion then reacts with the benzene, or the substituted benzene ring, to yield the carbocation intermediate **(XIV)**. Subsequent loss of H^+ gives the neutral substitution product **(XV)** (**Eq 2**, Scheme 3.10).

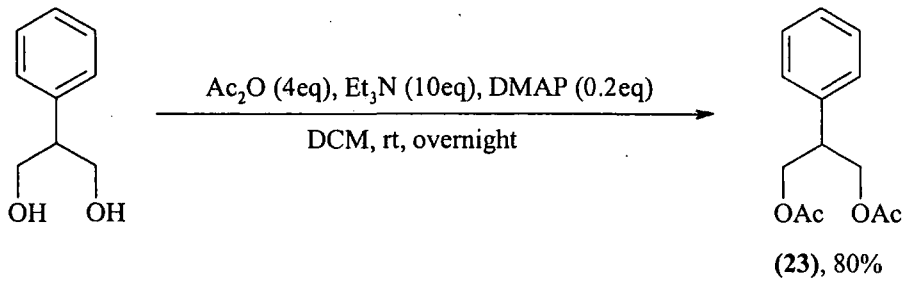


Scheme 3.10

Thus, the 2-phenylpropan-1,3-diol was carefully dissolved by the dropwise addition of concentrated H_2SO_4 and the reaction mixture cooled using an ice bath. At that particular time, problems of insolubility were encountered. However, a solution of concentrated H_2SO_4/HNO_3 (1:1) was carefully added and the reaction stirred for a further 10 mins at room temperature. After the addition of concentrated H_2SO_4/HNO_3, the reaction mixture turned orange-yellow. Analysis of the crude reaction by TLC and ^1H NMR showed that the process was not clean leading to a complex mixture. Consequently, the reaction was repeated with the diol first solubilised in $CHCl_3$ before treatment with the concentrated acids but again, the nitration led to a complex mixture and this time, problems of extraction arose due to the polarity of the diol material.

To overcome the extraction problems, it was decided to form the diacetate before nitration. Thus, the diol in solution in DCM was successively treated with Et_3N, DMAP and acetic anhydride. After completion, the reaction mixture was quenched by careful addition of aqueous HCl.

Subsequent purification by flash chromatography led to the 2-phenylpropane-1,3-diol diacetate **(23)** in 80% yield as a colorless oil (Scheme 3.11).[14]

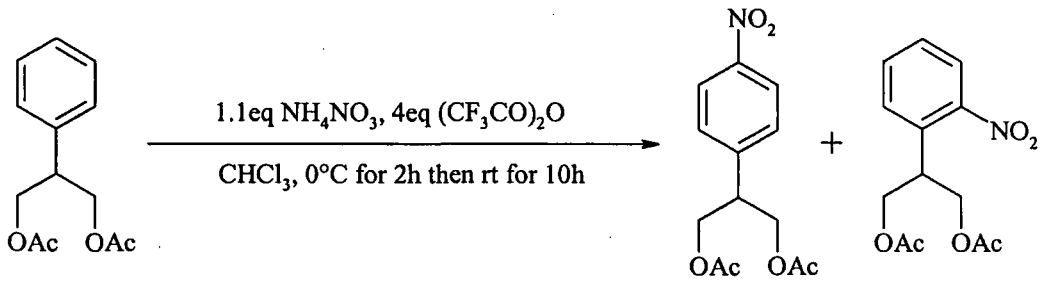


(23), 80%

Scheme 3.11

Evidence for the formation of the diacetate was found in IR, ^{1}H and ^{13}C NMR spectra. The study and comparison of the IR spectra of the starting material and the product showed the appearance of the carbonyl band at ~1734 cm^{-1} and the disappearance of the broad IR band characteristic of alcohols. The ^{1}H and ^{13}C NMR spectra confirmed the presence of the acetate with the singlet at 1.95 ppm, integrating for 6H and the carbonyl signal at 171.1 ppm.

Unfortunately, the nitration of 1,3-diacetoxy-2-phenylpropane **(23)** in solution in $CHCl_3$ led also to a complex mixture and therefore, another nitration process was explored.
In 2000, Hu and Mattern[15] successfully nitrated 1,3-diacetoxy-2-phenylpropane using ammonium nitrate and trifluoroacetic anhydride. This literature procedure was followed (Scheme 3.12) and the nitration proceeded to give a mixture of *para*-substituted and *ortho*-substituted products in a (4:1) ratio. Purification by flash chromatography gave the *para*-substituted desired product **(24)** in 65% yield as a pale yellow solid.



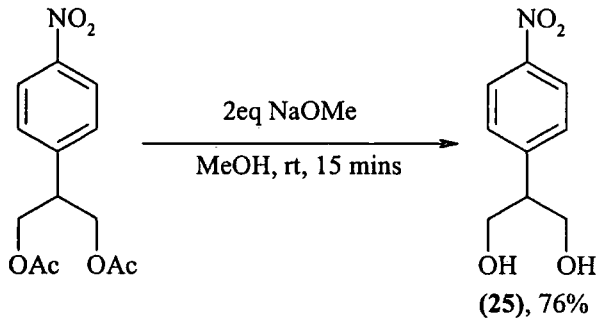
(24), 65%

4 : 1

Scheme 3.12

Evidence for the formation of the nitrated product **(24)** was found in the ^{1}H NMR spectrum with the two doublet signals for the aromatic protons at 7.43 ppm and 8.20 ppm with a coupling constant of 8.9Hz, characteristic of a *para*-substituted aromatic ring. The IR spectrum confirmed the presence of the nitro group with bands at 1525 cm^{-1} and 1345 cm^{-1}.

Finally, the acetate groups were removed using NaOMe in MeOH for 15 mins giving the diol **(25)** in 76% yield as a white solid after recrystallisation from cyclohexane (Scheme 3.13). An alternative attempt using NaOH in refluxing EtOH/H_2O (1:1) for 1 day gave the diol in poor yield.



Scheme 3.13

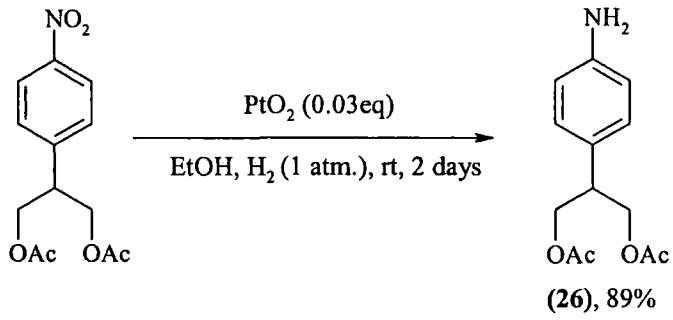
Evidence for the formation of the diol was found with the appearance of a broad band at ~3500-3000 cm^{-1} characteristic of alcohols and the disappearance of the carbonyls signal at ~1734 cm^{-1}. A correct elemental analysis was also obtained for the diol.

3.2.2.4-Reduction of the aromatic nitro group :

An initial attempt to reduce the nitro group of **(24)** using Zn metal dissolved in concentrated HCl led to a 100% conversion of the nitro group into the amine as shown by the ^{1}H NMR spectrum with the aromatic signals shifted from 7.43 and 8.20 ppm to 6.68 and 6.98 ppm. However, these conditions also caused the reduction of the diester into the free diol, which complicated the isolation of the product.

Following a literature procedure,[16] the reduction of the nitro group was successfully achieved using PtO_2 (0.3eq) catalysis under 1atm pressure of H_2, and the amino product **(26)** was isolated in 95% yield. However, it is worth noting that the use of 0.03 equivalents of PtO_2 also led to the complete reduction of the nitro group, after 2 days, in

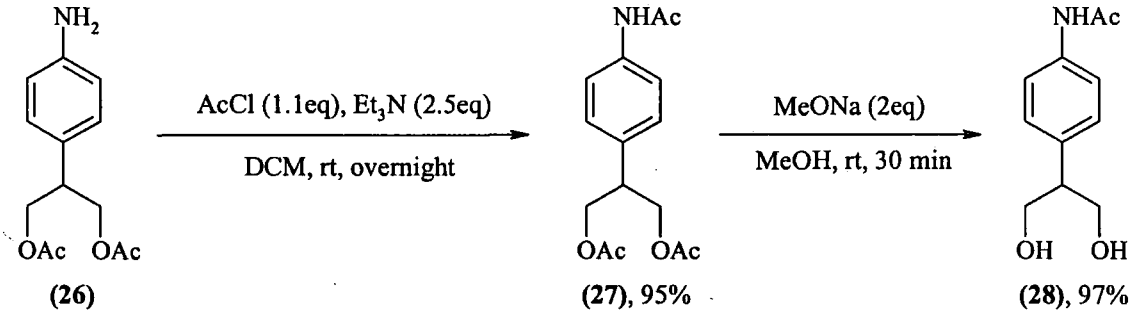
89% yield. Considering the price of PtO_2, this could be considered as more advantageous (Scheme 3.14).



Scheme 3.14

Evidence for the reduction of the nitro group was found in the IR spectrum with the disappearance of the nitro bands at 1525 and 1345 cm^{-1}, and in the ^1H NMR spectrum with the shift of the aromatic protons to 7.01 and 6.63 ppm together with the presence of a broad singlet at 3.64 ppm for the amine group.

An initial attempt to remove the diacetate groups using the conditions described above (Scheme 3.13) was successful, as judged by TLC and GC/MS, but the diol was difficult to isolate due to the presence of an additional polar amine group. Therefore, the amino group was first converted to acetamido before removing the diacetates (Scheme 3.15).



Scheme 3.15

Evidence for the formation of the intermediate **(27)** was found in the IR spectrum with the appearance of the amide band at 1686 cm^{-1}. This was confirmed with the presence of the carbonyl of the amide at 168.2 ppm in the ^{13}C NMR spectrum. Subsequent successful removal of the diacetates was confirmed by the disappearance of the carbonyl signal of the acetates at 170.8 ppm in the ^{13}C NMR spectrum.

After having successfully prepared a new set of diols, the next step of the study was to synthesise the corresponding bicyclic ketones and investigate whether the introduction of an electron-donating or electron-withdrawing group at C-4 would affect the C-H insertion process.

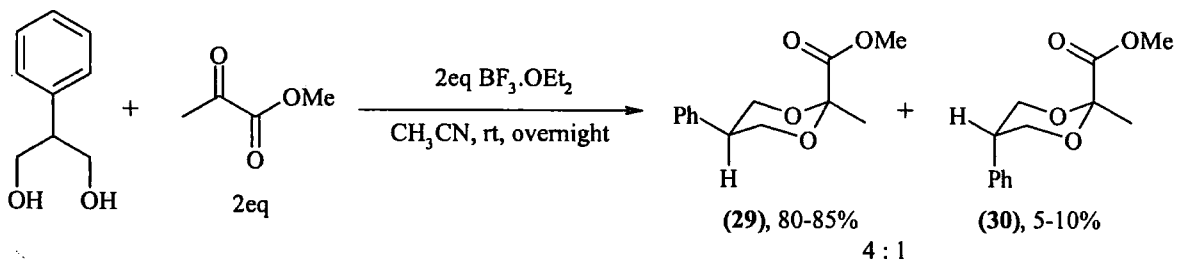
The following sections will successively present the catalyst screening experiments for the optimisation of the ester acetal preparation, the attempts to find an alternative method for the formation of the diazoketones, and a full study of the C-H insertion process by variation of several parameters.

3.3-Ester and acid acetals formation :

The Wardrop strategy for the synthesis of acid acetals, which requires the prior formation of the pyruvate ester acetals, was adopted.

3.3.1-Ester acetal formation :

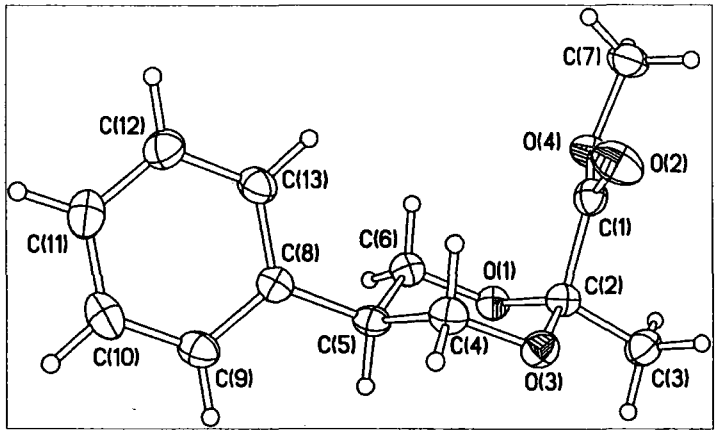
Thus, 2-phenylpropane-1,3-diol in solution in acetonitrile was treated with $BF_3.OEt_2$ and methyl pyruvate following the literature procedure (Scheme 3.16).[17]



Scheme 3.16

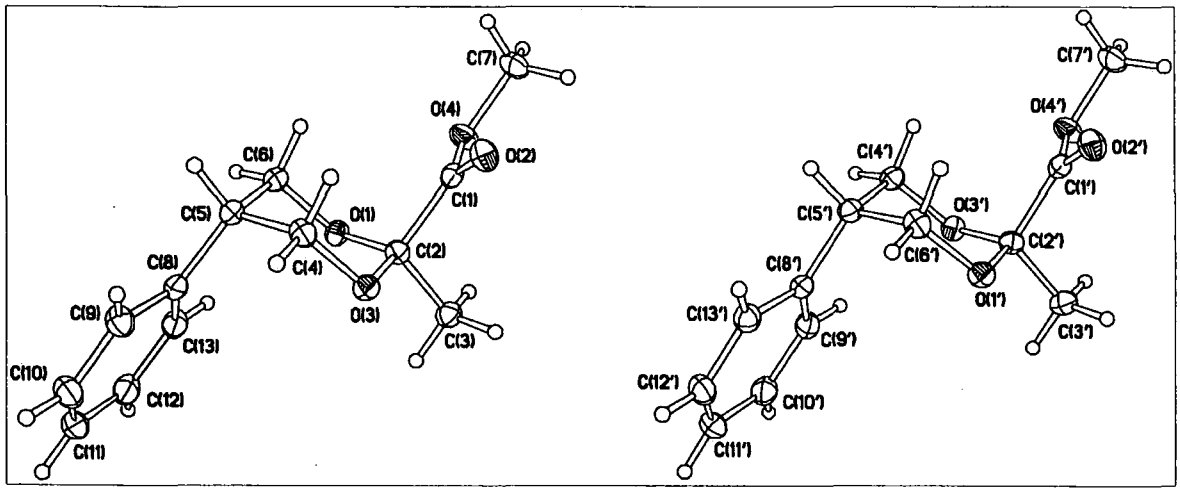
An isomeric mixture of two ester acetals in a 4:1 ratio **(29,30)**, easily separated by flash chromatography, was obtained. Key evidence for the formation of two ester acetals was found in the ^{13}C NMR spectrum where two quaternary C-2 signals were observed for the major and minor isomer at 98.1 and 97.6 ppm respectively together with two ester carbonyl signals observed at 171.0 and 170.3 ppm. In addition, the ^{1}H NMR spectrum showed two methoxy signals at 3.95 and 3.80 ppm. The major isomer **(29)** was recrystallized from cyclohexane and the X-ray crystallography showed that the phenyl

group adopted the equatorial position while the C-2 carboxylate group adopted the axial position (Scheme 3.17, Appendix A), as expected under thermodynamically controlled conditions.[18]



Scheme 3.17

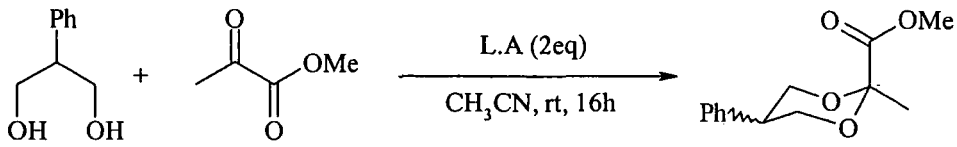
Similarly, the crystal structure of the minor ester acetal **(30)** was obtained after recrystallisation from cyclohexane (Scheme 3.18, Appendix A).



Scheme 3.18

As expected, the compound **(30)** possessed both the phenyl and the C-2 carboxylate groups in axial position.

Because an isomeric mixture of pyruvate ester acetals was obtained, attempts were made to form the major isomer **(29)** exclusively and therefore, several Lewis acids were screened. The results obtained are summarised below (Scheme 3.19, Table 3.2).



(2eq) **(29,30)**

Entry	Lewis Acid	Ratio **(29:30)**	Yield[a] + comments
1	Me_3SiOTf	4 : 1	76% no SM back
2	$SnCl_4$	9 : 1	43% + 34% SM
3	$TiCl_4$	major isomer	27% + 16% SM
4	Et_2AlCl	/	72% SM + decomposition
5	$AlCl_3$	/	27% SM + decomposition
6	$Ti(OiPr)_4$	/	Total decomposition

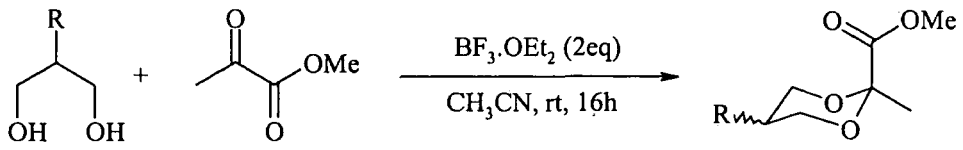
a) GC yields.

Scheme 3.19, Table 3.2

Unfortunately, none of the Lewis acids screened gave satisfactory results. Although $SnCl_4$ gave a 9:1 ratio, the yield was poor and 34% of starting material was recovered (entry 2). $TiCl_4$ led to the exclusive formation of the major isomer but in low yield (27%), and mostly decomposition occured (entry 3).

Therefore, $BF_3.OEt_2$ was kept as the Lewis acid of choice for the formation of the ester acetals.

The corresponding ester acetals of the four diols were then prepared. Preparation of **(35)** was completed with the collaboration of the PhD student taking over this project and his results will be included. The ratios, yields and evidences for the formation of the pyruvate ester acetals are summarised below (Scheme 3.19, Table 3.3).



(2eq) (29-35)

Entry	Subtituent R	Ratio	Yield (%)	^{13}C and ^{1}H NMR (in ppm)
1	Ph **(29,30)**	4 : 1	80-90	**(29)** : 171.0 (CO), 98.1 (C-2) 3.95 (OMe) **(30)** : 170.3 (CO), 97.6 (C-2) 3.80 (OMe)
2	Bn **(31,32)**	7 : 3	80-85	**(31)** : 171.3 (CO), 98.4 (C-2) 3.83 (OMe) **(32)** : 171.3 (CO), 98.7 (C-2) 3.81 (OMe)
3	*p*-NO_2Ph **(33,34)**	7 : 3	86	**(33)** : 170.5 (CO), 98.1 (C-2) 3.85 (OMe) **(34)** : 170.6 (CO), 98.3 (C-2) 3.85 (OMe)
4[a]	*p*-AcNHPh **(35)**	7 : 3	45	**(35)** : 171.5 5 (CO), 99.1 (C-2) 3.88 (OMe)

a) as mentioned, series realised in parallel to this work by John Mina (1st year PhD student). Alternatively, formation of **(35)** by reduction of **(33)** using PtO_2 (**36**,89%) and followed by acetalisation using Et_3N and acetyl chloride (**35**,88%) (see experimental section).

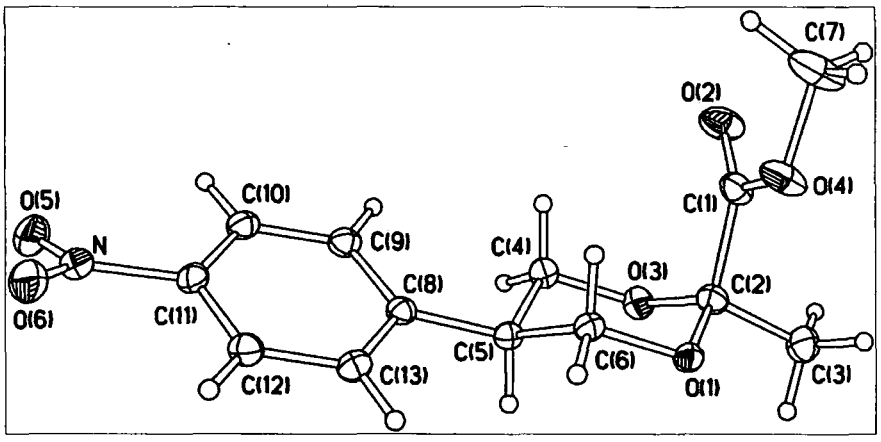
Scheme 3.20, Table 3.3

In all cases, an isomeric mixture was obtained and the variation of the nature of the R group at C-4 had little effect on the ratio of isomers formed. Apart from the phenyl series, the ester acetals were not separable. In all the cases studied, the major isomer formed was believed to be the one with the C-2 carboxylate group in the axial position and the R group in the preferential equatorial position. As for the minor isomer, the R group was believed to adopt the axial position. This was confirmed by the observation of similar signals and coupling constants for the protons 4,6-H_{ax} and 4,6-H_{eq} of each compound. The table below summarises these results (Table 3.4).

Entry	Substituent R	^{1}H NMR major isomer	^{1}H NMR minor isomer
1	Ph	4.10 (dd,J=11.7,4.8Hz,4,6-H_{eq}) 3.95 (t, J=11.7Hz, 4,6-H_{ax})	4.25(dd,J=12.1,3.3Hz,4,6-H_{eq}) 4.10 (dd,J=12.1,2.0Hz,4,6-H_{ax})
2	Bn	3.80(dd,J=11.5,4.4Hz, 4,6-H_{eq}) 3.50 (t, J=11.5Hz, 4,6-Hax)	3.90 (m, 4,6-Heq) 3.78 (d, J=11.0Hz, 4,6-Hax)
3	*p*-NO_2Ph	4.10(dd,J=11.2,4.6Hz, 4,6-H_{eq}) 3.90 (t, J=11.2Hz, 4,6-H_{ax})	4.28(dd,J=12.4,3.5Hz, 4,6-H_{eq}) 4.07 (m, 4,6-H_{ax})
4	*p*-AcNHPh	4.02(dd,J=12.0,4.5Hz, 4,6-H_{eq}) 3.82 (t, J=12.0Hz, 4,6-H_{ax})	N/A

Table 3.4

The *p*-nitrophenyl ester acetals were not fully separable; however, a small sample of the pure major isomer was obtained and recrystallisation from cyclohexane enabled the obtention of the crystal structure (Scheme 3.21, Appendix A).

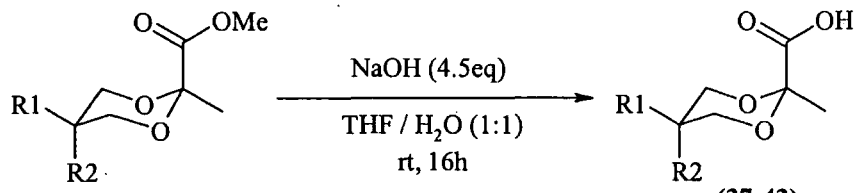


Scheme 3.21

Consistent with the phenyl series, the substituted phenyl ring preferentially adopted the equatorial position while the C-2 carboxylate group adopted the axial position.

3.3.2-Acid acetal formation :

The ester acetals **(29-35)** were then hydrolyzed to the corresponding acid acetals **(37-43)** by treatment with NaOH pellets. Evidence for the formation of the acid acetals are summarised in the following table (Scheme 3.22, Table 3.5).



(37-43)

Entry	Substituents	Yield (%)	^{1}H, ^{13}C NMR (δ in ppm)
1	R1=Ph, R2=H	80-95	**(37)**[a] : 8.2 (COOH); 175.0 (CO)
2	R1=H, R2=Ph	60-67	**(38)**[b] : 8.2 (COOH); 173.0 (CO)
3	R1=Bn, R2=H R1=H, R2=Bn	80	**(39)**[c] : 8.1 (COOH); 174.0 (CO) **(40)**[d] : 7.95 (COOH); 175.2 (CO)
4	R1=*p*-NO_2Ph, R2=H R1=H, R2=*p*-NO_2Ph	86	**(41)**[e] : 8.0 (COOH); 174.0 (CO) **(42)**[f] : 8.0 (COOH); 174.0 (CO)
5	R1=*p*-AcNHPh, R2=H	93	**(43)** : 7.38 (COOH); 173.6 (CO)

a) crystal structure (see appendix B) and elemental analysis; b) crystal structure (see appendix B) and HR/MS.
c) major isomer isolated by recrystallisation in 83% yield, elemental analysis; d) minor isomer not completely purified but as a mixture with the major isomer in a (3:1) ratio in favor of the minor isomer
e) major isomer isolated by recrystallisation in 50% yield, elemental analysis; f) minor isomer not completely purified but as a mixture with the major isomer in a (3:7) ratio in 36% yield

Scheme 3.22, Table 3.5

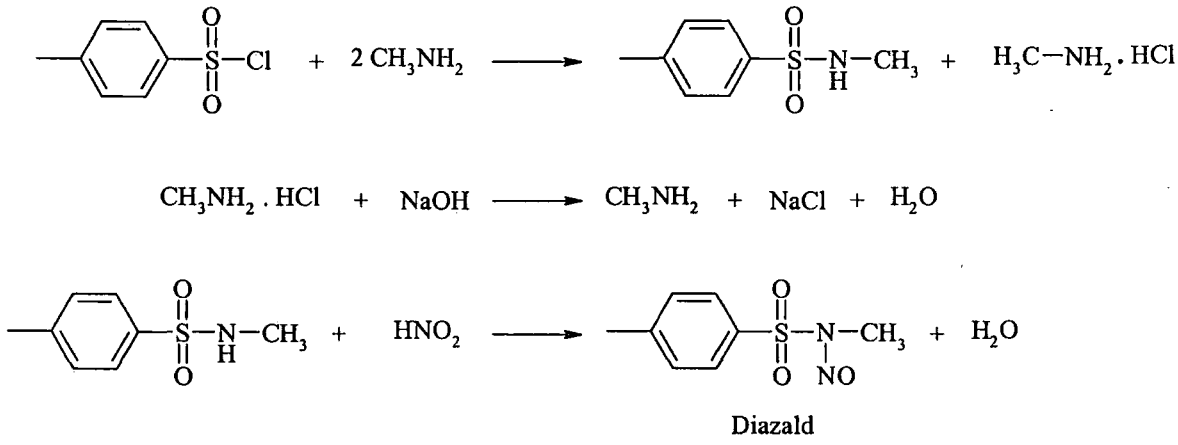
The acid acetals **(37-43)** were obtained in good yields. Pure samples of the major acid acetals were obtained by recrystallisation from cyclohexane (phenyl, benzyl and *p*-nitrophenyl series) but no minor isomers were obtained pure. Both the pure acid acetals and the mixtures were taken through the following step for the formation of the corresponding diazoketones.

3.4-Diazoketone formation :

As described in the preceding chapter, the diazoketones can be prepared by acylation of diazomethane[19] with mixed anhydrides formed *in situ* by treatment of the acid acetals

with chloroformates. The acylation strategy is limited in its use because diazomethane is explosive and should therefore be handled with care. And therefore, its use is generally limited in most industries for safety reasons. In addition, the sale of its precursor, Diazald® (N-methyl-N-nitroso-*p*-toluene sulfonamide), used in the earlier studies, had been stopped and its preparation became necessary.

Diazald was prepared from *p*-toluenesulfonyl chloride and methylamine following a DeBoer and Backer procedure (Scheme 3.23).[20]



Scheme 3.23

Its preparation necessitated a careful portionwise addition of the sulfonyl chloride to the methylamine with control of temperature and pH, followed by the addition of a solution of sodium nitrite in H_2O, which was time consuming; therefore, another alternative to synthesize diazoketones was explored, diazo-transfer.

3.4.1-Diazo-transfer reaction :

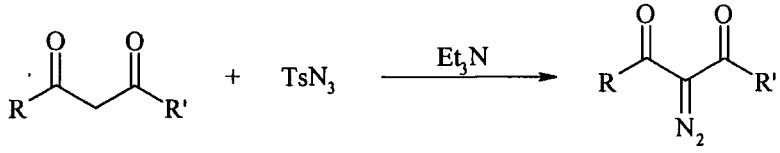
3.4.1.1-Introduction :

A widely used method for the formation of diazoketones is a diazo-transfer reaction. This involves the transfer of a diazo group from a diazo donor (usually a sulfonyl azide) to the α-methylene proton of an acceptor (usually an acid or a ketone).

As mentioned in the introduction chapter (section 1.3.2.2.2, p.12), there are two main classes of acceptors based on the acidity of the α-methylene proton.

- β-keto-esters, β-diketones, malonic esters :

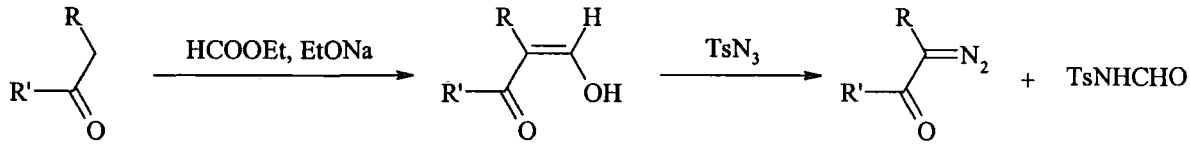
In these cases, the α-methylene position is reactive enough for the diazo-transfer and the substrates are readily converted into 2-diazo-1,3-dicarbonyl compounds by the standard Regitz procedure (Scheme 3.24).[21]



Scheme 3.24

- Simple ketone enolates :

In the case of simple ketone enolates, this process is not very efficient and gives poor yields.[22] However, diazo-transfer can be achieved by an "indirect" deformylative diazo-transfer (Scheme 3.25).[23]

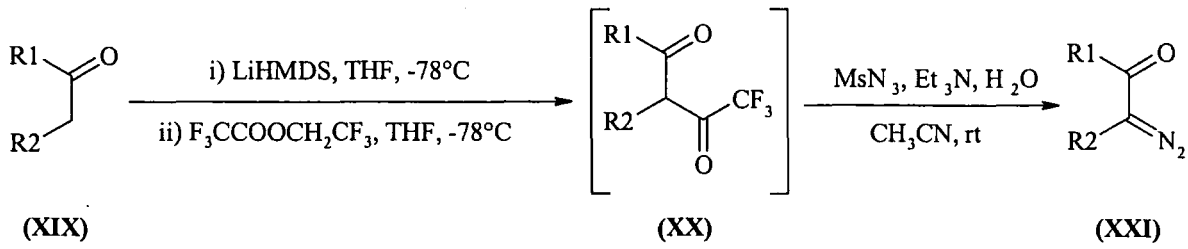


(XVI) **(XVII)** **(XVIII)**

Scheme 3.25

The ketone **(XVI)** is first formylated by a Claisen condensation leading to the intermediate **(XVII)**, which is then treated by an azide to give the diazoketone **(XVIII)**. However, this method can be problematic, and more specifically the Claisen condensation step can cause problems when applied to base-sensitive substrates such as α,β-enones.

In 1990, Danheiser[24] developed an "improved" diazo-transfer method for the synthesis of α-diazoketones, which can be applied to base-sensitive substrates (Scheme 3.26).



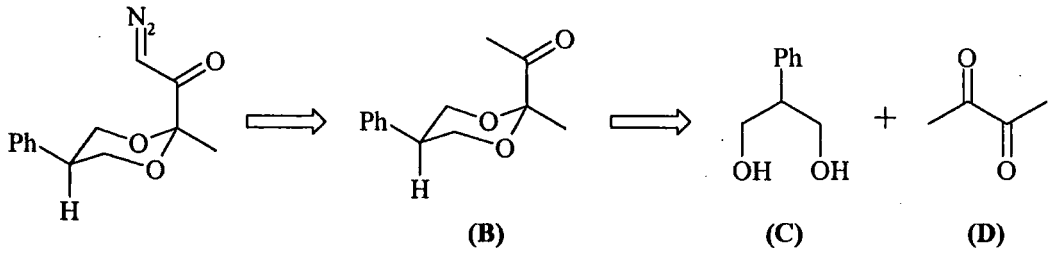
(XIX) (XX) (XXI)

Scheme 3.26

Reaction of a ketone substrate **(XIX)** with LiHMDS gave the corresponding lithium enolate, which was then acylated with trifluoroethyl trifluoroacetate. The resulting α-trifluoroacetyl ketone **(XX)** was finally treated with methanesulfonyl azide in the presence of Et_3N and H_2O to give the desired diazoketone **(XXI)**.

3.4.1.2-Application :

It was decided to evaluate this method, and therefore the preparation of the methyl ketone **(B)** was needed. The methyl ketone **(B)** can be formed by ketalisation of 2-phenylpropane-1,3-diol **(C)** with butane-2,3-dione **(D)** as shown in the following retrosynthetic scheme (Scheme 3.27).



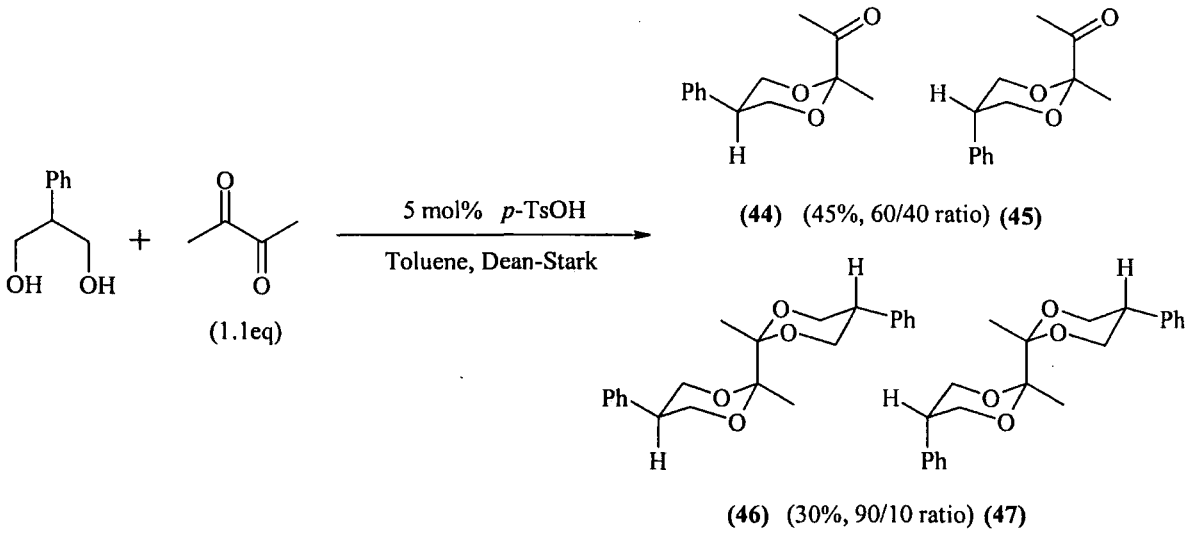
(B) **(C)** **(D)**

Scheme 3.27

Therefore conditions for the reaction of butane-2,3-dione **(D)** with 2-phenylpropane-1,3-diol **(C)** under acidic catalysis were examined.

In the presence of 5 mol% *p*-TsOH in refluxing toluene, the reaction led to a mixture of 4 different compounds as ascertained by GC. The GC/MS of the reaction mixture identified those compounds as being a mixture of the desired methyl ketone (45%, 2 isomers

(44,45) in a 3:2 ratio, m/z: 238, $[M+NH_4]^+$, 100%) and dimerization products (30%, 2 isomers **(46,47)** in a 9:1 ratio, m/z: 372 [M+NH_4]+, 10%) (Scheme 3.28).



Scheme 3.28

The formation of dimers could be explained by the reaction of the 2-phenylpropane-1,3-diol with the methyl ketones formed instead of the dione. That can be due to the loss of dione during the reaction, in the Dean-Stark trap, because of its low boiling point (b.p. : 88°C).

To avoid dimerization, further experiments were carried out varying different parameters (temperature, solvent, number of equivalents of dione, acid catalyst). The conditions and the results are summarised in the following table (Table 3.6).

Entry	Diol	Dione	Conditions	Comments
1[a,b]	1eq	1.1eq	5 mol% *p*-TsOH benzene reflux Dean-Stark	**(44,45)** : 45%, 60/40 ratio **(46,47)** : 30%, 90/10 ratio
2[c]	1eq	1.5eq	5 mol% *p*-TsOH benzene Δ~80°C Dean-Stark	**(44,45)** : 78%, 55/45 ratio **(46,47)** : 20%, 65/35 ratio
3[c]	1eq	1.5eq	5 mol% *p*-TsOH benzene reflux Soxhlet + molecular sieves	SM : 41% Unknown by-product : 33% **(44,45)** : 18%, 80/20 ratio **(46,47)** : 8%, 60/40 ratio
4[c]	1eq	1.5eq	5 mol% *p*-TsOH CH_2Cl_2 reflux Soxhlet + molecular sieves	SM : 16% Unknown by-product : 17% **(44,45)** : 55%, 60/40 **(46,47)** : 12%, 90/10
5[c]	1eq	1.5eq	Dowex 50WX-8 CH_2Cl_2 reflux	No reaction
6[c]	1.5eq	1eq	Amberlyst 15 (2.3g/g diol) CH_2Cl_2, rt	SM : 80% **(44,45)** : 7%, 50/50 No dimerization
7[c]	1.5eq	1eq	Amberlyst 15 (2.3g/g diol) 1.2eq $HC(OCH_3)_3$ CH_2Cl_2, rt	SM : 10% **(44,45)** : 75%, 55/45 **(46,47)** : 15%, 90/10
8[a]	1eq	1.5eq	Amberlyst 15 (2.3g/g diol) 1.2eq $HC(OCH_3)_3$ CH_2Cl_2, rt	**(44,45)** : 94%, 55/45 ratio No dimerisation

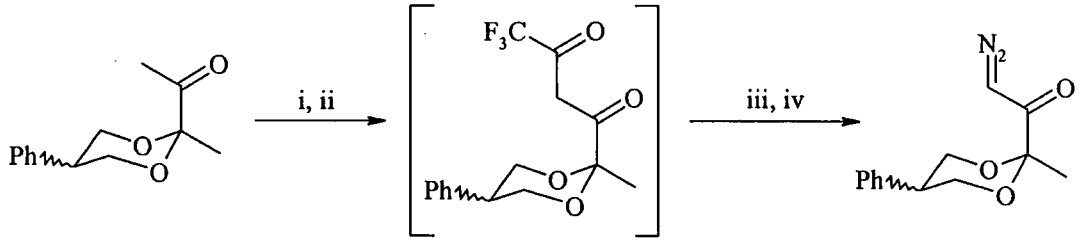
a) isolated yields.
b) methyl ketones separated from dimers by flash chromatography but isomers not separable.
c) GC yields, reaction followed by GC, no work-up, not purified.

Table 3.6

The first attempts used *p*-TsOH as catalyst, but with variation of the initial conditions. Lowering the temperature of the reaction led to the formation of methyl ketones in a better yield, but dimerization was still observed (entry 2). To avoid the loss of dione in the Dean-Stark trap, a soxhlet apparatus was used, together with the addition of molecular sieves to capture H_2O formed during the reaction and to force the equilibrium towards acetal formation (entry 3). The reaction did not go to completion (41% starting material recovered) and the formation of an unidentified by-product was observed. An increase in the yield of the methyl ketones was observed by changing the solvent (entry 4); however, dimerization was still observed. Finally, it was decided to use sulfonated cross-linked polystyrene resins as heterogeneous acid catalysts, which appeared to be an attractive

method since the beads can be filtered off and recycled. With the more flexible and less cross-linked Dowex 50WX-8, no reaction was observed (entry 5) and only 7% of methyl ketones were formed using Amberlyst 15 (entry 6).[25] The addition of methyl orthoformate as a drying agent forced the equilibrium towards the formation of acetals, but the excess of diol used led again to the formation of dimers (entry 7). Consequently, treatment of the diol with an excess of dione in presence of Amberlyst 15 and methyl orthoformate was performed and led to the exclusive formation of methyl ketones in good yield (94%, 55/45 ratio, entry 8).

The isomeric mixture was then submitted to the Danheiser diazo-transfer method (Scheme 3.29).



(44,45) **(48)** **(49,50)**

i) LiHMDS, THF, -78°C, 30 mins, ii) $F_3CCH_2OCOCF_3$, -78°C, 10 mins

iii) Et_3N, H_2O, CH_3CN, rt, iv) MsN_3, rt, 3h

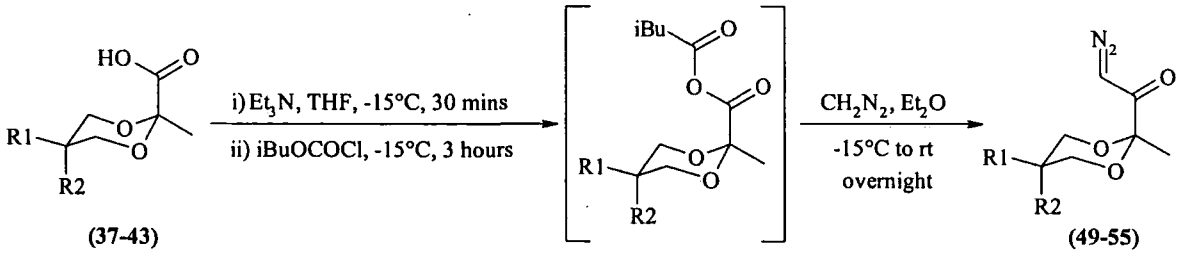
Scheme 3.29

The methyl ketones **(44,45)** were treated with 1.1 eq of LiHMDS producing the corresponding lithium enolate, which was then acylated using 1.2 eq of trifluoroethyl trifluoroacetate (TFEA). After work-up but no purification, the resulting α-trifluoroacetyl ketone **(48)** was treated, in presence of 1 eq of Et_3N and 1 eq of H_2O, with 1.5 eq of methanesulfonyl azide (prepared by reaction of methane sulfonyl chloride with sodium azide).[26] The diazoketones **(49,50)** were obtained in poor yield (<10%) in a 55/45 ratio and 25% of starting material was recovered. Evidence for their formation was found in the IR and ^1H NMR spectra with the appearance of bands at 2105 and 2107 cm^{-1} and singlets at 5.80 and 5.75 ppm corresponding to the CHN_2 group. The use of 1.5 eq of each LiHMDS and trifluoroacetic anhydride, $(CF_3CO)_2O$, led to an enhanced yield of 40%.

Due to time constraints, the conditions were not further optimised. This approach was abandoned and the usual method, using diazomethane, was applied to the synthesis of the diazoketones.

3.4.2-Acylation of diazomethane :[19]

Thus, the acid acetals **(37-43)** in solution in THF were each reacted with isobutyl chloroformate (1.2 eq) in the presence of Et_3N (1.5 eq). Complete consumption of the acids was ensured by monitoring the reactions by TLC. Treatment of the resulting mixed anhydrides with an ethereal solution of diazomethane provided the corresponding α-diazoketones **(49-55)** in good yields. Evidence for the formation of the diazoketones and yields obtained are summarised in the following table (Scheme 3.30, Table 3.7).



Entry	Substituents	Yield (%)	Evidence for the formation IR, ^{1}H NMR (N_2=C<u>H</u>-)
1	R1=Ph, R2=H	80	**(49)** : 2107 cm^{-1}, δ=5.80 ppm
2	R1=H, R2=Ph	82	**(50)** : 2105 cm^{-1}, δ=5.75 ppm
3	R1=Bn, R2=H	80-85	**(51)** : 2107 cm^{-1}, δ=5.70 ppm
4	R1=H, R2=Bn	80	**(52)**[a,b] : 2110 cm^{-1} δ=5.70 ppm
5	R1=*p*-NO_2Ph, R2=H	70-75	**(53)** : 2114 cm^{-1}, δ=5.71 ppm
6	R1=H, R2= *p*-NO_2Ph	70	**(54)**[c,d] : 2114 cm^{-1}, δ=5.81 ppm
7	R1=p-AcNHPh, R2=H	79	**(55)** : 2116 cm^{-1}, δ=5.77 ppm

a) from mixture of acid acetals **(39,40)** in (1:3). b) not separated from the major isomer.
c) from mixture of acid acetals **(41,42)** in a (3:7) ratio. d) separated from the major isomer.

Scheme 3.30, Table 3.7

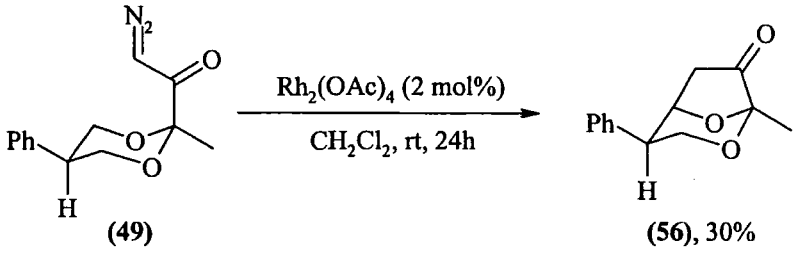
With a protocol for the preparation of the diazoketones then established and with a series of diazoketones in hand, attention turned to the study of the C-H insertion step.

3.5-Rhodium-mediated C-H insertion process :

3.5.1-Initial conditions :

As seen in the previous chapter, $Rh_2(OAc)_4$ treatment of the diazoketones did lead to the bicyclic acetal core but in low yield, which was mostly due to the volatility of the C-H insertion products. The new diazoketones **(49-55)** possess a chromophore (phenyl, substituted phenyl or benzyl ring), which had already made the earlier reactions easier to follow, but would also, hopefully, make the C-H insertion products less volatile.

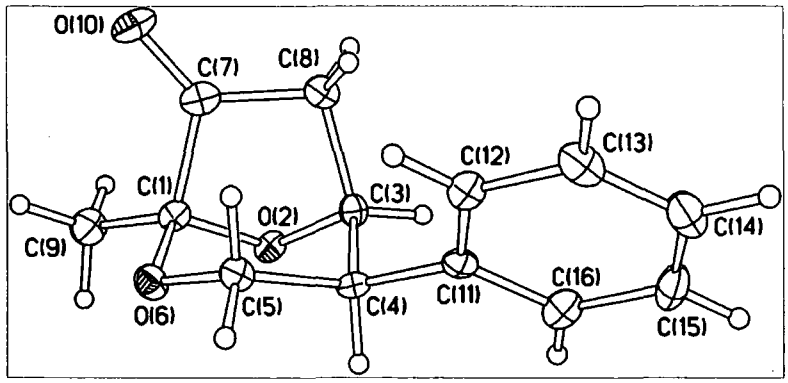
Following the conditions described in chapter 2 (section 2.3.1, p.78), the diazoketone **(49)** in solution in CH_2Cl_2 was added at room temperature to a solution of $Rh_2(OAc)_4$ (2 mol%) in CH_2Cl_2 over 24 hours to avoid dimerization. After purification by flash chromatography, the C-H insertion product **(56)** was obtained in 30% yield (Scheme 3.31).



(49) **(56)**, 30%

Scheme 3.31

Evidence for the formation of the C-H insertion product **(56)** was found in the ^{13}C NMR spectrum where a tertiary C-5 signal was observed at 76.1 ppm and a carbonyl signal at 210.7 ppm. Confirmation was obtained with the observation of the carbonyl signal at 1763 cm^{-1} and the disappearance of the diazoketone signals at 2107 cm^{-1} (CHN_2) and at 1654 cm^{-1} (C=O), by IR spectroscopy. Recrystallisation of the C-H insertion product from cyclohexane enabled the isolation of a white crystalline solid, which was suitable for the determination of its crystal structure (Scheme 3.32, Appendix C).



Scheme 3.32

The insertion process was stereospecific and occured at the C-H bond α to the heteroatom. It is worth noting that the C-H insertion could occur into C-H(3ax) or into C-H(5ax) bond. Both C-H bonds are equivalent and therefore, a racemic mixture of C-H insertion products was obtained.

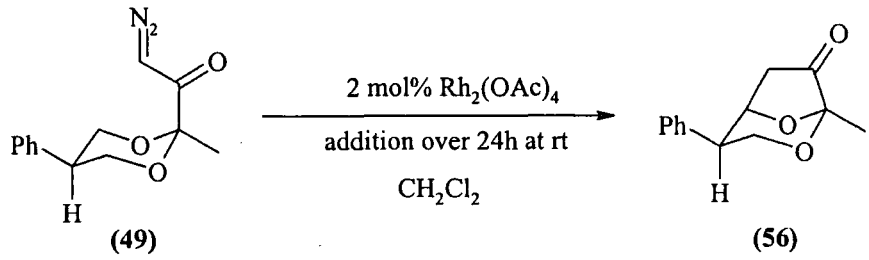
In view of the poor yield obtained, it was decided to try to optimise the C-H insertion process, the limiting step in the strategy, by screening the parameters of the reaction (concentration of diazoketone, concentration of catalyst, catalyst loading, catalyst, temperature and rate of addition).

3.5.2-Optimisation studies :

3.5.2.1-Concentrations of diazoketone and catalyst :

The diazoketone in solution in CH_2Cl_2 was added dropwise *via* a syringe pump to a solution of $Rh_2(OAc)_4$ in CH_2Cl_2. The effect of the concentration of each reactant on the yield was determined.

Consequently, several experiments were carried out varying the concentration of diazoketone and the concentration of catalyst. The results of this study are summarised below (Scheme 3.33, Table 3.8).



(49) (56)

Entry	Scale (mmol)	[diazo] (mmol/L)	[cat.] (mmol/L)	Total Volume (mL)	Yield[a] (%)
1	2.5	100	0.5	125	28
2	2.5	50	0.5	150	24
3	2.5	50	1.0	100	32
4	2.5	100	1.0	75	40-42

a) isolated yields

Scheme 3.33, Table 3.8

The best yield was obtained when a more concentrated solution of diazoketone was added to a more concentrated solution of $Rh_2(OAc)_4$ (entry 4). However, the yield remained moderate.

3.5.2.2-Rate of addition :

The rate of addition was the next parameter studied. A 100 mmol/L solution of diazoketone **(48)** in CH_2Cl_2 was added to a 1 mmol/L solution of $Rh_2(OAc)_4$ in CH_2Cl_2 at different rates. The results are summarised in the following table (Table 3.9).

Entry	Scale (mmol)	Time of addition (h)	Yield[a] (%)
1	2.5	12	30
2	2.5	24	40-42
3	2.5	48	34

a) isolated yields

Table 3.9

The addition of the diazoketone over 12 hours gave, after flash chromatography, the insertion product in 30% yield together with the recovery of 30% of starting material. A

complex mixture, difficult to purify, was obtained when the diazoketone was added over 48 hours.

3.5.2.3-Temperature :

Another parameter studied was the temperature of the reaction. A 100 mmol/L solution of diazoketone **(49)** in CH_2Cl_2 was added to a 1 mmol/L solution of $Rh_2(OAc)_4$ in CH_2Cl_2 over 24 hours using a syringe pump but at different temperatures. The results are summarised in Table 3.10).

Entry	Scale (mmol)	Temperature (°C)	Yield[a] (%)
1	2.5	0	SM
2	2.5	25	40-42
3	2.5	50	22

a) isolated yields

Table 3.10

At 0°C, no reaction was observed and the starting material was recovered (entry 1). At 50°C, the reaction was less clean and difficult to purify (entry 3).

3.5.2.4-Catalyst loading :

The catalyst loading was finally examined using the optimised conditions for the other parameters. Thus, a 100 mmol/L solution of diazoketone **(49)** in CH_2Cl_2 was added at room temperature, over 24 hours *via* a syringe pump, to a 1 mmol/L solution of $Rh_2(OAc)_4$ in CH_2Cl_2. The results of this study are summarised in Table 3.11.

Entry	Scale (mmol)	% of $Rh_2(OAc)_4$	Yield[a] (%)
1	2.5	1 mol%	31
2	2.5	2 mol%	40-42
3	2.5	5 mol%	44
4	2.5	7 mol%	46

a) isolated yield

Table 3.11

With only 1 mol% of catalyst used, the reaction did not go to completion and 51% of starting material was recovered (entry 1). An increase in the catalyst loading to 5 and 7 mol% led to a small enhancement in the yield over the 2 mol% catalyst. Considering the price of $Rh_2(OAc)_4$ (£150.80/1g, Aldrich), this increase was not worthwhile.

A possible explanation for the moderate yield could be the loss of the catalyst efficiency during the reaction by being in solution in CH_2Cl_2 for so many hours. Hence, to complete the study, it was decided to gradually add some "fresh" catalyst. Half the diazoketone was initially added to a 1 mol% $Rh_2(OAc)_4$ solution in CH_2Cl_2 and after 12 hours an extra 1 mol% solution of Rh_2OAc_4 in CH_2Cl_2 was added. The remaining diazoketone was added over 12 hours. After purification, the C-H insertion product was isolated in 30% yield with some starting material recovered.

A final attempt involved the gradual addition of a 5 mol% solution of catalyst in CH_2Cl_2 *via* a second syringe pump over 24 hours at the same rate of addition as the diazoketone. This caused problems since the catalyst is not readily soluble in CH_2Cl_2, but was in suspension.

The addition of a 100 mmol/L solution of diazoketone in CH_2Cl_2, over 24 hours at room temperature to a 1 mmol/L solution of $Rh_2(OAc)_4$ in CH_2Cl_2 was therefore the optimum conditions. It is worth noting that the GC/MS analysis of the crude reaction mixture showed that the reaction was clean with no by-product formed and only a small amount of unreacted diazoketone recovered. Therefore, the moderate yield obtained after purification can possibly be explained by some decomposition of the C-H insertion product on silica gel.

3.5.2.5-Catalyst :

Nevertheless, it was decided to screen several catalysts varying both ligands and metals in order to complete the study.

Independent extensive studies by Teyssie, Wenkert, Doyle[27] and Padwa[28] showed that Rhodium catalysts were effective catalysts for intramolecular C-H insertion processes and that the different electron-withdrawing abilities of the ligands could have a significant influence (cf section 1.3.3 of introduction chapter).

In general, strong electron-withdrawing ligands on the rhodium showed a high reactivity towards diazo-decomposition, but the carbenoids generated were highly reactive. Strong

electron-donating ligands, on the other hand, showed lower reactivity towards diazo-decomposition but higher selectivity. Considering those factors, both rhodium catalysts with electron-withdrawing and electron-donating ligands were screened. Copper and palladium catalysts had been reported to be mostly effective for cyclopropanation. However, other metal carbene transformations using palladium catalysts have not been thoroughly examined. Thus, copper and palladium catalysts with electron-withdrawing and electron-donating ligands were also investigated in this study.

The catalysts screened and the results of the reactions are summarised in Table 3.12.

Entry	Catalyst	Observations[a]
1	$Rh_2(tfa)_4$	Not clean, many by-products but no insertion product
2	$Rh_2(hfb)_4$	Not clean, many by-products but no insertion product
3	$Rh_2(hexanoate)_4$	No SM, no decomposition (clean reaction) **(56)**, 45% yield
4	$Cu(OAc)_2$	SM + decomposition but no insertion product
5	$Cu(acac)_2$	SM
6	$Cu(tfacac)_2$	SM + decomposition
7	$Cu(hfacac)_2$	SM + decomposition
8	$Pd(OAc)_2$	SM + decomposition and no insertion product
9	$Pd(acac)_2$	SM

a) GC yields and use of methyl stereate as standard; reactions not purified

Table 3.12

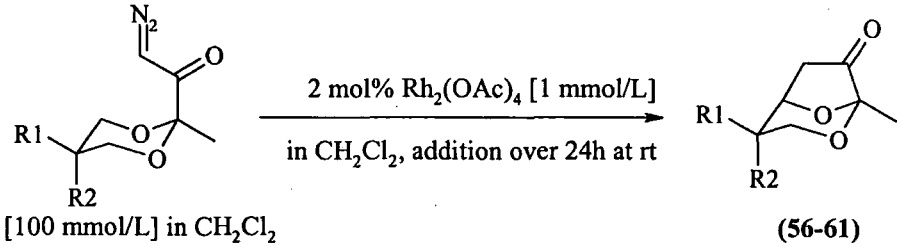
Rhodium catalysts possessing electron-withdrawing groups, $Rh_2(tfa)_4$ and $Rh_2(hfb)_4$, led to very complex mixtures which did not contain the C-H insertion product (entries 1,2). These catalysts are highly electrophilic and acidic which may cause dimerization or decomposition of the by-products formed. Unfortunately, because this extensive study on the C-H insertion step was time consuming, the reactions were not purified and thus the by-products were neither isolated nor characterised. The formation of by-products could be explained by the strong electron-withdrawing ability of the ligands. Indeed, although the diazo decomposition is supposed to be faster, the reaction is less chemoselective because the carbenoids generated are less stable and thus, more reactive.[29] Ylide formation followed by a subsequent rearrangement could have happened. Taber[30] reported that strongly electron-withdrawing ligands favoured β-hydride elimination while

the intramolecular C-H insertion process was favoured by electron donating ligands. Thus, as expected, Rh(II) hexanoate gave a clean reaction with only the C-H insertion product formed in a yield comparable to the reaction with $Rh_2(OAc)_4$ (entry 3).
No reaction was observed with palladium and copper catalysts with electron-donating ligands ($Pd(acac)_2$ and $Cu(acac)_2$, entries 5,9), while catalysts with electron-withdrawing ligands led to a high decomposition (entries 4,6-8). Copper and palladium catalysts have been reported to be efficient for cyclopropanation but to present limitated reactivity towards C-H insertion. Indeed, in competitive pathways they showed preference for cyclopropanation and ylide formation over C-H insertion.

After this extensive study, the initial catalyst used, $Rh_2(OAc)_4$ appeared to be the most effective catalyst for the C-H insertion of the diazoketone **(49)**. The C-H insertion product **(56)** was obtained in moderate but reproducible yield. Optimum conditions for the reaction were determined. Thus, a 100 mmol/L solution of diazoketone in CH_2Cl_2 should be added, *via* a syringe pump, over 24 hours at room temperature to a 1 mmol/L solution of $Rh_2(OAc)_4$ in CH_2Cl_2

3.5.3-Application of the optimum conditions to the diazoketones (50,51,53-55) :

The diazoketones **(50,51,53-55)** were submitted to diazo-decomposition by $Rh_2(OAc)_4$ treatment using the optimum conditions. The yields obtained and evidence for the formation of the C-H insertion products are summarized in the following table (Scheme 3.34, Table 3.13).



[100 mmol/L] in CH_2Cl_2 **(56-61)**

Scheme 3.34

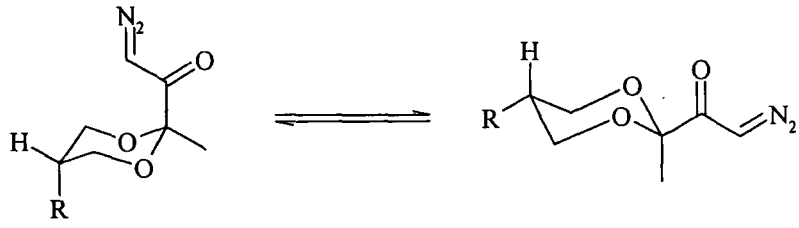
Entry	Diazoketone substituents	Yield (%)	Evidence	
			^{1}H NMR (5-H)	^{13}C NMR and IR (C=O)
1	**(49)** : R1=Ph, R2=H	**(56)** : 45	4.83 ppm	210.7 ppm, 1763 cm^{-1}
2	**(50)** : R1=H, R2=Ph	**(57)**[a] : N/A	4.77 ppm	211.0 ppm, 1769 cm^{-1}
3	**(51)** : R1=Bn, R2=H	**(58)** : 50	4.55 ppm	211.0 ppm, 1752 cm^{-1}
4	**(53)** : R1=*p*-NO_2Ph, R2=H	**(59)** : 20	4.98 ppm	210.0 ppm, 1771 cm^{-1}
5	**(54)** : R1=H, R2=*p*-NO_2Ph	**(60)**[b]: 10	4.69 ppm	210.1 ppm, 1769 cm^{-1}
6	**(55)** : R1=*p*-AcNHPh, R2=H	**(61)** : 30	4.86 ppm	210.8 ppm, 1764 cm^{-1}

a) complex mixture, C-H insertion product as an inseparable mixture with an unknown by-product + 20% SM recovered.
b) complex mixture, C-H insertion isolated in 10% yield + isolation of a by-product (8%) + 7% SM recovered.

Table 3.13

For the phenyl and benzyl series, the diazo decomposition of the major diazoketone isomers (**49,51** : entries 1,3) led to the formation of the C-H insertion products in ~50% yield. The slightly better yield observed for the benzyl substituted compounds could possibly be due to the electronic donation by inductive effect of the benzyl group, which increases the electron density of the C5-H bond favouring its attack by the electrophilic metallocarbene. The decomposition of the *p*-acetamidophenyl diazoketone (**55** : entry 6) was expected to give a similar yield considering the fact that the acetamido group can donate electrons by conjugation; however, the C-H insertion proceeded in 30% yield only. It was postulated in that latter case that the rhodium catalyst could possibly exchange its acetate ligands against acetamido ones. As expected, the decomposition of the *p*-nitrophenyl diazoketone (**53** : entry 4) led to the C-H insertion product (**59**) in 20% yield. This poor yield was attributed to the electron-withdrawing character of the nitro group by conjugation, which decreased the reactivity of the adjacent C-H bond. The decomposition of both phenyl and *p*-nitro phenyl substituted minor diazoketone isomers (**50,54** : entries 2,5) led to the formation of C-H insertion products in poor yields (10%). In these latter cases, the diazoketones possess both diazo and phenyl groups in the axial position, which does not correspond to the more stable conformer. A ring inversion or

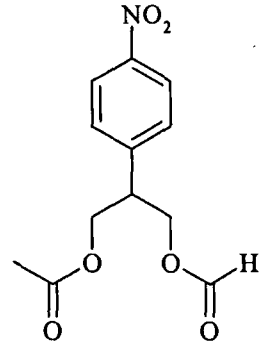
'flip' takes place in order for both substituents to adopt an equatorial position (Scheme 3.35).



R=Ph, *p*-NO_2Ph

Scheme 3.35

In that case, the C-2 diazo center looses its ideal coplanar arrangement with the C-4/6 C-H bonds and C-H insertion can no longer take place. Thus, side reactions can occur such as insertion into one of the C-H bond of the methyl group, ylide formation followed by rearrangement or simply decomposition of the diazoketone. The crude reaction was a complex mixture; however, one side product has been isolated in the *p*-nitrophenyl series. The structure of this by-product (**62**, Scheme 3.36) was fully determined by 1D (^1H, ^{13}C) and 2D (HSQC, HMBC) NMR experiments (see appendix D).



(62)

Scheme 3.36

It has not been possible to explain mechanistically the formation of this unexpected by-product.

3.6-Conclusion :

To overcome problems of volatility encountered during the isolation of the C-H insertion products at the beginning of this project, introduction of heavier substitutents which also contained chromophores was necessary. In conjunction with this aim, the introduction of electron-withdrawing and electron-donating groups was targeted, which would also permit us to probe the electronic effects of the substituents on the C-H insertion process.

After the successful preparation of a set of 2-aryl-propane-1,3-diols (phenyl, benzyl, *p*-nitrophenyl and *p*-acetamidophenyl), the corresponding esters, acids and diazoketones were formed using the methodology established in Chapter 2. The reactions were, in general, easier to follow and good yields were obtained.

During the ester formation, an isomeric mixture of two ester acetals was obtained but attempts to promote the formation of one isomer by screening different Lewis acids remained fruitless.

The variation of the electronic nature of the aryl group had little effect on the stereoselectivity of the acetalisation step.

A diazo-transfer method was tested for the synthesis of the diazoketones as an alternative to the use of diazomethane since the precursor, Diazald®, was no longer commercially available. After having successfully overcome problems of dimerization encountered during the synthesis of the methyl ketone starting materials, the diazotransfer proceeded but in moderate yields. Due to the lack of time, no further optimisation was achieved and the diazoketones were prepared by acylation of diazomethane in good yields.

After studying all the parameters of the C-H insertion reaction (concentration of both diazoketone and catalyst, rate of addition, temperature, catalyst loading and metal/ligands combination), optimum conditions were determined. A 100 mmol/L solution of diazoketone in CH_2Cl_2 should be added to a 1 mmol/L solution of $Rh_2(OAc)_4$ (2 mol%) in CH_2Cl_2, over 24 hours *via* a syringe pump and at room temperature. The C-H insertions proceeded in moderate but reproducible yields.

With a series of bicyclic ketones in hand, attention then turned to the study of their reductive cleavage towards the formation of functionalised tetrahydrofurans.

3.7-References :

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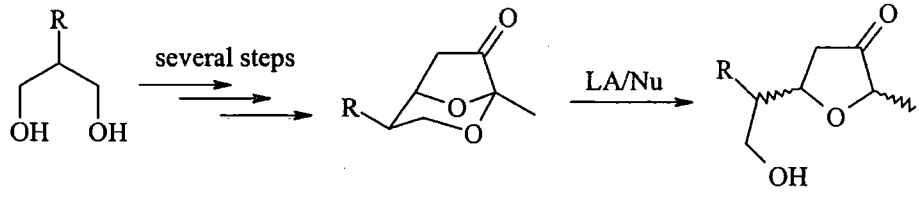
CHAPTER IV:
REDUCTIVE CLEAVAGE

4.1-Introduction :

As mentioned earlier in the introduction chapter, our strategic plan was to prepare bicyclic ketones and then to explore their reductive cleavage for the synthesis of highly functionalized tetrahydrofurans, the target molecules (Scheme 4.1).



Scheme 4.1

After having successfully prepared a new set of bicyclic ketone acetals **(56-61)**, attention now turned to the study of their reductive cleavage. At that particular time, several questions arose such as with what type of nucleophile would the ring opening occur and what would be the regio- and stereochemistry of the reaction. A literature search was therefore undertaken. The Lewis acid mediated reaction of acetals, and particularly acetals prepared from chiral diols, with nucleophiles had been widely studied. After a brief summary of related published work, the results of our studies of the reductive cleavage of the bicyclic ketones will be presented.

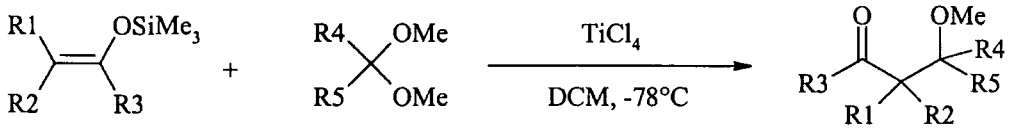
4.2-Lewis-acid mediated cleavage of acetals :

4.2.1-Introduction :

Aldehydes and ketones are usually protected from nucleophilic reagents through formation of acetals. The latter are usually stable towards organometallic reagents such as organolithiums, Grignard reagents and organocoppers. However, cleavage under some conditions has been observed.

In 1962, the reagent combination of $Et_3SiH/ZnCl_2$ was reported to reduce non-cyclic acetals to ethers.[1]

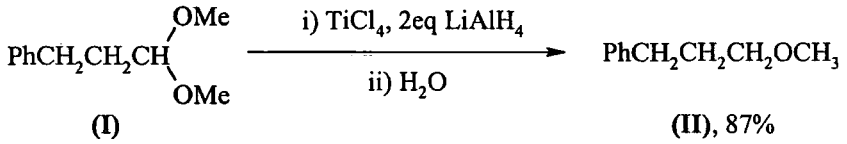
Few years later, Mukaiyama showed that the association of a silicon derivative such as trialkylsilyl enol ether with stoichiometric amounts of $TiCl_4$ afforded the corresponding aldol products in high yields (Scheme 4.2).[2]



R1=R2=H; R3=Ph; R4=NC$(CH_2)_2$; R5=H	60%
R1=Ph; R2=H; R3=Me; R4=R5=$(CH_2)_4CH_3$	91%
R1=H; R2=R3=$(CH_2)_3CH_3$; R4=H; R5=OMe	71%

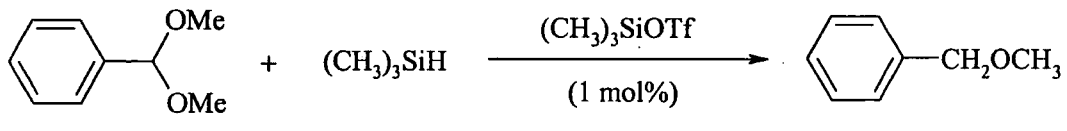
Scheme 4.2

In 1978, Ishikawa and Mukaiyama reported the reduction of the dimethyl acetal of 3-phenylpropanal **(I)** to the corresponding ether **(II)** in good yield upon treatment with $TiCl_4$ and 2 equivalents of $LiAlH_4$ (Scheme 4.3).[3]



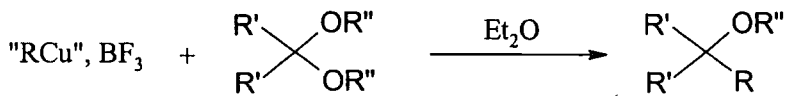
Scheme 4.3

The following year, Tsunoda, Suzuki and Noyori described a method for converting both aliphatic and aromatic acetals to ethers using Me_3SiH (or Et_3SiH) in the presence of TMSOTf (trimethylsilyl trifluoromethane sulfonate) (Scheme 4.4).[4]



Scheme 4.4

Alexakis and Normant showed that organocoppers, or cuprate reagents, in the presence of a Lewis acid were also able to cleave acetals (Scheme 4.5).[5]



Scheme 4.5

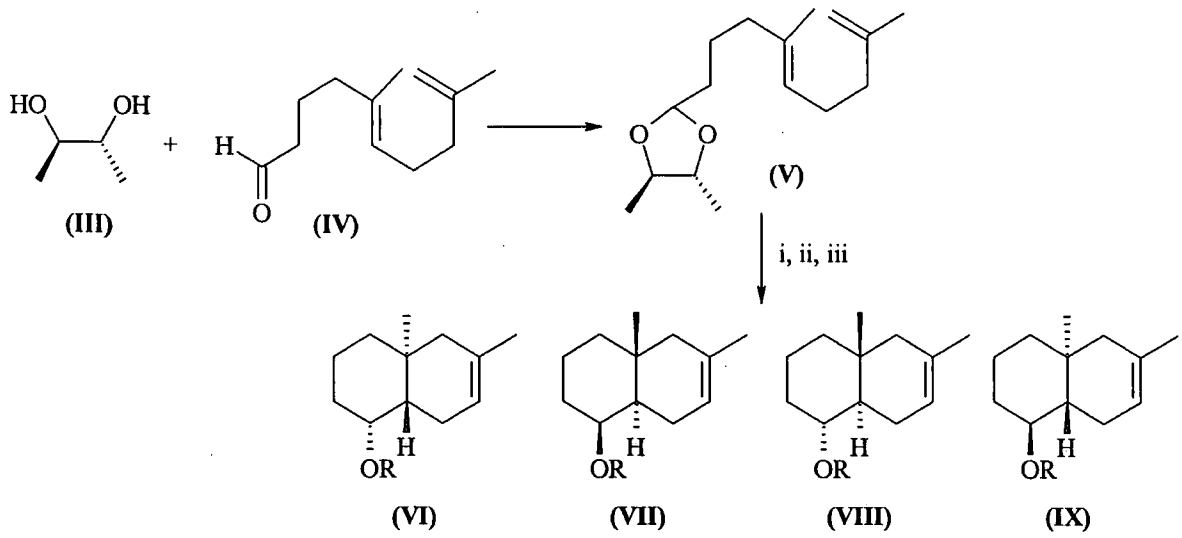
Thus, there was a growing interest in the cleavage of acetals with the combination of nucleophile/Lewis acid and organometallic reagents having a Lewis acid character such as aluminium hydrides.

Some groups have studied the nucleophilic opening of cyclic acetals[6] and most particularly of cyclic chiral acetals derived from (R,R)-2,3-butanediol or (R,R)-2,4-pentanediol. In the particular case of cyclic acetals, the cleavage involves the generation of a new chiral center. High asymmetric induction has been observed. The selectivity of the reaction depends on which C-O bond is broken and the direction of attack of the nucleophile compared to the departing oxygen (*syn* or *anti*).
Cleavage of cyclic chiral acetals and the mechanistic considerations will be discussed below.

4.2.2-Cyclic chiral acetals :

4.2.2.1-Introduction :

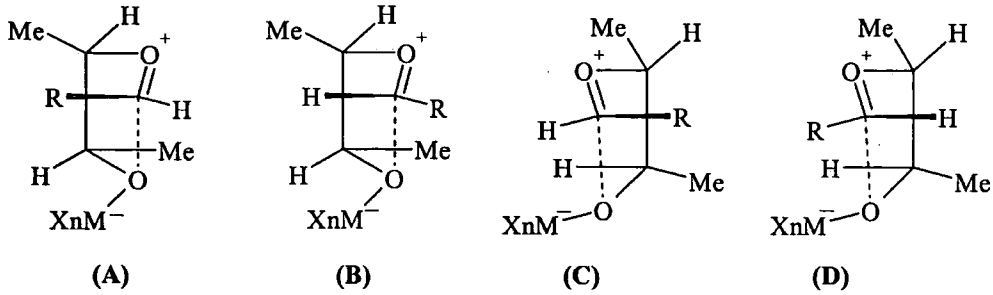
The pioneer was Johnson[7] who developed an acetal-initiated cationic cyclization of chiral dienic acetal **(V)** derived from (R,R)-2,3-butanediol **(III)**. The alcohols **(VI-IX)** were formed in high yield after treatment of **(V)** with stannic chloride followed by cleavage of the ether side (Scheme 4.6).



i) $SnCl_4$, benzene, rt , R= $CH(CH_3)CH(OH)CH_3$, *d/l* mixture, 80%; ii) Collins oxidation, R= $CH(CH_3)COCH_3$ iii) Li, $EtNH_2$, R=H, **(VI,VII)** : 52% (93/7); **(VIII,IX)** : 21% (94/6).

Scheme 4.6

Later, Johnson[8] postulated that the acetal **(V),** after specific coordination of the Lewis-acid to one of the two oxygen atoms, was partially cleaved in the transition state leading to a cationic acetal. As the acetal opened, the configuration of the oxocarbenium ion approaches a planar sp^2-hybridized geometry with the departing oxygen leaving in a roughly perpendicular direction. Four diastereomeric structures can be considered (Scheme 4.7).

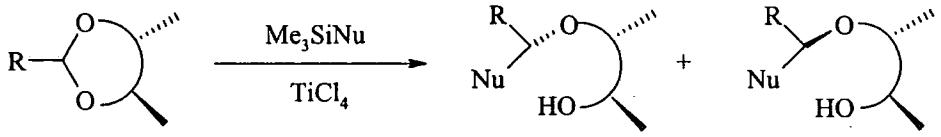


Scheme 4.7

The structure **D** corresponds to the least sterically congested isomer and thus the most favorable structure. The double bond attacks from the direction *anti* to the departing oxygen.

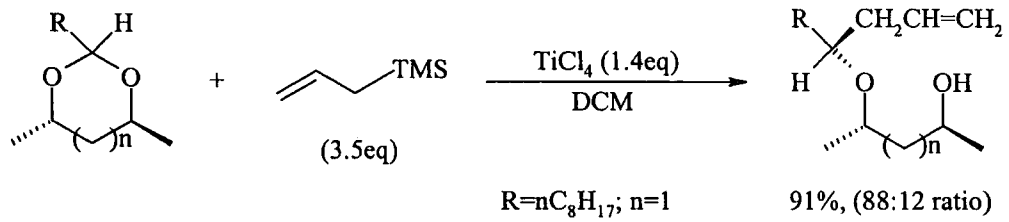
4.2.2.2-$TiCl_4$-mediated reductive cleavage of acetals :

Independant studies realised by Johnson,[9] Kishi[10] and Yamamoto[11] showed that silicon derivatives in the presence of $TiCl_4$ were able to cleave chiral cyclic acetals with high asymmetric induction. A general scheme is presented below (Scheme 4.8).



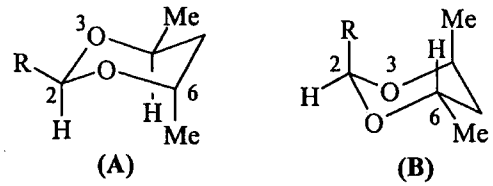
Scheme 4.8

Johnson *et al* reported that $TiCl_4$ promoted the allylation reaction of chiral acetals with allyltrimethylsilane with good diastereoselectivity (Scheme 4.9).[8a]



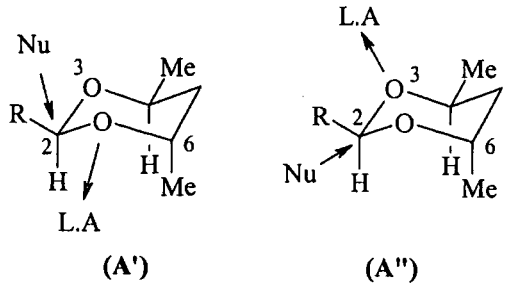
Scheme 4.9

Acetals of 2,4-pentanediol exist largely if not exclusively in conformation **(A)** where only two 1,3-diaxial interactions (H↔Me) are present. Conformation **(B)** is destabilized by one (R↔Me) and one (H↔Me) diaxial interaction (Scheme 4.10).



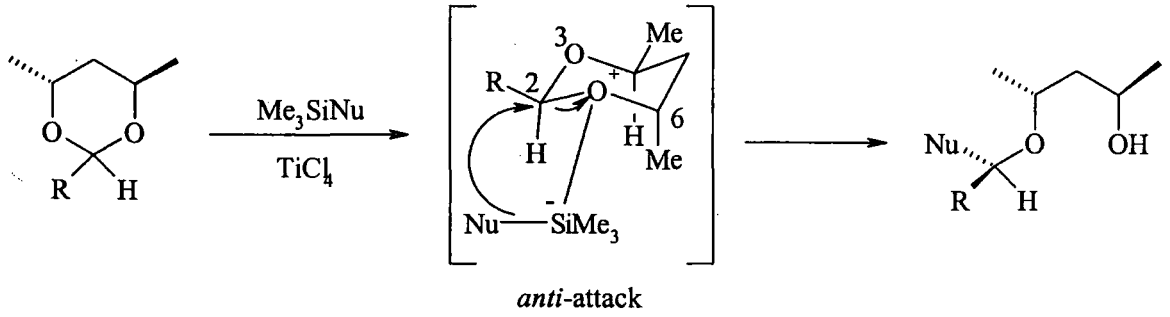
Scheme 4.10

Thus, two complexes are possible upon chelation of acetal **(A)** with a Lewis acid (Scheme 4.11).



Scheme 4.11

In complex **(A')**, the Lewis acid chelates to the oxygen next to the axial methyl group. Therefore, the C2-O1 bond is elongated and conversely, by anomeric effect, the C2-O3 bond is shortened. This situation is favourable since the elongation of the C2-O1 bond increases the distance between H-2 and CH_3-6 releasing part of the strain of the molecule. In complex **(A")**, the C2-O3 bond is elongated and because of the anomeric effect, the C2-O1 bond is shortened increasing the 1,3-diaxial interactions between H-2 and CH_3-6. Therefore, the formation of this complex is relatively unlikely. The exclusive formation of complex **(A')** was observed by Denmark[12] using temperature-calibrated ^{13}C probes. In 1984, an S_N2-like transition state was proposed to explain the high asymmetric induction where the nucleophile is believed to attack in an *anti*-manner to the departing oxygen (Scheme 4.12).[13]

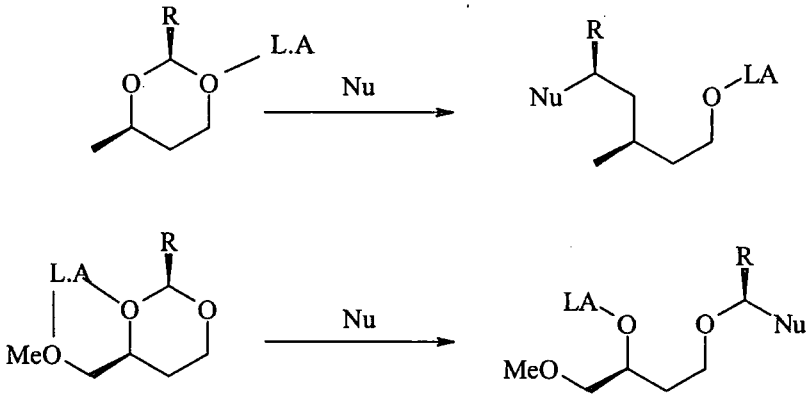


Scheme 4.12

Two years later, Yamamoto[14] suggested that bond breaking and bond making are in fact concerted, strongly dependent upon the Lewis-acidity of the organometallic reagent and the nucleophilicity of the nucleophile. Organometallic reagents with low nucleophilicity, such as silicon or boron compounds, react after the bond-breaking process while

organometallics with higher nucleophilicity react simultaneously with the bond breaking. A Lewis acid with low Lewis-acidity delays the bond-breaking process. Additionally, Johnson[15] observed that the cleavage is more diastereoselective when using a milder Lewis acid (i.e. combination of $TiCl_4$ and $Ti(OiPr)_4$), and that a slow addition of the Lewis acid improved the ratio to 96:4 in the case of the allylation reaction of chiral acetals with allyl trimethyl silane (Scheme 4.9).

It is worth noting that in 1990, Corcoran[16] had already reported that bidendate Lewis acids can reverse the regioselectivity of the reaction, but that this is strongly dependent on the nature of the acetal, as shown on the following scheme (Scheme 4.13).

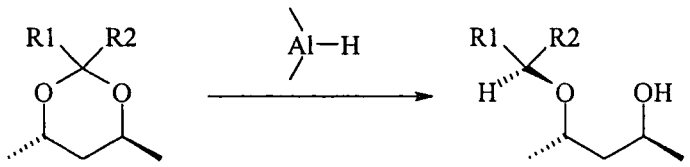


Scheme 4.13

Chiral acetals of 2,3-butanediol and 2,4-pentanediol have been cleaved diastereoselectively using a variety of nucleophiles.[8a,10,13,17] In most cases $TiCl_4$ has proved to be the Lewis acid of choice. In general, better selectivity was obtained with the more rigid dioxane ring rather than the more flexible dioxalane ring.

4.2.2.3-Dibal-H mediated reductive cleavage of acetals :

Yamamoto[11,16,18] showed that optically active acetals could be cleaved regio- and stereoselectively by organoaluminium reagents, leading to the reversed stereochemistry to the one observed when using $TiCl_4$ (Scheme 4.14).

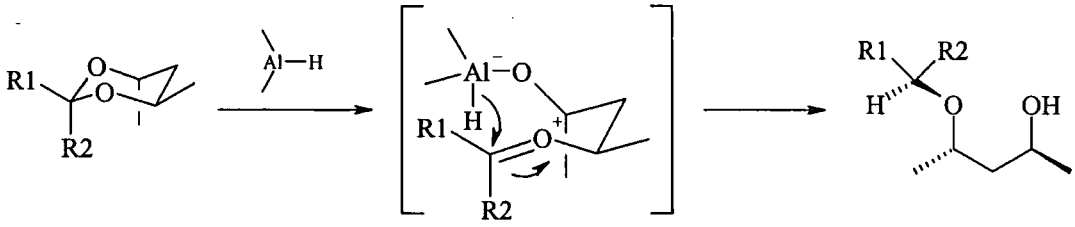


R1=c-hex, R2=Me 88%

Scheme 4.14

Organoaluminium compounds are not typical Lewis acids because they also have a latent nucleophilic character, which will be increased upon coordination with an oxygen-containing functional group. Here, the aluminium atom primarily acts as the coordination site for the substrate. Then, the nucleophilic centre, attached to aluminium and activated by the formation of the coordination complex, attacks the substrate.

The reaction is believed to proceed *via* a tight ion-paired S_N1-like mechanism (Scheme 4.15).[19]



syn-attack

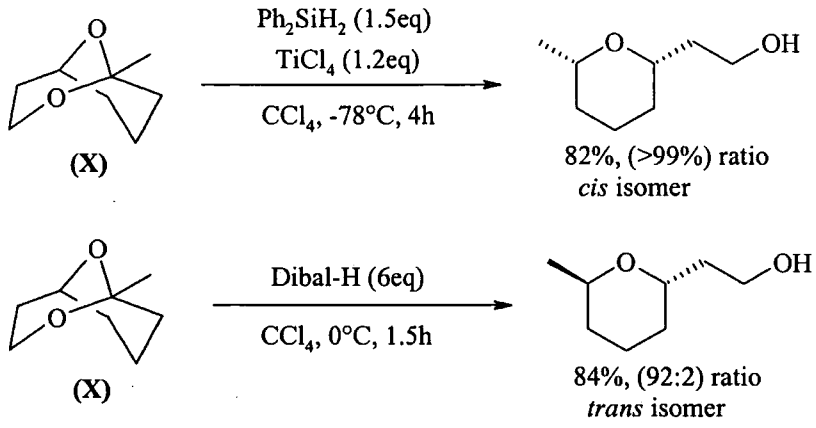
Scheme 4.15

Steric effects influence the reactivity of the acetal oxygen atoms and hence the relative ease of coordination to the aluminium compound. Thus, in the case of 2,4-pentanediol, the organoaluminium reagent stereospecifically coordinates to the oxygen next to the axial methyl group forming an oxocarbenium ion. This is followed by the attack of the hydride *syn* to the cleaved C-O bond.

4.2.3-Bicyclic acetals :

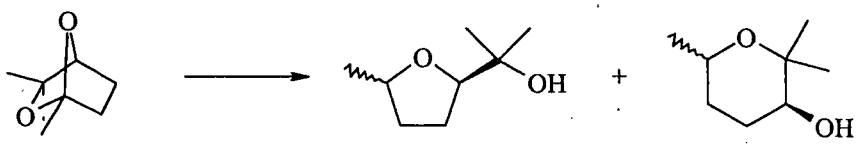
In 1987, Yamamoto[20] transposed the stereochemical information gained from work with cyclic chiral acetals to bicyclic frameworks and reported a new synthetic route for the

construction of cyclic ether compounds from bicyclic acetals by stereoselective reductive cleavage of the acetal group (Scheme 4.16).



Scheme 4.16

The reaction of the acetal **(X)** with Dibal-H resulted in the formation of the *trans*-reduced alcohol while treatment with $Ph_2SiH_2/TiCl_4$ mainly afforded the *cis*-isomer. The stereochemistry observed is similar to that observed in the cyclic series. They extended their study to other bicyclic ethers to explore the generality of the method, and to study the influence of ring size and substituents. An interesting example where both 5- and 6-membered rings were obtained is illustrated in the following scheme (Scheme 4.17).[21]



	yield	*cis/trans*	*cis/trans*
Dibal-H (6eq) DCM,0°C,1h	61%	0.6 : 55.5	2.1 : 41.8
Et_3SiH (1.5eq) / $TiCl_4$ (1.2eq) DCM,-78°C, 0.4h	61%	42.6 : 0.8	48.7 : 7.9

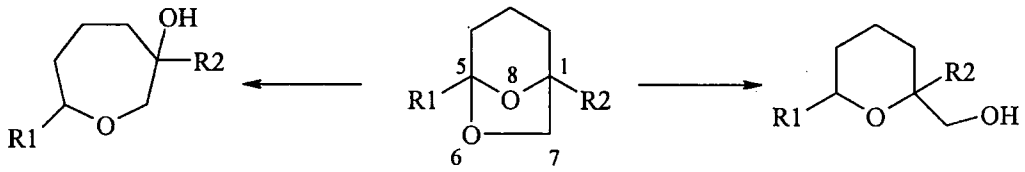
Scheme 4.17

In both cases, a mixture of 5- and 6-membered rings were obtained in an approximately 1:1 ratio with predominantly *trans*-isomers formed when using Dibal-H and

predominantly *cis*-isomers formed when using the $Et_3SiH/TiCl_4$ system. For this specific substrate, no preferential complexation of the Lewis acid to one particular oxygens has been observed, which implies that both oxygens are equally accessible for coordination.

Yamamoto[11] and Kotsuki[22] focused on the reductive cleavage of various types of bicyclic acetals.

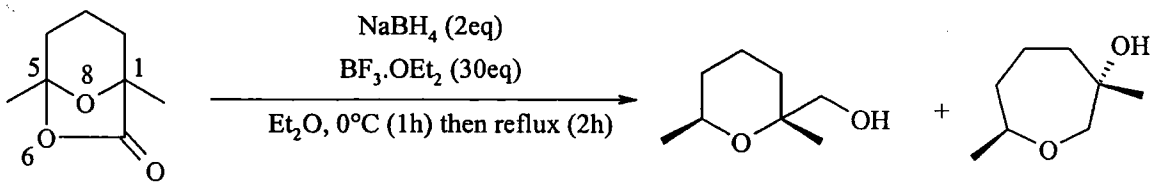
It is worth noting that both groups were particularly interested in the reductive cleavage of the 6,8-dioxabicyclo[3.2.1]octane systems **(XI)**, *en route* to the preparation of oxepane rings **(XII)** by O8-C5 bond breaking. Disappointingly, reductive cleavage produced exclusively oxane rings **(XIII)** using Dibal-H or Et_3SiH/L.A (Scheme 4.18).



(XII) **(XI)** **(XIII)**

Scheme 4.18

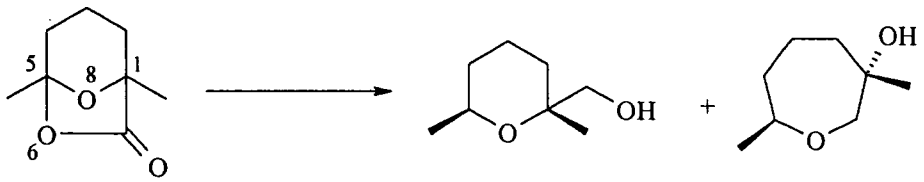
In 1983, Utaka[23] was the first to report oxepane formation by reductive cleavage of a ketal lactone **(XIV)** with $NaBH_4$ in the presence of $BF_3.OEt_2$ (Scheme 4.19). However, the oxepane **(XVI)** was obtained in poor yield (26%) and as a mixture with the 6-membered ring **(XV)**.



(XIV) **(XV), 36%** **(XVI), 26%**

Scheme 4.19

Following this precedent, Jun[24] investigated the regioselective reductive cleavage of the same ketal lactone **(XIV)** and found conditions to form the 6- or 7-membered ring stereoselectively (Scheme 4.20).

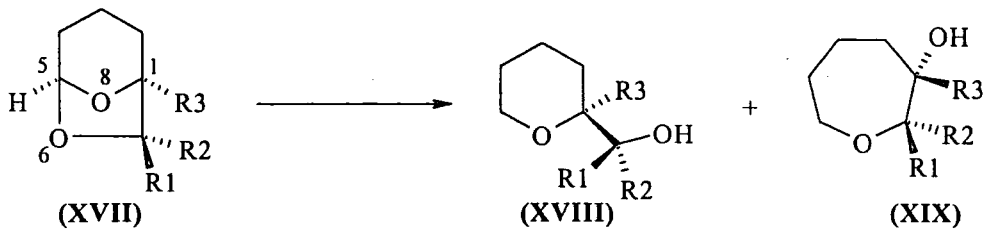


(XIV)	(XV)	(XVI)
$NaBH_4$ (4eq), $BF_3.OEt_2$ (30eq), 15h	93%	/
$NaBH_4$ (6eq), $AlCl_3$ (30eq), 2.5h	/	94%

Scheme 4.20

Jun suggested that the exclusive formation of the oxepane ring, by treatment with $NaBH_4$ in the presence of $AlCl_3$, could be explained by the preferential coordination of $AlCl_3$ to O-8 due to the decrease of electron density of O-6 by the resonance effect of the lactone. He also suggested that the difference in selectivity observed when using $BF_3.Et_2O$ and $AlCl_3$ could be explained by the presence of a vacant d-orbital in the case of $AlCl_3$. However, it is worth noting that his attempts at using other Lewis acids ($TiCl_4$, $ZnCl_2$, TMSOMs-$BF_3.Et_2O$) with $NaBH_4$ or at using other hydrides (Dibal-H, $NaBH_3CN$, Et_3SiH, $LiAlH_4$) yielded different products, which were not identified. Furthermore, no explanation as for the use of 30 equivalents of Lewis acid was given.

In 2000, Fujiwara and Murai[25] showed that the presence of an alkoxymethyl group at the C1 position of the 6,8-dioxabicyclo[3.2.1]octane system enabled the formation of oxepane rings but that the substituents at the C7 position also had an effect on the selectivity of oxepane formation. Selected examples of their studies are summarized in the following table (Scheme 4.21, Table 4.1).



(XVII) **(XVIII)** **(XIX)**

Entry		Reagent (eq)	Time	Yield (%)	SM Recovery (%)	Ratio **XVIII/XIX**
1	**XVIIa**	Dibal-H (4)	3 days	46	52	100 : 0
		Et_3SiH (8)/$TiCl_4$ (2.4)	0.5 h	65	/	100 : 0
2	**XVIIb**	Dibal-H (4)	2 days	100	/	100 : 0
		Et_3SiH (8)/$TiCl_4$ (2.4)	1 h	74	/	26 : 74
		Et_3SiH (12)/$SnCl_4$ (3.6)	5.5h	43	/	100 :0
3	**XVIIc**	Dibal-H (4)	3 days	77	/	100 : 0
		Et_3SiH (8)/$TiCl_4$ (2.4)	1 h	98	/	1 : 99
		Et_3SiH (8)/$SnCl_4$ (2.4)	2 h	60	/	100 : 0
4	**XVIId**	Dibal-H (8)	2 days	81	/	100 : 0
		Et_3SiH (8)/$TiCl_4$ (4)	1 h	62	17	46 : 56

Dibal-H reaction temperature : 20°C; $Et_3SiH/TiCl_4$ or $SnCl_4$ reaction temperature : -78°C.

XVIIa : R1=R2=H, R3=Me; XVIIb : R1=Me, R2=H, R3=CH_2OMe;
XVIIc : R1=H, R2=Me, R3=CH_2OMe; XVIId : R1=R2=H, R3=CH_2OMe

Scheme 4.21, Table 4.1

The use of Dibal-H led to the exclusive formation of an oxane ring **(XVIII)** in all cases. For the $Et_3SiH/TiCl_4$ system, the presence of an alkoxymethyl group at C1 reversed the regioselectivity. This was explained by the probable chelation of the bidentate Lewis-Acid ($TiCl_4$) between O8 and the oxygen of the alkoxymethyl group at C1 enhancing the ease of cleavage of the C5-O8 bond leading to the oxepane ring **(XIX)**.

Interestingly, when $SnCl_4$, which is also a bidentate Lewis-Acid, was used, the oxane ring **(XVIII)** was produced exclusively (entries 2 and 3). This difference was explained by the lower acidity of $SnCl_4$ compared to $TiCl_4$. Thus, the selectivity depends also on the acidity of the Lewis acid used.

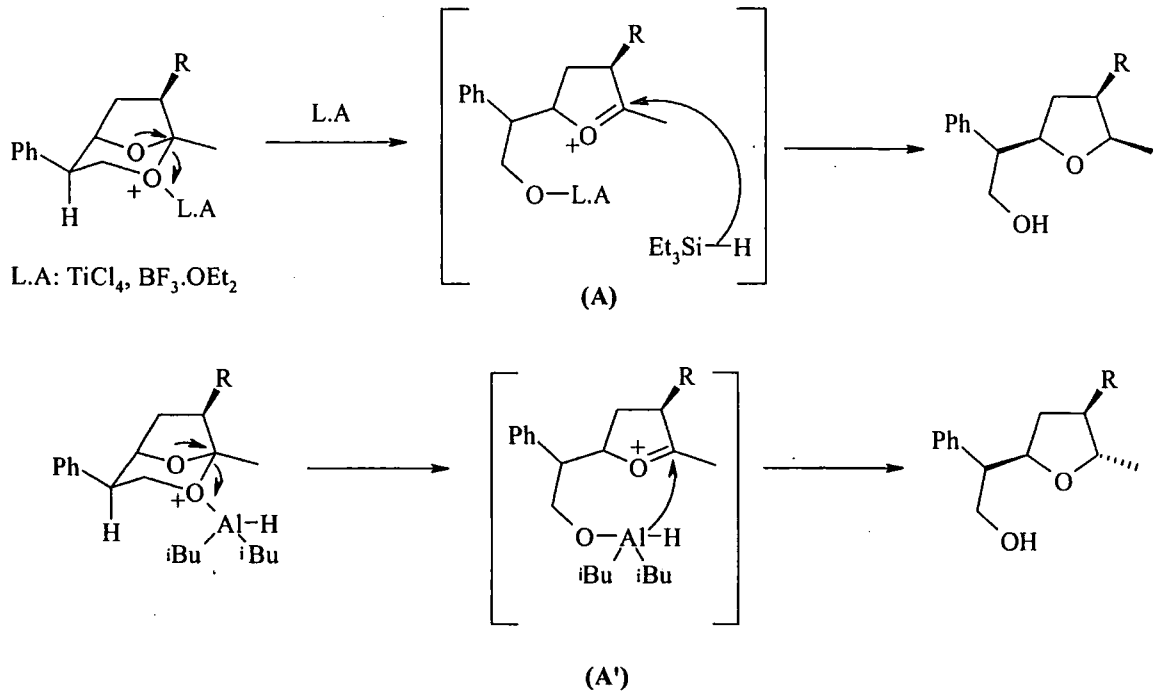
The best selectivity was observed when the bicyclic acetal **(XVII)** also possessed an α-methyl group at C7 (**XVIIc**, entry 3). The stereochemistry of the methyl substituent at C7 also affected the selectivity. Indeed, the bicyclic acetal **(XVIIc)** showed higher oxepane selectivity than the bicyclic acetal **(XVIIb)** possessing a β-methyl group at C7 (entries 2 and 3). The bulkiness of the C7-methyl group may obstruct the coordination of $TiCl_4$ to O6 and thus improve the ease of cleavage of the C5-O8 bond (entries 2,3 and 4). Fujiwara also speculated that the steric repulsion of the C7-methyl group with the methylene at C3 might improve the cleavability of the C5-O8 bond but more detailed mechanistic studies are required to explain the influence of the stereochemistry at C-7 on the selectivity.

In conclusion, it clearly appears that selectivity in the reductive cleavage of bicyclic acetal structures depends strongly on the Lewis acid, but also on the structure of the starting materials, and is mostly governed by steric and anomeric effects.

4.2.4-Proposed work :

The Lewis acid catalyzed nucleophilic cleavage of bicyclic acetals is therefore a well-established and attractive method for the synthesis of cyclic ethers. Consequently, the reductive cleavage of the 2,8-dioxabicyclo[3.2.1]octan-7-ones prepared **(56-61)** was examined *en route* to the stereoselective construction of 2,3,5-trisubstituted tetrahydrofurans.

As outlined in the following scheme (Scheme 4.22), the stereocontrolled reduction of the bicyclic acetals is expected to generate specifically a *cis*-tetrahydrofuran when using a Et_3SiH/L.A combination or a *trans*-tetrahydrofuran when using Dibal-H.



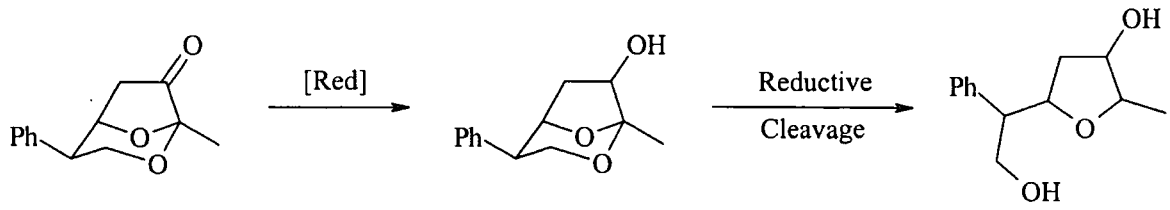
Scheme 4.22

The reactions are believed to proceed via nucleophilic attack on the cationic centre of an oxocarbenium intermediate formed upon coordination with the Lewis-Acid. Et_3SiH attacks from the rear side of the complex **(A)** formed; whereas the reduction proceeds by intramolecular transfer of hydride from the *syn*-face of the complex **(A')** formed in the case of Dibal-H.

The study and results of the Lewis-acid-catalyzed reduction of the 2,8-dioxabicyclo[3.2.1]octan-7-ones **(56-61)** are presented in the following section.

4.3-Reductive cleavage of the bicyclic ketones (56-61) :

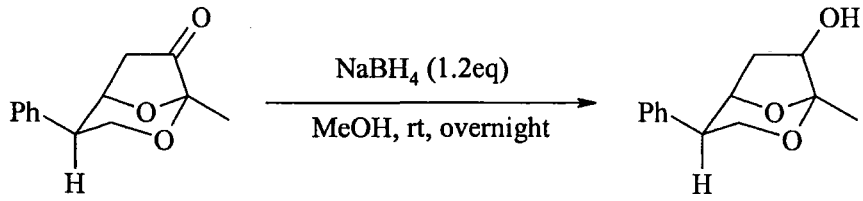
Following Yamamoto, Mori and Ishihara conditions,[20] initial attempts at carrying out the ring- opening of the bicyclic ketone **(56)** using Dibal-H (6eq) and Et_3SiH (1.5eq)/$TiCl_4$ (1.2eq) system resulted in highly complex mixtures in both cases. Attributing this to the presence of the ketone functionality, it was decided to reduce the bicyclic ketones into the corresponding alcohols before performing the ring opening (Scheme 4.23).



Scheme 4.23

4.3.1-Reduction of the bicyclic ketones :

$NaBH_4$, a most widely used mild-reducing agent, was chosen. The bicyclic ketone **(56)** was added dropwise to a solution of $NaBH_4$ in methanol. The reaction mixture was stirred at room temperature and followed by TLC. After 6 hours, the reaction had not gone to completion and was therefore left to stir overnight. After work up and purification by flash chromatography, the alcohol **(63)** was obtained in 80% yield as a single product (Scheme 4.24).



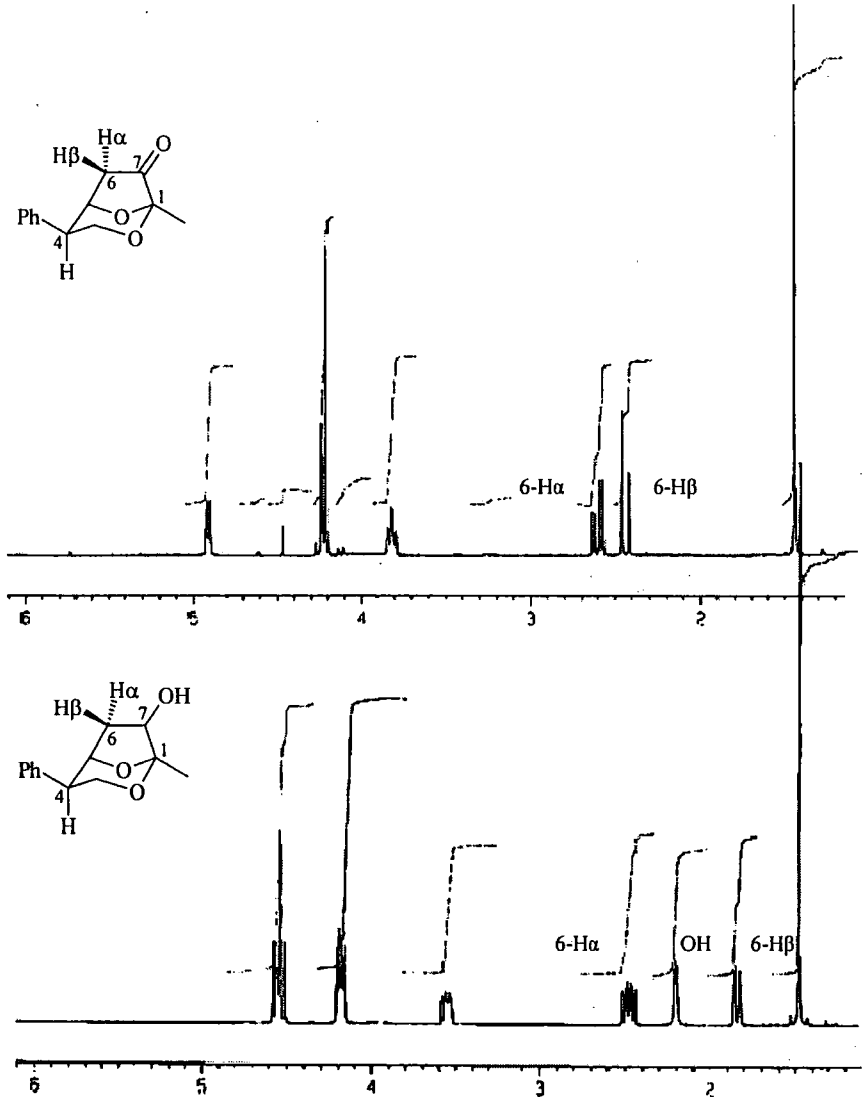
(56)

(63), 87%
1 single isomer

Scheme 4.24

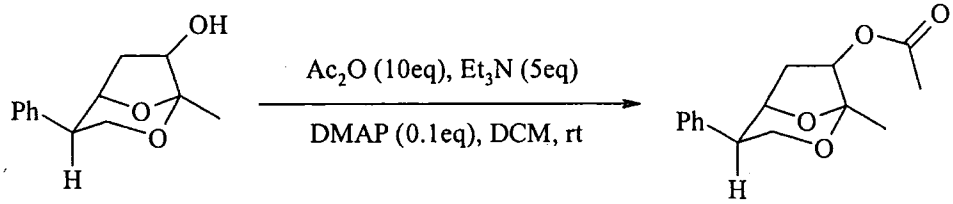
Evidence for the formation of the alcohol **(63)** was found in the IR spectrum with the appearance of the broad OH-band at 3600-3150 cm^{-1} characteristic of alcohols, and the disappearance of the carbonyl signal at 1763 cm^{-1}. This was also confirmed by the ^{13}C NMR spectrum with the presence of the C-7 signal at 75.5 ppm and the disappearance of the carbonyl signal at 210.7 ppm. The comparison of the ^{1}H NMR spectra showed clearly the reduction of the ketone through the change in the signals of 6-Hα and 6-Hβ (Scheme 4.25). The doublet (d) of 6-Hβ, due to its coupling with 6-Hα, became a doublet of doublet (dd) because of the additional coupling with 7-H. Similarly, the dd of 6-Hα, due

to its coupling to 6-Hβ and 5-H, became a ddd (doublet of doublet of doublet) resulting from its coupling with 6-Hβ, 5-H and 7-H.



Scheme 4.25

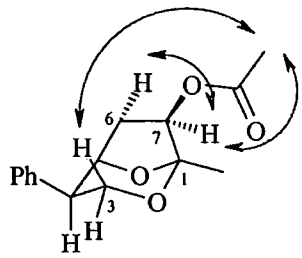
As mentioned above, the alcohol **(63)** was formed as a single diastereoisomer. To determine the stereochemistry at C-7, the acetate derivative was synthesised. The alcohol was treated successively with Et_3N and acetic anhydride in the presence of a catalytic amount of DMAP (Scheme 4.26).[26]



(63) **(64), 75%**

Scheme 4.26

Evidence for the formation of the acetate **(64)** was found in the IR spectrum with the disappearance of the broad OH-bond at 3600-3150 cm^{-1} and the appearance of a carbonyl signal at 1735 cm^{-1}. 2D NMR experiments (COSY, HSQC, HMBC) permitted the full assignment of the ^1H spectrum while the stereochemistry was ascertained by nOe experiments. Irradiation of the CH_3 of the acetate gave a strong nOe to H-7 but also to axial H-3, which implied that the acetate group and the axial H-3 were on the same side of the molecule. Consistent with this, the irradiation of H-7 gave a strong nOe to H-6α, which implied that H-6α and H-7 were on the same side of the molecule (Scheme 4.27).



Scheme 4.27

With the aim of preparing the alternative alcohol epimer, it was decided to screen a set of reducing conditions, and the results of that study are summarized in Table 4.2.

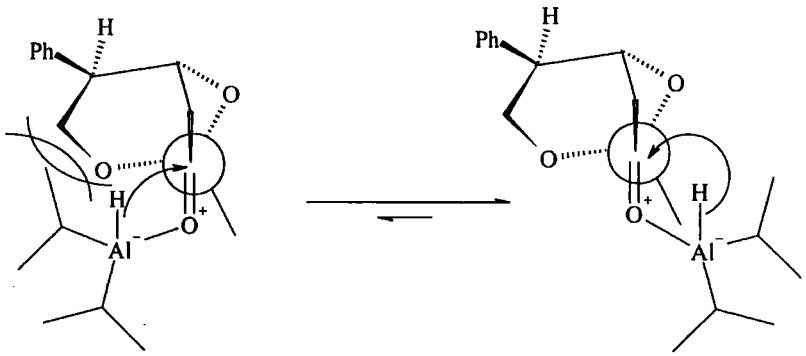
Entry	Reducing agent	Solvent	Temp	Yield (%)	Ratio[a]
1	$NaBH_4$ (1.2eq)	MeOH	rt	80	100:0
2	Dibal-H (2eq)	DCM	-78°C	51	97:3
3	Dibal-H (2eq)	DCM	0°C	40	92:8
4	Dibal-H (2eq)	DCM	rt	74	88:12
5	BH_3.THF (2eq)	THF	-78°C	80	96:4
6	Dibal-H (2eq)	THF	-78°C	no reaction	/
7[b]	Dibal-H (3eq)+ MAD (3eq)	Toluene	-78°C	60	94:6

a) ratio of diastereoisomers, b) MAD: methyl aluminium bis (2,6-di-*tert*-butyl-4-methyl phenoxide) (see experimental for the in situ formation of MAD).

Table 4.2

Attempts to control the selectivity through the use of Dibal-H and BH_3-THF were not successful, leading to the same isomer as major product, in moderate or good yield. Even the pre-formation of a bulky aluminium complex upon coordination of MAD,[27] thus forcing Dibal-H to attack from the other side to give the opposite stereochemistry, was not successful, leading again to the same isomer but in a reduced yield.

These results can be rationalized by preferential formation of the oxocarbenium ion **(II)**, the formation of the alternative oxocarbenium ion species **(I)** being disfavoured by steric interactions, and attack on the less-hindered face (Scheme 4.28).



(I) **(II)**

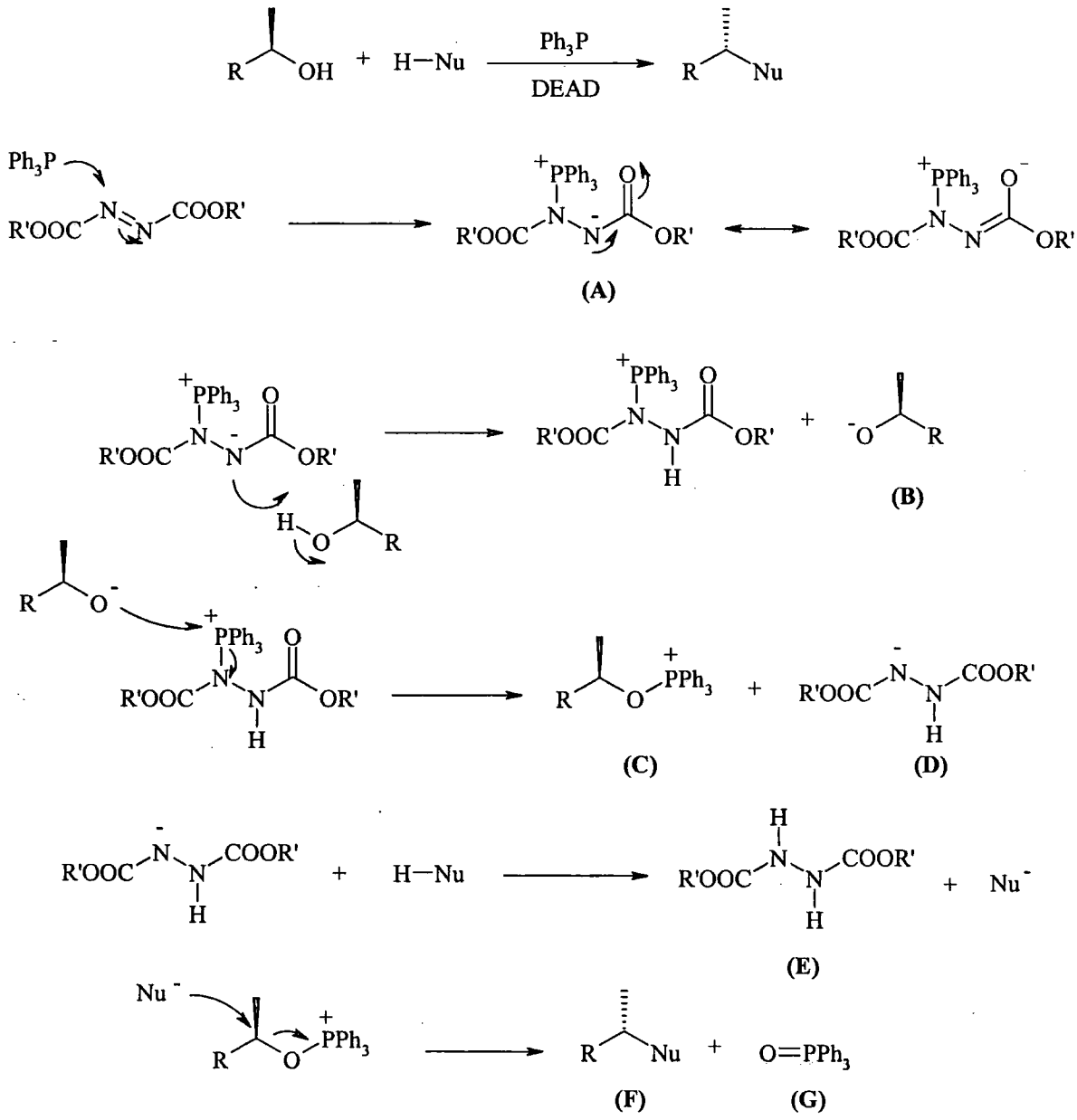
Scheme 4.28

The lack of formation of the epimer led us to explore other methods for the inversion of the alcohol moiety at C-7 and these will be discussed in the following section.

4.3.2- Inversion of the bicyclic alcohol :

4.3.2.1-Mitsunobu reaction :

A versatile method for alcohol inversion is the Mitsunobu reaction, which enables the replacement of the hydroxyl group of an alcohol by a nucleophile in a one-pot process with inversion of the stereochemistry. The general reaction mechanism is detailed below (Scheme 4.29).

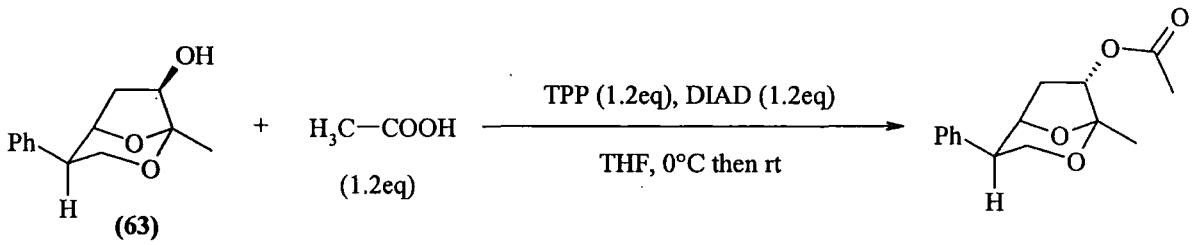


Scheme 4.29

In the first step, the phosphine (PPh_3) adds to the weak N=N π bond of the azo ester (DEAD : diethyl azodicarboxylate) to give an anion **(A)** stabilized by one of the ester groups. The anion **(A)** is basic enough to remove the proton of the alcohol and the new alkoxide ion formed **(B)**, which immediately attacks the positively charged phosphorus atom leading to the species **(C)** and **(D)**. The second basic nitrogen anion in **(D)** removes the proton of the nucleophile leading to the reduced azo diester **(E)** and the nucleophile anion. Finally, the nucleophile anion attacks the phosphorus derivative of the alcohol **(C)** in a normal S_N2 reaction at carbon with triphenyl phosphine oxide as the leaving group. The products of the reaction are the S_N2 product, the reduced azo diester and triphenyl phosphine oxide.

Examples of nucleophile that can be used include carboxylic acids, thioacids, phenols, thiols, imides and sulfonamides.

The initial attempt was performed using acetic acid, Ph_3P and DIAD (diisopropyl azodicarboxylate), an alternative to DEAD as it is more stable and works as well (Scheme 4.30).

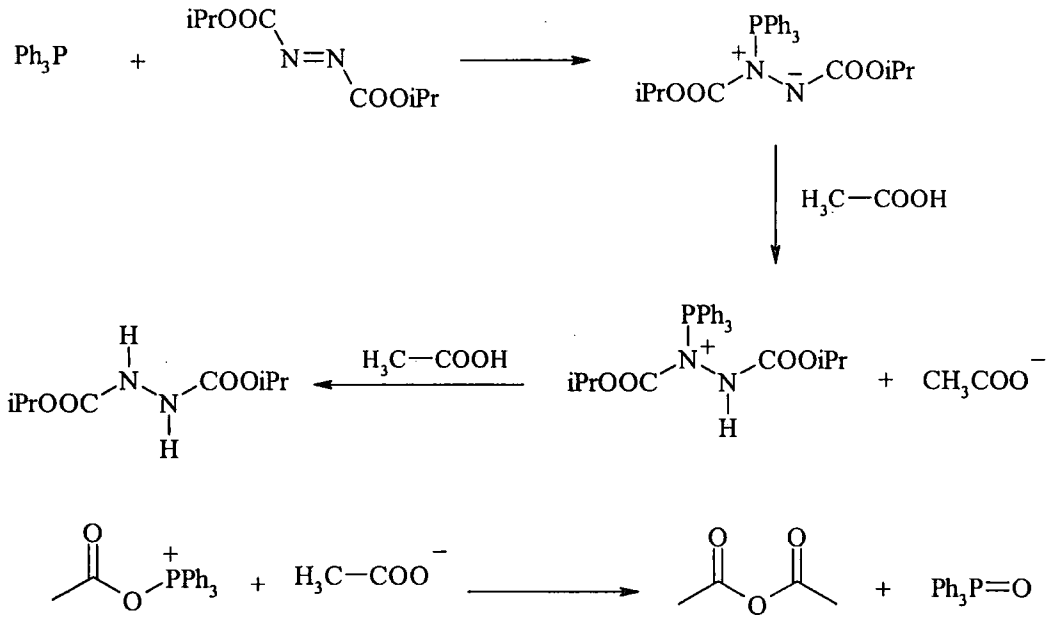


Scheme 4.30

The alcohol **(63)**, the acid and Ph_3P were dissolved in THF and the reaction mixture was cooled to 0°C. DIAD was slowly added at that temperature and the reaction mixture was then stirred at room temperature for several hours. The analysis of the reaction mixture by TLC and GC/MS showed no formation of the desired product.

It was decided to preform the betaine (Ph_3P-DIAD adduct) by addition of DIAD to Ph_3P at 0°C. This was followed by the addition of a mixture of the alcohol and acid but again the GC/MS analysis showed no formation of product. However, the formation of both the reduced azo diester and triphenylphosphine oxide were observed this time. This was

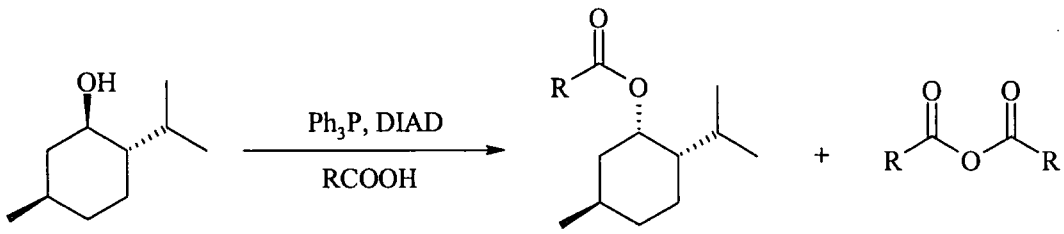
explained by competitive anhydride formation being favoured due to the steric hindrance on the alcohol (Scheme 4.31).[28]



Scheme 4.31

Harvey[28] studied the competitive formation of anhydrides in the Mitsunobu reaction of the hindered alcohol, menthol and found that the use of 4 equivalents of both betaine (Ph_3P-DIAD adduct) and acid, relative to menthol resulted in a decrease in anhydride formation. Following this precedent, 1 equivalent of alcohol **(63)** was mixed with 4 equivalents of acetic acid and 4 equivalents of Ph_3P followed by the addition of 4 equivalents of DIAD at 0°C. As before, the reaction was stirred at room temperature and followed by GC/MS. Unfortunately no desired product was detected.

In the same paper, Harvey[28] showed that anhydride formation did not occur when the more acidic *p*-nitro-benzoic acid (pK_a=3.41) was used instead of benzoic acid (pK_a=4.19) and an improved yield was observed when using 4 equivalents of both betaine and acid. Similar results had also been reported by Dodge[29] few years earlier. The results of both studies are summarized below (Scheme 4.32, Table 4.3).



Entry	Acid	pK_a	Number of eq	Solvent	Ester yield (%)	Anhydride yield (%)
1	CH_3COOH	4.76	1	PhH	0	n/c
2	CH_3COOH	4.76	4	PhH	0	n/c
3	C_6H_5COOH	4.19	1	THF	54	16
4	C_6H_5COOH	4.19	4	THF	76	14
6	*p*-$NO_2C_6H_4CO_2H$	3.41	1	THF	52	0
7	*p*-$NO_2C_6H_4CO_2H$	3.41	4	THF	83-100	n/c-0

Scheme 4.32, Table 4.3

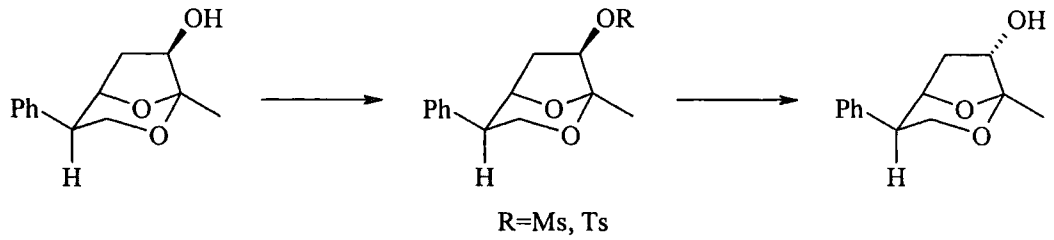
It appears clearly that the Mitsunobu inversion of menthol, a sterically encumbered alcohol, is influenced by the acid component. Introduction of electron withdrawing substituents on the acid led to higher yield of ester product and no formation of anhydride.

In view of these results, two more experiments were undertaken. The bicyclic alcohol **(63)** was mixed with 1 equivalent of *p*-nitrobenzoic acid, 1 equivalent of Ph_3P and 1 equivalent of DIAD at 0°C. The reaction was again stirred at room temperature and followed by GC/MS. No formation of the desired ester product was observed, but no anhydride was formed either. A similar result was observed when an analogous experiment was performed with 4 equivalents of both betaine (pre-formed Ph_3P-DIAD adduct) and *p*-nitrobenzoic acid.

4.3.2.2-Alternative to the Mitsunobu reaction :

Since all attempts at performing inversion at the C-7 position *via* Mitsunobu failed, an alternative approach, which involved the conversion of the hydroxyl functionality into a

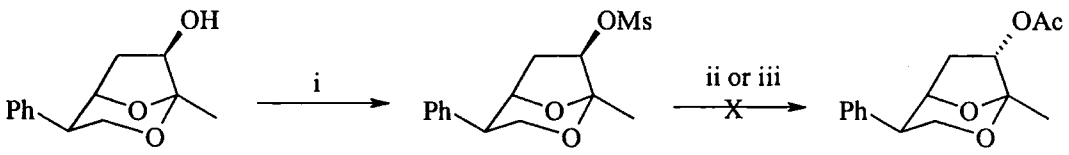
good leaving group (mesylate or tosylate) followed by an S_N2 reaction on the sulfonate formed, was then explored (Scheme 4.33).



R=Ms, Ts

Scheme 4.33

To this end, following a protocol by Diaz,[30] the bicyclic alcohol **(63)** in solution in DCM was first treated by methane sulfonyl chloride (1.5eq) in presence of Et_3N (2eq) giving the activated derivative in almost quantitative yield (98%). Evidence for the formation of the mesylate **(65)** was found in the ^1H and ^{13}C NMR spectra with the singlet at 3.12 ppm and signal at 38.7 ppm of the methyl sulfonate, and confirmed by IR with the disappearance of the broad OH signal at 3600-3150 cm^{-1} characteristic of the alcohol. Disappointingly, further treatment of the mesylate **(65)** in solution in benzene with KOAc (1eq) in presence of 18-crown-6 (1eq) led to the recovery of the mesylate **(65),** even after the reaction mixture was heated at reflux overnight. The same procedure was repeated using DMF as solvent but even after heating the reaction mixture at 150°C over 24 hours no trace of the desired acetate was detected (Scheme 4.34).



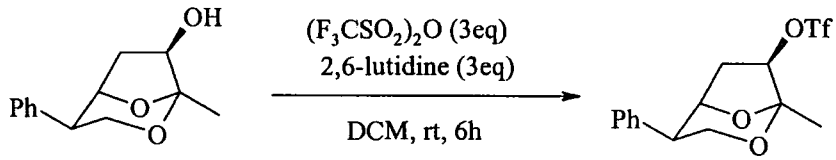
(63) **(65), 98%**

reaction conditions :
i) CH_3SO_2Cl (1.5eq), Et_3N (2eq), DCM, rt, 4h
ii) KOAc (1eq), 18-crown-6 (1eq), benzene, rt and reflux
iii) KOAc (1eq), 18-crown-6 (1eq), DMF, reflux.

Scheme 4.34

Subsequently, attempts were made to explore better nucleophiles. Towards this end, LiOH (2eq) and H_2O_2 (30 wt% in H_2O, 6eq) were added to a solution of mesylate **(65)** in a THF/H_2O mixed solvent (3:1 ratio) at 0°C.[31] The reaction, stirred at 0°C, was followed by GC/MS but no inverted alcohol product was detected. The reaction mixture was then warmed to room temperature and stirred overnight but disappointingly, the GC/MS showed only the presence of the mesylate **(65)**.

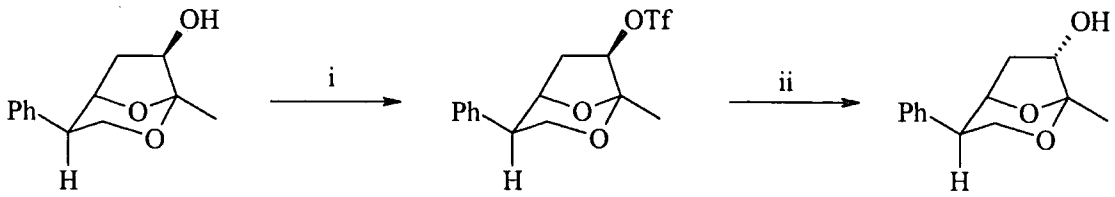
Since all these attempts failed, and realising that the mesylate **(65)** was more stable than anticipated, it was decided to convert the hydroxyl functionality in a better leaving group. Thus, the bicyclic alcohol **(63)** in solution in DCM was treated with trifluoromethane sulfonic anhydride (3eq) in the presence of 2,6-lutidine (3eq) at room temperature. The reaction was followed by TLC and GC/MS and showed complete conversion to the triflate derivative **(66)** after 6 hours (Scheme 4.35). It is worth noting that 2,6-lutidine proved to be a superior base than Et_3N or pyridine. Indeed, initial attempts using Et_3N or pyridine did not show total conversion of the alcohol **(63)** into the triflate derivative **(66)**.



(63) **(66)**

Scheme 4.35

Evidence for the formation of the triflate **(66)** was found in the ^{19}F and ^{13}C NMR spectra with the fluorine signal at -74.78 ppm and the quadruplet at 119.0 ppm corresponding to the CF_3, and confirmed by the IR with the disappearance of the broad OH signal at 3600-3150 cm^{-1} characteristic of the alcohol. After work up and without any further purification, the triflate **(66)** was submitted to LiOH/H_2O_2 treatment following the conditions described above.[31] After 24 hours, no inverted alcohol product was detected and purification by flash chromatography led to poor recovery of the triflate derivative (20%). Eventually, the inverted alcohol was successfully obtained in reasonable yield by treatment of a further sample of the triflate **(66)** with KOH (2eq) in presence of 18-crown-6 in refluxing DMF (Scheme 4.36).

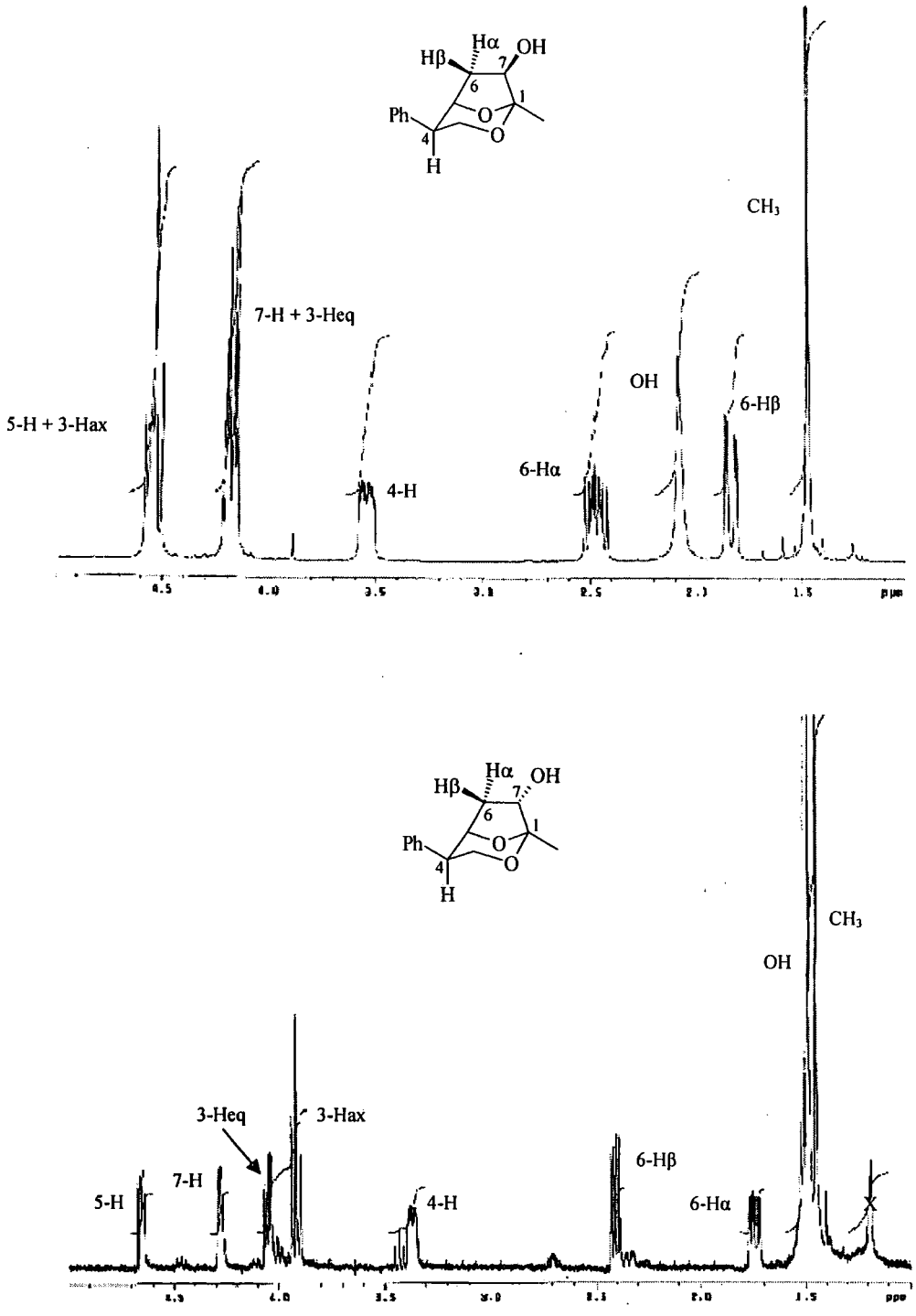


(63) **(66)** **(67)**
60%, 2 steps

i) Tf_2O (3eq), 2,6-lutidine (3eq), DCM, rt, 8h
ii) KOH (2eq), 18-crown-6 (2eq), DMF, reflux, 16h

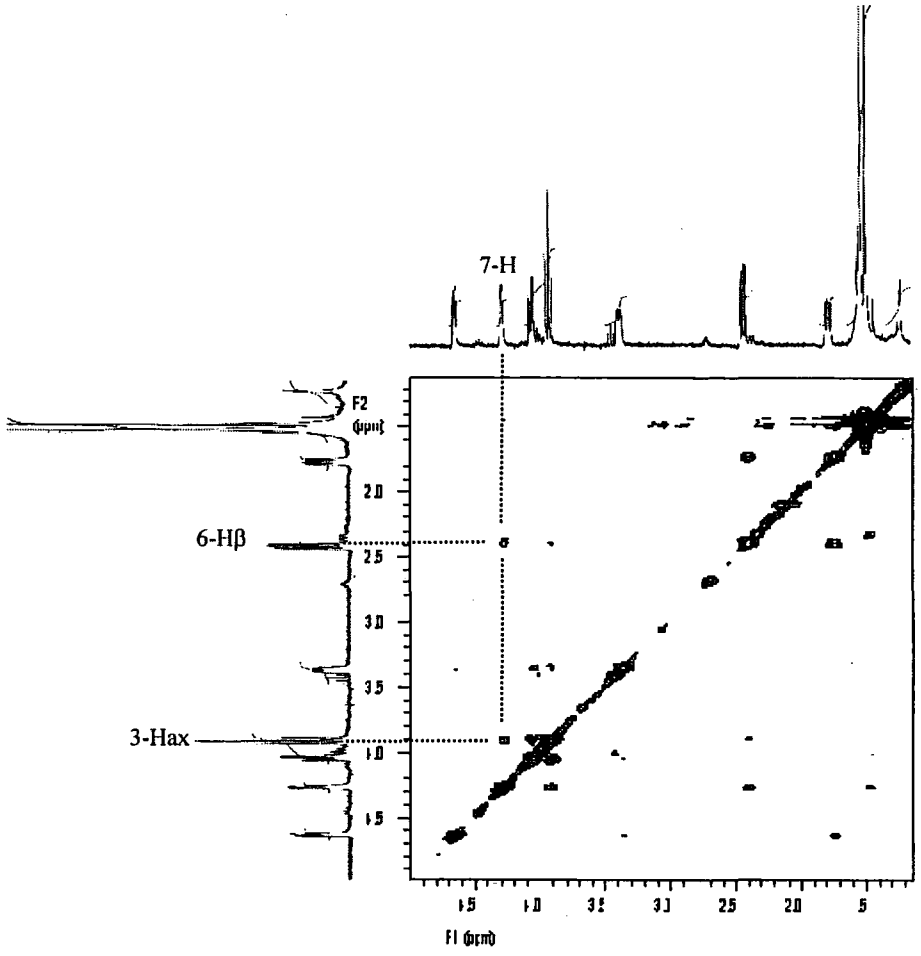
Scheme 4.36

Evidence for the formation of the inverted alcohol was found by comparison of the ^{19}F and ^{13}C NMR spectra of the product **(67)** and the triflate **(66)** which showed the disappearance of the fluorine signal at -74.78 ppm and the quadruplet at 119.0 ppm of the CF_3 replaced by the signal at 75.5 ppm of the 7-CH. Formation of the alcohol was also confirmed by IR with the appearance of a broad OH signal at 3680-3197 cm^{-1}. 2D NMR experiments (COSY, HSQC, HMBC) permitted the assignment of the ^1H spectrum. Comparison of the ^1H NMR spectra of the bicyclic alcohol **(63)** and the product **(67)** showed that they were two different products (Scheme 4.37).


Hα
OH
Hβ
7
6
1
Ph
4
O
O
H
CH3
7-H + 3-Heq
OH
6-Hβ
5-H + 3-Hax
6-Hα
4-H
3-Heq
3-Hax
6-Hβ
7-H
5-H
4-H
6-Hα
CH3
OH

Scheme 4.37

The signals were almost all different with the exception of 4-H and 1-CH_3. nOesy experiments proved that the compound **(67)** was the inverted alcohol by showing a strong nOe between H-7 and H-3ax (Scheme 4.38).



Scheme 4.38

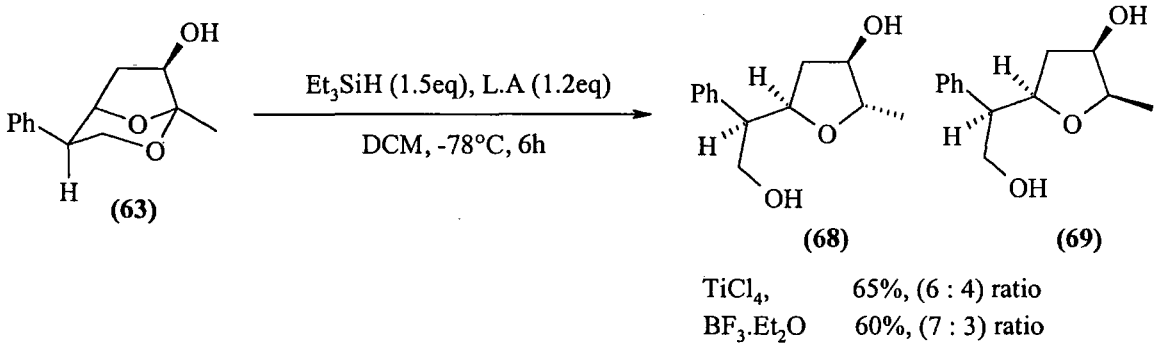
With routes to both diastereoisomers established, attention turned to the reductive cleavage of the bicyclic alcohols.

4.3.3-Reductive cleavage :

4.3.3.1-Reductive cleavage of bicyclic alcohol (63) :

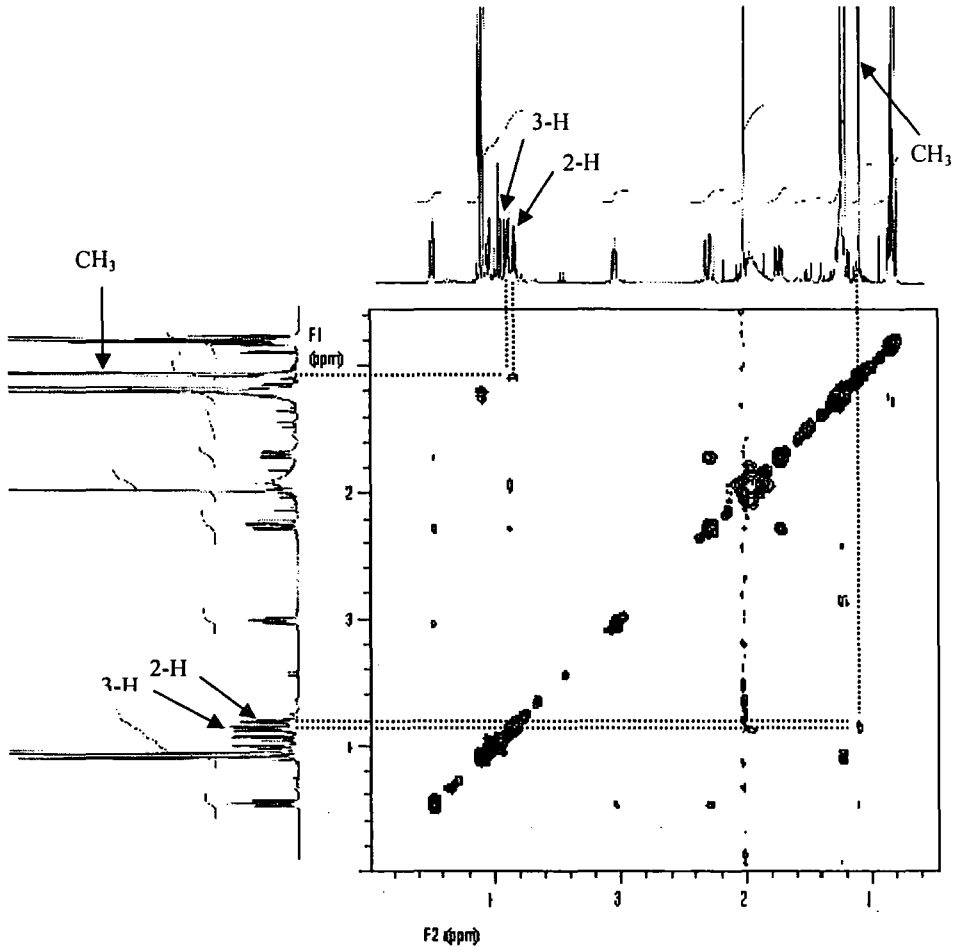
Following Yamamoto, Mori and Ishihara conditions,[20] the bicyclic alcohol **(63)** in solution in DCM was first treated with $TiCl_4$ or $BF_3.Et_2O$ at low temperature (-78°C) for 30 mins followed by the slow addition of Et_3SiH. The reaction mixture was stirred at

-78°C and followed by TLC. After 6 hours, the reaction went to completion and the ^1H NMR of the crude reaction mixture showed formation of two products **(68,69)** in a (6:4) ratio in the case of $TiCl_4$ and in a (7:3) ratio in the case of $BF_3.Et_2O$. The structure and relative stereochemistry of the products were established by a detailed analysis of their NMR data (Scheme 4.39).



Scheme 4.39

Evidence for the formation of the tetrahydrofurans **(68,69)** was found in the ^1H NMR spectrum of the mixture with the methyl signal appearing as a set of 2 doublets due to the coupling of the methyl with H-2 (J~6.5Hz). After full assignment of the ^1H NMR spectrum thanks to COSY experiments, the stereochemistry of the isolated major product **(68)** was determined by nOesy experiments (Scheme 4.40). Unfortunately, it was not possible to isolate the minor isomer **(69)** from the major **(68).**



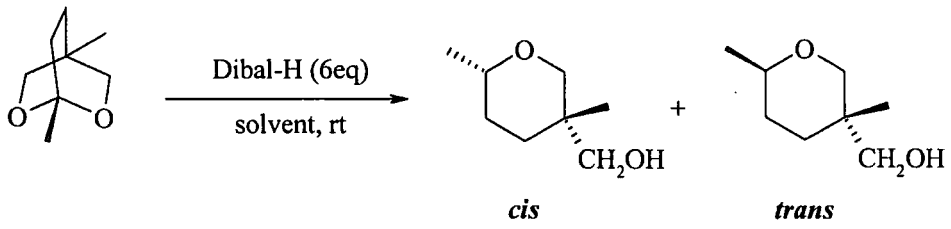
Scheme 4.40

The nOesy showed a strong correlation between the methyl and H-2 but also between the methyl and H-3, which implied that CH_3 and H-3 were on the same side of the molecule. This was confirmed by the absence of correlation between H-2 and H-3.

Surprisingly, the reductive cleavage of the bicyclic alcohol using $TiCl_4$ showed poor selectivity and more surprising the major isomer formed possessed the reverse stereochemistry to the one predicted. Variation of the Lewis acid did not provide a significant enhancement in selectivity.

In the same paper, Yamamoto et al[20] reported that the stereoselectivity of the reductive cleavage using Dibal-H could be affected by the nature of the solvent (Scheme 4.41, Table 4.4). The reaction in non-polar solvents gave the *trans*-alcohol by intramolecular

hydride attack, whereas, the *cis*-alcohol was obtained in polar solvents by hydride attack of a second molecule of Dibal-H on the cationic center of the oxocarbenium ion.



cis *trans*

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

Scheme 4.41, Table 4.4

In view of these results, attempts to control the selectivity through the use of Dibal-H by varying solvent (DCM and THF) and temperature (-78°C and room temperature) were undertaken. The bicyclic alcohol **(63)** in solution in THF or in DCM was treated with Dibal-H (6eq) at room temperature and at -78°C. Disappointingly, the reactions resulted in complicated mixtures that were impossible to purify.

Since these attempts to enhance the stereoselectivity were not successful, it was decided to explore the effect of steric bulk at C7 of the alcohol **(63).** Towards this end, the acetate and TBDMS ether derivatives were prepared.

4.3.3.2-Reductive cleavage of the acetate and TBDMS derivatives :

4.3.3.2.1-Preparation of the acetate and TBDMS derivatives :

a) Acetate formation :

The acetate derivative was formed by successive treatment of the alcohol **(63)** with Et_3N (5eq) and acetic anhydride (10eq) in the presence of a catalytic amount of DMAP (0.1eq) as described in section (4.3.1), Scheme 4.27 (**64**,75%).[26]

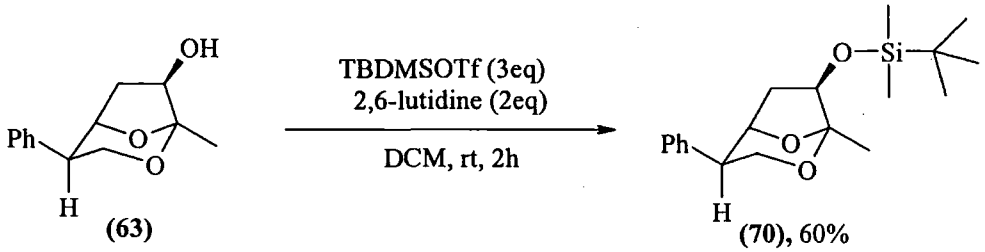
b) Silylation of the bicyclic alcohol (63) :

Attention then turned to finding conditions for the silylation of the alcohol. Protection is normally accomplished using TBDMS chloride in the presence of imidazole.[32] To that

aim, the alcohol **(63)** in solution in DCM was successively treated by TBDMS chloride (1.2eq) and imidazole (1.1eq) at room temperature. The reaction mixture was stirred at that temperature and followed by TLC and GC/MS but no trace of silylated alcohol was found and the starting material was recovered intact even after refluxing the reaction mixture overnight. The same procedure was repeated in THF at room temperature and at reflux but again the attempts was unsuccessful and the starting material was recovered intact.

A literature search into the silylation of hindered alcohols indicated other approaches to this challenging reaction. In 1986, Braish and Fuchs[33] published a method for the protection of hindered alcohols using a KH/18-crown-6 combination with TBDMS chloride. Thus, the alcohol **(63)** in solution in THF was added at 0°C to a suspension of KH (1.1eq) and 18-crown-6 (1 mol%) in THF. After 10 mins, TBDMS chloride (1.2eq) was added and the reaction warmed up to room temperature. The reaction mixture was stirred at room temperature and followed by GC/MS but once more no silylated product was detected.

Corey *et al.*[34] reported that silyl triflates (TIPS-OTf, TBDMS-OTf) showed higher reactivity than the corresponding silyl chlorides in silylation reactions of hindered alcohols. Silyl triflates are the most electrophilic silicon compounds, and thus will react faster with oxygen nucleophiles. In view of these results, the alcohol **(63)** in solution in DCM was treated at room temperature with TBDMS triflate in presence of 2,6-lutidine. In 2 hours, the reaction was complete and the silylated product **(70)** was isolated in 60% yield after purification by flash chromatography (Scheme 4.42).



Scheme 4.42

Evidence for the formation of the silylated product **(70)** was found in the ^1H NMR spectrum with the singlet at 0.95 ppm integrating for the 9 protons of the t-butyl group and the two singlets at 0.10 and 0.12 ppm of the two methyls on the silicon atom. Formation of the silylated alcohol **(70)** was also confirmed by IR with the disappearance of the large band at 3600-3150 cm^{-1}.

Results of the attempts in silylating the alcohol **(63)** are summarised in the following table (Table 4.5).

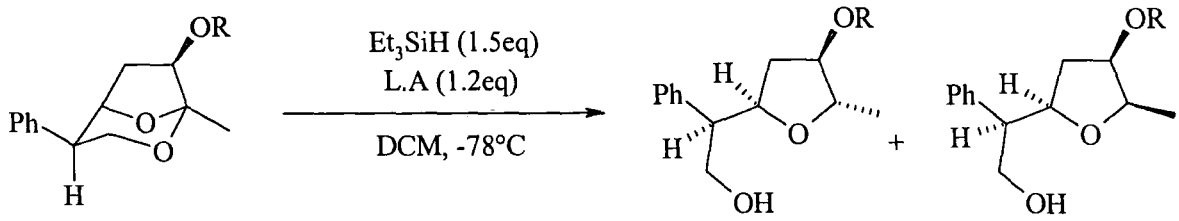
Entry	Reagents (eq)	Solvent	Temp (°C), time (h)	Yield (%)
1	TBDMSCl (1.2eq) Imidazole (1.1eq)	DCM	rt overnight reflux overnight	No reaction
2	TBDMSCl (1.2eq) KH (1.1eq)/18-crown-6 (1mol%)	THF	rt overnight	No reaction
3	TBDMSOTf (3eq) 2,6-lutidine (2eq)	DCM	rt, 2h	60%

Table 4.5

The silylation conditions were not further optimised due to the lack of time, and both the acetate **(64)** and TBDMS derivative **(70)** were submitted to reductive cleavage.

4.3.3.2.2-Reductive cleavage of the acetate and TBDMS derivatives (64,70) :

The acetate and TBDMS ether derivatives **(64,70)** were submitted to reductive cleavage using Et_3SiH and $TiCl_4$ or $BF_3.Et_2O$. The results of that study are summarized below (Scheme 4.43, Table 4.6).



R=H, Ac, TBDMS **(68,71,73)** **(69,72,74)**

Entry	Substrate	Lewis-Acid	Time (h)	Yield (%)	Ratio
1[a]	**(63)**, R=H	$TiCl_4$	6	65	**(68,69)**, (6 : 4)
		$BF_3.Et_2O$	6	60	**(68,69)**, (7 : 3)
2	**(64)**, R=Ac	$TiCl_4$	6	85	**(71,72)**, (6 : 4)
		$BF_3.Et_2O$	8	70	**(71,72)**, (7 : 3)
3	**(70)**, R=TBDMS	$TiCl_4$	8	80	**(73,74)**, (95 : 5)
		$BF_3.Et_2O$	9	70	**(73,74)**, (95 : 5)

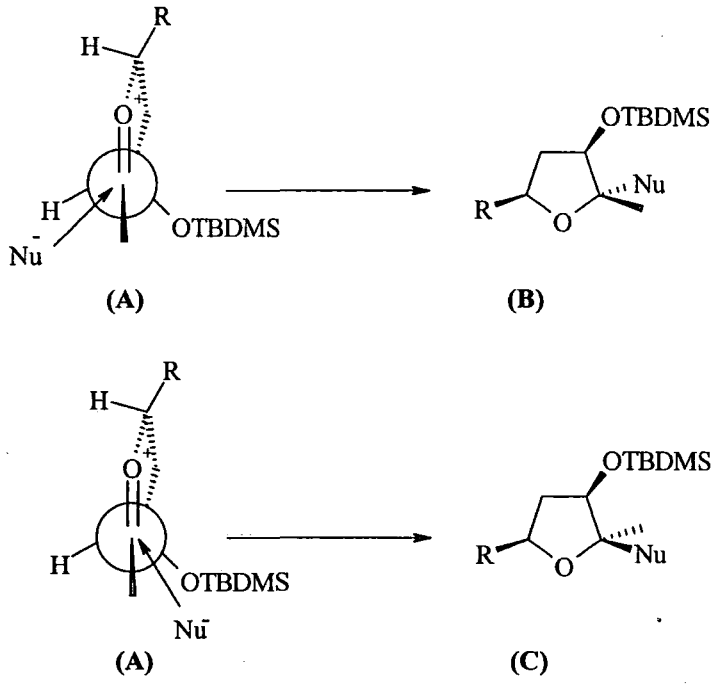
a) entry 1 : results of the reductive cleavage of the alcohol **(63)** given for comparison.

Scheme 4.43, Table 4.6

The ratio of isomers was determined by ^1H NMR and the stereochemistry of the products by nOesy experiments. The major isomers were isolated but none of the minor isomers were obtained pure. The reductive cleavage of the acetate derivative **(64)** gave similar results to that observed with the alcohol **(63)**, but satisfyingly the reductive cleavage of the TBDMS derivative **(70)** was achieved in high yields and good selectivity (70-80 %, 95 : 5).

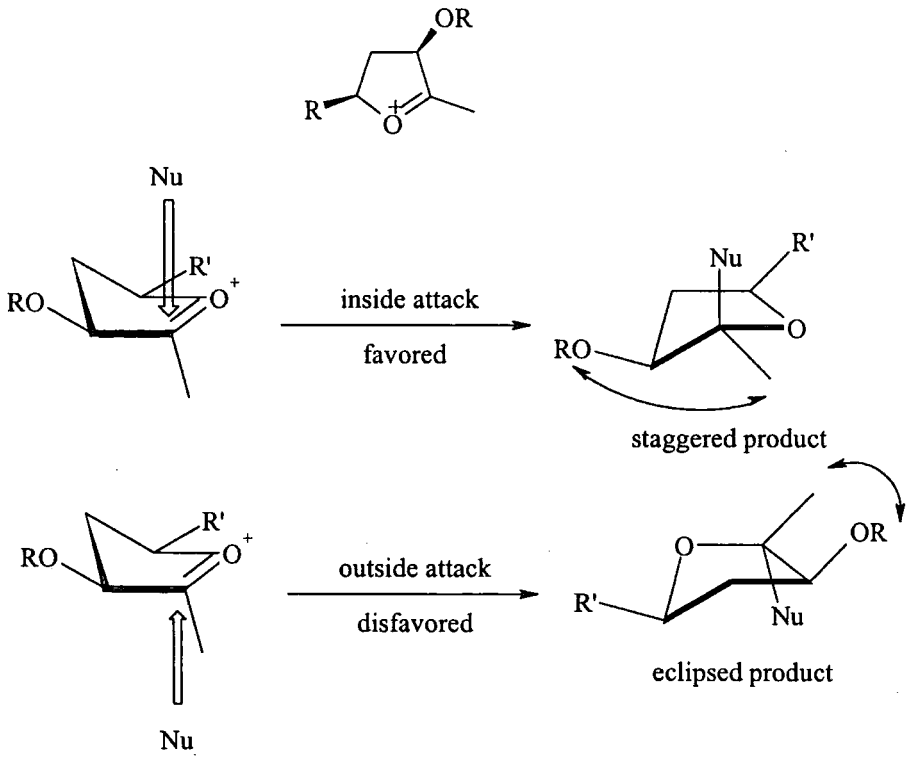
Surprisingly, the stereochemistry of the major isomers **(68,71,73)** was the opposite of the one expected in theory.

Rationalized on the basis of steric effects, the oxocarbenium **(A)** would be the most likely transition state minimizing steric interactions between the bulky OTBDMS group at C3 and R group at C5. The nucleophile (the hydride ion in this case) could either attack from the Si face of the carbonyl and in that case would give the *syn* product **(B)** or attack from the Re face and the *anti* product **(C)** would be formed (Scheme 4.44).



Scheme 4.44

A priori, the nucleophile would have preferred to attack the Si face of the carbonyl, the less sterically hindered one. However, the stereochemistry of the major products obtained corresponds to the attack from the Re face. Therefore, other effects must govern this stereoselectivity. Woerpel has also observed opposite stereoselectivities during the nucleophilic attack of highly substituted five-membered-ring oxocarbenium ions.[35] In 1999, Woerpel introduced a stereoelectronic model to explain the stereoselectivity observed.[36] This model postulates that nucleophilic attack occurs from the "inside" of the preferred envelope conformation of the five-membered-ring oxocarbenium ion to form the product in the lowest energy conformation. Application of this model to our system is illustrated below and explains the stereoselectivity observed (Scheme 4.45).

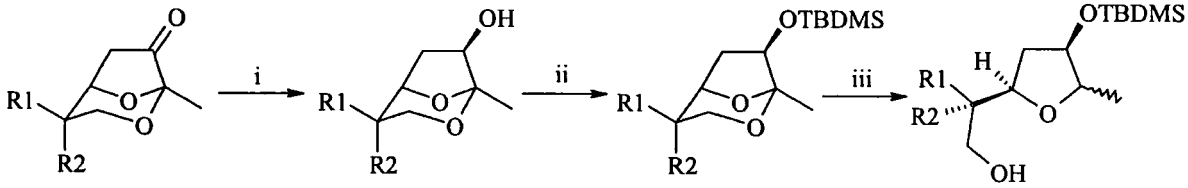


Scheme 4.45

The stereoselectivity towards the formation of the staggered product increases with the bulk of the R group (R=H, (7:3) ratio; R=TBDMS, (95:5) ratio).

4.3.3.3-Preparation and reductive cleavage of TBDMS derivatives of other series :

In view of these results, the remaining bicyclic ketones **(57-60)** were successively submitted to reduction, TBDMS protection and ring opening using the optimum conditions (Scheme 4.46).



Reactions conditions :
i) $NaBH_4$ (1.2eq), MeOH, rt, overnight.
ii) TBDMSOTf (3eq), 2,6-lutidine (2eq), DCM, rt, overnight
iii) Et_3SiH (1.5eq), $BF_3.Et_2O$ (1.2eq), DCM, -78°C, 6-8h

Scheme 4.46

The results of the reduction using $NaBH_4$ in MeOH are summarized in the following table (Table 4.7).

Entry	Ketone	Substituents	Alcohol	Yield (%)
1[a]	**(56)**	R1=Ph, R2=H	**(63)**	87
2[b]	**(57)**	R1=H, R2=Ph	**(75)**	N/A
3	**(58)**	R1=$PhCH_2$, R2=H	**(76)**	70
4	**(59)**	R1=*p*-$NO_2C_6H_4$, R2=H	**(77)**	84
5	**(60)**	R1=H, R2=*p*-$NO_2C_6H_4$	**(78)**	87

a) Result of the reduction of the ketone **(56)** given for comparison.
b) The ketone **(57)** was not pure (inseparable mixture with a by-product);its reduction led to an inseperable mixture of the alcohol **(75)** with an unknown product.

Table 4.7

The alcohols **(63,76-78)** were obtained in good yields. Again, the reduction of the ketone afforded the alcohol as a single diastereoisomer.

The alcohols **(63,76-78)** were then silylated. The results of the protection are summarized in the following table (Table 4.8).

Entry	Alcohol	Substituents	TBDMS ether	Yield (%)
1[a]	**(63)**	R1=Ph, R2=H	**(70)**	60
2	**(76)**	R1=$PhCH_2$, R2=H	**(79)**	85
3	**(77)**	R1=*p*-$NO_2C_6H_4$, R2=H	**(80)**	65
4	**(78)**	R1=H, R2=*p*-$NO_2C_6H_4$	**(81)**	60

a) Result of the silylation of the alcohol **(63)** given for comparison.
The alcohol (R1=H, R2=Ph, **75**) has not been isolated and therefore has not been silylated.

Table 4.8

Finally, the TBDMS ethers **(79-81)** were submitted to reductive cleavage through treatment with the $Et_3SiH/BF_3.Et_2O$ combination. The yield and ratio of the tetrahydrofurans formed are summarized in the following table (Table 4.9).

TBDMS ether	Substituents	THFs	Yield (%)	Ratio[b]
(70)[a]	R1=Ph, R2=H	**(73,74)**	70	95 : 5
(79)	R1=$PhCH_2$, R2=H	**(82,83)**	80	95 : 5
(80)	R1=*p*-$NO_2C_6H_4$, R2=H	**(84,85)**	79	97 : 3
(81)	R1=H, R2=*p*-$NO_2C_6H_4$	**(86,87)**	86	99 : 1

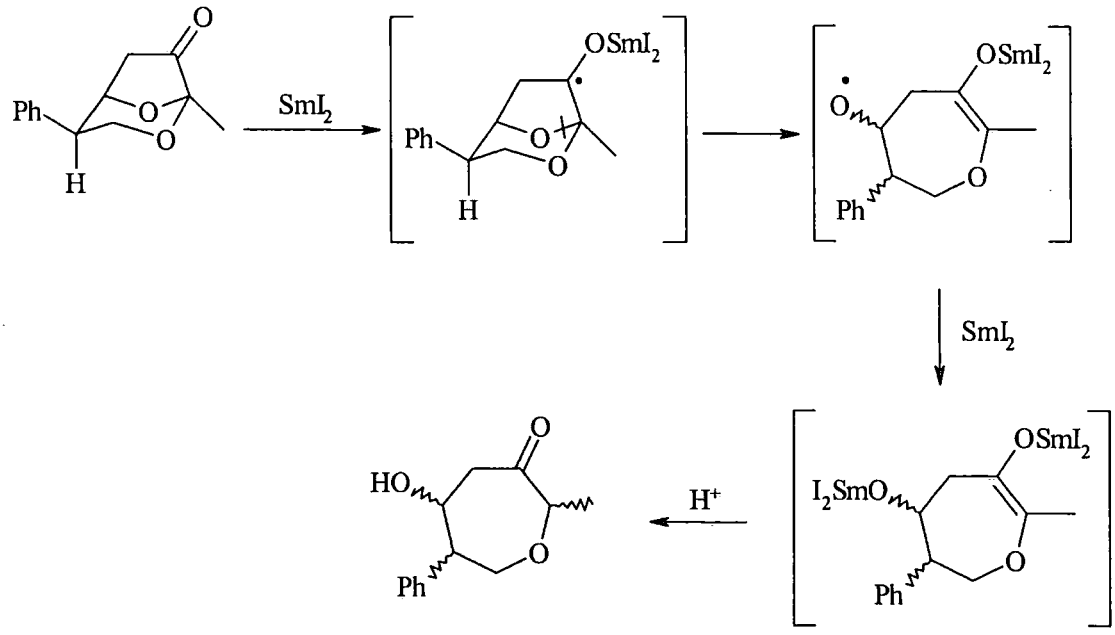
a) Result of the reductive cleavage of the silyl ether **(70)**, for comparison.
b) The ratio of isomers was determined by ^1H NMR spectroscopy. Assignments of the major and minor peaks were made by nOesy experiments

Table 4.9

In all the cases, the reductive cleavage of the TBDMS ethers led to 2,3,5-trisubstituted tetrahydrofurans with good yields and good stereoselectivity.

4.4-Reductive cleavage attempt using SmI_2 :

During the study of the reductive cleavage using $Et_3SiH/TiCl_4$ or $BF_3.OEt_2$, some experiments were carried out in parallel. SmI_2 is a powerful one-electron reducing agent, which has been used for the reduction of carbonyl compounds. Ring opening of cyclic ethers with $SmI_2/BF_3.OEt_2$/HMPA in benzene have been reported[37] as well as the regioselective radical ring-opening of bicyclo[4.2.0]octan-2-ones.[38] The reaction is usually carried out in the presence of a proton donor, such as alcohols or water, in THF as solvent. HMPA is generally used as co-solvent to increase the rate of the reaction. Honda and Katoh[39] have reported that the combination of SmI_2 and trimethylsilyl chloride in THF-HMPA accelerate the reduction of sterically hindered ketones. In view of these precedents, it was decided to submit the bicyclic ketone **(56)** to treatment with SmI_2 (3eq), Me_3SiCl (3eq), THF (solvent)/HMPA (5% v/v_{total}). The reaction led to a complex mixture. However, after purification by chromatography, a sample containing a mixture of two isomers in (60/40) ratio, which were not the 5-membered ring products as ascertained by GC, was also isolated (see appendix E). Unfortunately, elucidation of the structure of these products was not possible due to the small amount of sample for a full characterization and lack of time to repeat the reaction in a larger scale. Ring opening of the C1-O8 bond might have happened leading to the formation of 7-membered ring products (Scheme 4.47).



Scheme 4.47

This is speculation, as the structure of the products has not been determined. There is also no reason why the C1-O8 bond will break rather than the C1-O2 one. The reaction needs to be repeated and conditions to be optimized.

4.5-Conclusion :

The stereoselective preparation of 2,3,5-trisubstituted-tetrahydrofurans, by Lewis-acid-mediated reductive cleavage of bicyclic acetal templates, was achieved in good yields and good selectivity. The reaction proceeded *via* an oxocarbenium ion, on which nucleophilic attack followed the "inside attack" model of Woerpel. The Et_3SiH/L.A combination proved to be an efficient system for the reductive cleavage. $TiCl_4$ and $BF_3.OEt_2$ gave similar results (Table 4.6); surprisingly attempts to ring open the bicyclic core using Dibal-H led to a complex mixture, from which no product has been isolated. The stereoselectivity increased with the size of the OR group in C-3 position (Table 4.6). The electronic nature of the aryl group showed little effect on the stereochemistry of the reductive cleavage (Table 4.9).

4.6-References :

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CHAPTER V: CONCLUSIONS AND FUTURE WORK

5.1-General Conclusion :

The research described in this thesis has involved the development of a methodology for the stereoselective synthesis of highly functionalized tetrahydrofurans.

2,3-*trans*-3,5-*cis*-tetrahydrofurans were obtained by stereoselective reductive cleavage of O,O-bicyclic ketone acetals in high yields upon Et_3SiH/L.A treatment. Stereoselectivity increased with the size of the OR group at C-7.

The bicyclic ketone acetals were prepared by diazodecomposition of the corresponding O,O-diazoketone acetals upon treatment with rhodium(II) acetate. The metallocarbene intermediates regioselectively inserted into the C-H bonds α to the oxygen leading to a racemic mixture of bicyclic ketones. Optimum conditions for the C-H insertion process have been determined by variation of several parameters of the reaction such as concentration of diazoketone and catalyst, rate of addition, temperature, catalyst (metal/ligands combination) and catalyst loading. A variety of bicyclic ketones were prepared in moderate but reproducible yields.

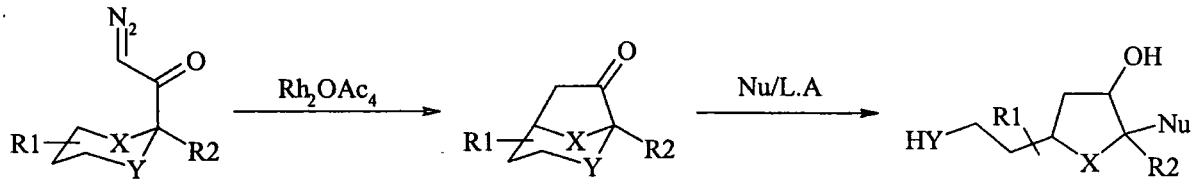
The diazoketones were prepared in good yield (70-85%) from the corresponding acid acetals by acylation of diazomethane, which necessitated the initial activation of the acid group into an anhydride. Two alternative methods for the synthesis of diazoketones were examined. TMS diazomethane, a safe substitute for diazomethane, led to the formation of the diazoketones, but in poor yield (13%). A diazotransfer method was then examined. This was an attractive method, as it would lead to the formation of the diazoketones in only two steps. Disappointingly, after having successfully overcome problems of dimerization encountered during the preparation of the necessary methyl ketone acetal precursors, the diazotransfer proceeded in moderate yield (40%).

O,O-diazoketone acetals were prepared from the corresponding acid acetals. Two routes for the synthesis of these acid acetals were examined. The first route was a one-pot process involving the treatment of 1,3- and 2,2-disubstituted-propane-1,3-diols with pyruvic acid. Acid acetals were obtained in low yields (30-38%) despite much experimentation modifying solvent and catalyst. The second route was a two-step process involving the hydrolysis of pyruvate ester acetals prepared by ketalisation of 2-arylpropane-1,3-diols with methyl pyruvate. Anomeric control provided preferential formation of compounds with the ester group in axial position. Acid acetals were obtained in good overall yields (~75% after 2 steps).

Initial studies encountered problems of isolation of the C-H insertion products due to their volatility and lack of chromophoric groups. 2-Aryl-propane-1,3-diols with electron-withdrawing and electron-donating groups were prepared, which allowed us to explore the electronic effect of the substituents on both C-H insertion and reductive cleavage processes.

5.2-Future work :

In future, this procedure could be applied for the synthesis of a variety of highly functionalized 5-membered ring heterocycles (Scheme 5.1).



X=Y=O,N,S
X≠Y : O,N or S
R1,R2=alkyl, aryl

Scheme 5.1

By the preparation of O,O-, N,N- or S,S-diazoketone acetals or mixed acetals and varying both R1 and R2 groups, synthesis of bicyclic natural products and synthesis of functionalized 5-membered ring heterocycles of both natural and unnatural origin could be achieved.

It is worth noting that the reductive cleavage of the bicyclic ketones upon Et_3SiH/L.A treatment afforded exclusively tetrahydrofurans; however, their reductive cleavage could also provide access to oxygen containing 7-membered rings. During the study of the reductive cleavage step, we have run some experiments using SmI_2, which resulted to the isolation of products (in low yield) which were not the 2,3-*trans*-3,5-*cis*-tetrahydrofurans. Unfortunately elucidation of the product structures was not possible. Further studies are needed. SmI_2 might provide an entry to 7-membered ring heterocycles.

CHAPTER VI:
EXPERIMENTAL PROCEDURES

6.1- General procedures :

All solvents were dried and distilled by standard procedures[1] and stored under nitrogen before use.

- THF and ether were distilled over sodium / benzophenone
- Benzene and dichloromethane were distilled over calcium hydride
- Toluene was distilled over sodium.

Petroleum ether (Petrol) was distilled and fractions collected corresponding to a boiling point of 40-60°C

All sensitive reactions were performed under an inert atmosphere and oven-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 sprays or stains (e.g : phosphomolybdic acid in ethanol, vanilin) and revealed by heating (heat-gun) or followed by Gas Chromatography (GC) carried out on a Hewlett-Packard 5890 series II gas chromatograph fitted with a 25 cm column and connected to a flame ionisation detector.

Purification of the products was performed by flash column chromatography with normal phase silica gel (Kieselger 40-60 μm silica), unless otherwise stated, using an appropriate choice of eluant (or solvent system).

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

^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$, unless otherwise stated, on a Varian Mercury 200 (^{1}H at 199.975 MHz, ^{13}C at 50.289 MHz, ^{19}F at 282.2 MHz), Brucker AM-250 (^{1}H at 250.133 MHz, ^{13}C at 62.896 MHz), Varian Unity 300 (^{1}H at 299.908 MHz, ^{13}C

1/ Perrin, D.D.; Armarego, W. L. F. in *Purification of Laboratory Chemicals*, 3rd edition **1988**, Butterworth-Heinemann Ltd. Oxford.

at 75.412 MHz, ^{19}F at 376 MHz) or Varian VXR-400 (^{1}H 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 :

$CHCl_3$ $\delta_H = 7.26$ ppm ; $\delta_C = 77.0$ ppm

CH_3OH $\delta_H = 3.41$ ppm, 1.09 ppm ; $\delta_C = 49.9$ ppm

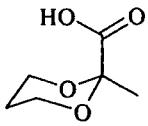
Assignment and determination of stereochemistry were realised using DEPT, COSY, HSQC, HMBC and NOESY experiments.

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

Gas-Chromatography Mass Spectra (GC-MS : EI, CI) 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 a micromass LCT Mass Spectrometer. High-resolution mass spectra (HRMS) were performed on a Micromass Autospec Mass Spectrometer by Durham University Mass Spectrometry service.

6.2-Experimental details:

2-Carboxy-2-methyl-1,3-dioxane (4) :[2]



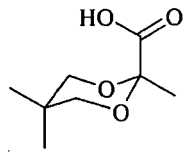
Pyruvic acid (10 g, 0.113 mol) and 1,3-propanediol (12.3 ml, 0.170 mol, 1.5 eq.) were dissolved in benzene (100 ml). Dowex 50WX8-200, acid-ion exchange resin (2 g, ~10 mol%), was then added as catalyst. The mixture was heated at reflux overnight using a Dean-Stark trap to collect the water formed during the reaction. After cooling to room temperature, the reaction mixture was filtered in order to remove the catalyst and then concentrated by rotary evaporation. The resulting residue was dissolved in a 3M aqueous

2/ Wardrop, D. J.; Velter, A. I.; Forslund, R. E. *Org.Lett.* **2001**, 3, 2261.

NaOH solution until basic (pH 10). The reaction mixture was then heated at reflux for 2h, cooled to 0°C and acidified carefully in cold conditions with cold 5M aqueous HCl (pH 1) and quickly extracted with EtOAc (3×25 ml). The combined organic extracts were then dried over $MgSO_4$, concentrated *in vacuo* and the resulting residue recrystallised from petrol with a small amount of EtOAc to give **(4)** as a white solid. (5.81 g, 35%).

mp : 94-95°C *(lit.[2] 94-95°C)*. ν_{max} (KBr disc) : 3600-3100 (CO***OH***), 1730 (***C=O***) cm^{-1}. δ_H (300 MHz): 8.5 (1H, s, ***OH***); 4.1-4.0 (2H, m, ***4-H,6-H***), 4.0-3.9 (2H, m, ***4-H,6-H***), 2.2-2.0 (2H, m, 2×***5-H***), 1.54 (3H, s, CH_3). δ_C (75.4 MHz) : 175.3 (*C*OOH), 98.1 (***C-2***), 63.2 (***C-4,C-6***), 25.9 (CH_3), 24.6 (***C-5***). *m/z* (ES^+) : 169.1 ($M+Na^+$, 100%).

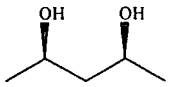
2-Carboxy-2,5,5-trimethyl-1,3-dioxane (5) :[2]



Following the same procedure as described for the acetal **(4)**, the 5,5-dimethyl analogue **(5)** was prepared from pyruvic acid (10 g, 0.113 mol) and 2,2-dimethyl-1,3-propanediol (17.8 g, 0.170 mol, 1.5 eq.) dissolved in benzene (100 ml) using Dowex 50WX8-200, acid ion exchange resin, (2 g, ~10 mol %). After the same acid-base treatment described above, the combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and the resulting residue recrystallised from petrol to give **(5)** as a white solid. (7.51 g, 38%).

m.p : 115-116°C *(lit.[2] 115-116°C)*. ν_{max} (KBr disc) : 3600-3000 (CO***OH***), 1715 (***C=O***) cm^{-1}. δ_H (250 MHz) : 9.2 (1H, s, ***OH***), 3.56 (4H, m, 2×***4-H***, 2×***6-H***), 1.60 (3H, s, ***2-CH_3***), 1.20 (3H, s, ***5-CH_3***), 0.75 (3H, s, ***5-CH_3***). δ_C (62.9 MHz) : 174.8 (*C*OOH), 97.8 (***C-2***), 73.5 (***C-4,C-6***), 29.4 (***C-5***), 25.5 (***CH_3-2***), 22.5 and 21.8 (2×***CH_3-5***). *m/z* (ES^+) : 197.1 ($M+Na^+$, 100%).

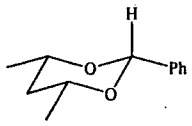
***Meso*-2,4-pentanediol (6) :**[3]



To a solution of 2,4-pentanedione (10.3 ml, 100 mmol) in anhydrous CH_2Cl_2 (100 ml), $TiCl_4$ (1M solution in CH_2Cl_2) (110 ml, 110 mmol, 1.1 eq.) was added at room temperature under argon atmosphere. The reaction was cooled to -30°C, using a cryocooler, pyridine (0.81 ml, 10 mmol, 0.1 eq.) was added and the mixture stirred for 30 min. The reaction mixture was then cooled to -78°C and a solution of BH_3-pyridine complex (40.4 ml, 400 mmol, 4 eq.) in CH_2Cl_2 (100 ml), precooled to -78°C, was slowly added *via* a cannula. After 2h, the reaction mixture was quenched with 1M aqueous HCl and the mixture left to stir overnight. After a continuous extraction [CH_2Cl_2/H_2O], and after removing the solvent, the resulting organic extract was dissolved in THF and submitted to hydrogen peroxide treatment in a basic medium. To that aim, 1eq. of 3M aqueous NaOH (33.3 ml, 100 mmol) was added and the reaction mixture refluxed for 2h. The mixture was then cooled to 0°C with an ice-bath and 2.5 eq. of H_2O_2 solution 35 % w/w (26.4 ml, 0.25 mol) were added. The mixture was then refluxed overnight. A continuous extraction [CH_2Cl_2/H_2O] followed by a distillation using a Kugelrhor apparatus (50-100°C/8×10^{-1}mbar) gave the pure diol as a colorless oil **(6)** (3.12 g, 30%).

ν_{max} (ATR) : (*lit.*[4]) 3350-3010 (***OH***), 1378, 1134, 1049, 931, 833. δ_H (CD_3OD, 250 MHz) : 4.0-3.9 (2H, m, ***2-H,4-H***), 3.4 (2H, s, 2×***OH***), 1.7-1.4 (2H, m, 2×***3-H***), 1.2 (6H, d, J= 6.1 Hz, 2×$\boldsymbol{CH_3}$). δ_C (CD_3OD, 62.9 MHz) : 69.3 (***C-2,C-4***), 46.6 (***C-3***), 24.4 (***C-1***, ***C-5***). *m/z* (ES^+) : 127.1 ($M+Na^+$, 100%).

2-Phenyl-4,6-dimethyl-1,3-dioxane (7) :[3c]

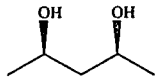


3a/ Bonner, L.; Frescas, S.; Nichols, D. E. *Synth.Commun.* **2004**, 34, 2767.
b/ Gordillo, B.; Hernandez, J. *Org.Prep.Proc.Int.* **1997**, 29, 195.
c/ Denmark, S. E., Almstead, N. G. *J.Am.Chem.Soc.* **1991**, 113, 8089.
4/ Ikeda, H.; Sato, E.; Sugai, T.; Ohta, H. *Tetrahedron* **1996**, 52, 8113.

A solution of benzaldehyde (4.4 ml, 43.3 mmol, 0.45 eq), a mixture of *meso/d,l*-2,4-pentanediol (50/50) (10g, 96.1 mmol) and *p*-toluene sulfonic acid monohydrate (1.83 g, 9.61 mmol, 10 mol %) in dry benzene (250 ml) was heated at reflux overnight using a Dean-Stark trap. After cooling, the reaction mixture was washed with aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The isomers were separated by chromatography (Hexane/Et_2O : 98/2) to give *meso* acetal **(7)** as a colorless oil (7.06 g, 40%).

δ_H (250 MHz) : 7.6-7.5 (2H, m, ***Ar-H***), 7.40-7.30 (3H, m, ***Ar-H***), 5.50 (1H, s, ***2-H***) (*lit.*[5] *5.49 (1H, s)*), 4.00-3.90 (2H, qdd, J= 12.4, 7.2, 2.5 Hz, ***4-H,6-H***), 1.60 (1H, m, ***5-H***), 1.40 (1H, m, ***5-H***), 1.35 (6H, d, J= 6.2 Hz, ***4- CH_3,6-CH_3***). δ_C (62.9 MHz) : 139.1 (***C-1'***), 128.9, 128.5, 126.5 (2×***C-2'***,2×***C-3'***,***C-4'***), 101.2 (***C-2***), 73.2 (***C-4,C-6***), 40.6 (***C-5***), 21.9 (***CH_3-4,CH_3-6***). *m/z* (ES^+) : 215.1 ($M+Na^+$, 100%).

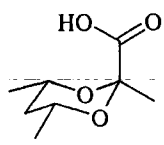
Meso-2,4-pentanediol (6) :[3c]



To a solution of meso acetal **(7)** (7.06 g, 36.8 mmol) in solution in MeOH (70 ml), Pd/C (204.3 mg, 5 mol%) and 16 drops of concentrated H_2SO_4 were added. The suspension was stirred overnight at room temperature under 1 atm of H_2. The reaction mixture was filtered through a plug of celite and concentrated *in vacuo*. Distillation using a Kugelrhor apparatus (50-100°C/8×10^{-1}mbar) gave pure diol **(6)** (2.7 g, 70%).

Analytical data were identical in all respects with that obtained from Bartoli procedure above in which the diol was prepared by reduction of the corresponding dione.

2-Carboxy-2,4,6-trimethyl-1,3-dioxane (9) :[2]

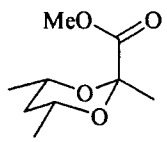


5/ Kurihara, M.; Hakamata, W. *J.Org.Chem.* **2003**, 68, 3413.

Following the same procedure as described for the acetal **(4)**, the acetal **(9)** was prepared from pyruvic acid (0.28 g, 3.2 mmol) and *meso*-2,4-pentanediol **(6)** (0.5 g, 4.8 mmol, 1.5 eq.) dissolved in benzene (10 ml) using Dowex 50WX8-200 (56 mg, ~10 mol%) as catalyst. After an identical acid-base treatment, the combined organic extracts were then dried over $MgSO_4$, concentrated *in vacuo* and the resulting residue recrystallised to give **(9)** as a white solid (0.18 g, 32%).

m.p : 117-118 °C *(lit.[2] 117-118°C)*. ν_{max} (KBr disc) : 3400-3000 (CO***OH***), 1735 (***C=O***) cm^{-1}. δ_H (250 MHz) : 8.2 ppm (1H, s, COO***H***), 4.0-3.8 (2H, m, ***4-H,6-H***), 1.7-1.5 (2H, m, 2×***5-H***), 1.58 (3H, s, ***2-CH$_3$***), 1.23 (6H, d, J= 6.2 Hz, ***4-CH$_3$,6-CH$_3$***). δ_C (62.9 MHz) : 175.7 (***CO***), 98.4 (***C-2***), 69.1 (***C-4,C-6***), 39.1 (***C-5***), 26.5 (***CH$_3$-2***), 21.6 (***CH$_3$-4, CH$_3$-6***). *m/z* (ES^+) : 197.1 ($M+Na^+$, 100%).

2-Carboxymethyl-2,4,6-trimethyl-1,3-dioxane (10) :[2]

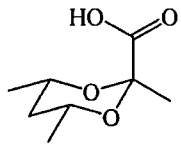


To a stirred solution of *meso*-2,4-pentanediol **(6)** (0.4 g, 3.85 mmol) and methyl pyruvate (0.70 ml, 7.7 mmol, 2 eq) in CH_3CN, $BF_3.OEt_2$ (0.95 ml, 7.7 mmol, 2 eq) was added dropwise at room temperature and the reaction mixture stirred overnight. The reaction was then quenched with saturated aqueous sodium bicarbonate and stirred for 20 min. The resulting mixture was concentrated under reduced pressure to 1/3 of its original volume and then extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (Petrol/EtOAc : 1/1) to provide **(10)** as an yellow oil (0.62 g, 85%).

ν_{max} (film) : 3100, 2950, 2875, 1746 (***C=O***) *(lit.[2] 1744 cm^{-1})*, 1475, 1375, 1015, 880, 807, 670 cm^{-1}. δ_H (250 MHz) : 3.85-3.75 (2H, m, ***4-H,6-H***), 3.77 (3H, s, O***CH$_3$***), 1.50 (3H, s, ***2-CH$_3$***), 1.46-1.44 (1H, m, ***5-H***), 1.24-1.22 (1H, m, ***5-H***), 1.20 (6H, d, J= 6.2 Hz, ***4-***

CH₃,6-CH₃). δ_C (62.9 MHz) : 171.8 (***C***OOMe), 98.8 (***C-2***), 68.9 (***C-4,C-6***), 52.4 (O***CH₃***), 39.4 (***C-5***), 26.7 (***CH₃-2***), 21.6 (***CH₃-4, CH₃-6***). *m/z* (ES^+) : 211.1 ($M+Na^+$, 100%).

2-Carboxy-2,4,6-trimethyl-1,3-dioxane (9) :[2]



To a solution of ester **(10)** (0.62 g, 3.3 mmol) in a mixture of THF/H_2O (1:1) was added a 3M aqueous NaOH (4.95 ml, 15 mmol, 4.5 eq). The reaction mixture was stirred at room temperature overnight. After cooling to 0°C, the reaction mixture was then acidified to pH 1 with ice cold 5M aqueous HCl and quickly extracted with EtOAc (5×20 ml). The combined organic extracts were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The recrystallisation from cyclohexane gave **(9)** as white crystals. (0.51 g, 86%). Analytical data were identical in all respects with that obtained from the Newman and Chen procedure.[6]

Non ethanolic diazomethane preparation :

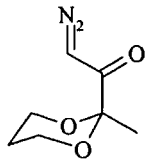
CAUTION : EXPLOSIVE ! USE NON GROUND GLASS JOINTED APPARATUS.

N-methyl-N-nitroso-*p*-toluene sulphonamide, Diazald® (10 g, 46.7 mmol) was dissolved in ether (60 ml) and slowly dripped into a solution of potassium hydroxide (2.8 g, 50 mmol), di(ethyleneglycol)methylether (16.4 ml, 140 mmol), ether (4.7 ml) and water (4.7 ml) at 60°C. The diazomethane was distilled over as an ethereal solution. Additional ether (20 ml) was then added at the previous rate until the distillate was colorless. The diazomethane solution was then stored in the fridge protected from direct sunlight or strong artificial light.

N.B : literature[7] reports the yield as 70%, so 46.7 mmol of Diazald gives 32.7 mmol of diazomethane in ~100 ml of ether.

6/ Newman, M. S.; Chen, C. H. *J.Org.Chem.* **1973**, 38, 1173.
7/ De Boer, T. J.; Backer, H. *J. Org.Synth.* 1963, Coll.Vol.4, 250.

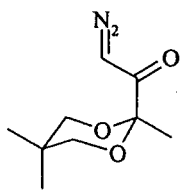
2-Diazoacetyl-2-methyl-1,3-dioxane (11) :[2]



Acid **(4)** (1 g, 6.8 mmol) and Et_3N (1.44 ml, 10.3 mmol, 1.5 eq) were dissolved in anhydrous THF (70 ml) and cooled to -15°C. Ethyl chloroformate (0.72 ml, 7.5 mmol, 1.1 eq) was added dropwise *via* syringe at a rate such that the temperature was maintained at -15°C. The reaction was stirred at this temperature until all the acid had been converted (~2h, TLC). An excess of an ethereal solution of diazomethane was added *via* syringe and the reaction mixture was stirred at -5°C and followed by TLC. When the reaction was complete, argon was bubbled through the solution with vigorous stirring to remove the excess diazomethane and a small amount of dilute ethanoic acid was added. The resulting mixture was then extracted with EtOAc and the combined organic extracts washed with ammonium chloride (NH_4Cl), sodium bicarbonate ($NaHCO_3$) and brine (NaCl), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by chromatography (EtOAc/Petrol : 1/1) to provide **(11)** as a yellow oil (0.87 g, 75%).

ν_{max} (thin film) : 3100, 2969, 2873, 2108 (***C*=*N*=*N***), 1640 (***CO***CHN_2) *(lit.*[2] *1635 cm*$^{-1}$*)*, 1341 cm^{-1}. δ_H (250 MHz) : 5.72 (1H, s, ***CH***N_2), 3.96-3.83 (4H, m, 2×***4-H,*** 2×***6-H***), 2.07-2.00 (2H, m, 2×***5-H***), 1.42 (3H, s, ***2-CH***$_3$). δ_C (62.9 MHz) : 194.1 (***CO***), 100.2 (***C-2***), 62.7 (***C-4,C-6***), 53.8 (***CH***N_2), 25.9 (***CH***$_3$***-2***), 24.6 (***C-5***). *m/z* (ES^+) : 193.1 ($M+Na^+$, 100%).

2-Diazoacetyl-2,5,5-trimethyl-1,3-dioxane (12) :[2]

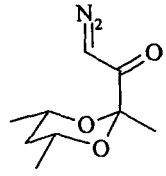


Following the same procedure as described for the preparation of the diazoketone **(11)**, the 5,5-dimethyl analogue **(12)** was prepared from acid **(5)** (1.0 g, 5.7 mmol) and Et_3N

(1.20 ml, 8.6 mmol, 1.5 eq) in anhydrous THF (70 ml), cooled to -15°C. Ethylchloroformate (0.60 ml, 6.3 mmol, 1.1 eq) was added dropwise *via* syringe. When the reaction was complete, an excess of an ethereal solution of diazomethane was added dropwise via a syringe and the reaction was stirred at -5°C. After an identical work-up, the resulting residue was purified by chromatography (EtOAc/Petrol : 1/1) to provide **(12)** as a yellow oil (0.89 g, 79%).

ν_{max} (thin film) : 2958, 2872, 2110 (***C=N=N***) (*lit.*[2] *2106 cm^{-1}*), 1637 (***CO***CHN_2) (*lit.*[2] *1645 cm^{-1}*), 1474 cm^{-1}. δ_H (250 MHz) : 5.70 (1H, s, ***CH***N_2), 3.45 (4H, m, 2×***4-H,*** 2×***6-H***), 1.40 (3H, s, ***2-CH$_3$***), 1.10 (3H, s, ***5-CH$_3$***), 0.70 (3H, s, ***5-CH$_3$***). δ_C (62.9 MHz) : 194.3 (***CO***), 100.1 (***C-2***), 72.9 (***C-4,C-6***), 53.5 (***CH***N_2), 29.4 (***C-5***), 25.4 (***CH$_3$-2***), 22.3 (***CH$_3$-5***), 21.7 (***CH$_3$-5***). *m/z* (ES^+) : 221.2 ($M+Na^+$, 100%).

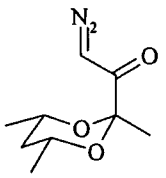
2-Diazoacetyl-2,4,6-trimethyl-1,3-dioxane (13) :[2]



Following the same procedure, a solution of acid **(9)** (0.17 g, 0.98 mmol) and Et_3N (0.20 ml, 1.47 mmol, 1.5 eq) in anhydrous THF (10 ml) was treated with ethyl chloroformate (0.10 ml, 1.08 mmol, 1.1 eq) followed by the addition of an excess of an ethereal solution of diazomethane. After an identical work-up, the resulting residue was purified by chromatography (EtOAc/Petrol : 1/1) to provide **(13)** as a yellow oil (0.12 g, 62%)

ν_{max} (thin film) : 3100; 2957; 2914; 2108 (***C=N=N***), 1645 (***CO***CHN_2) *(lit.*[2] *1646 cm^{-1})* cm^{-1}. δ_H (250 MHz) : 5.6 (1H, s, ***CH***N_2); 3.8-3.7 (2H, m, ***4-CH,6-CH***), 1.4 (1H, s, ***2-CH$_3$***), 1.3-1.2 (2H, m, 2×***5-H***), 1.1 (d, 6H, ***4-CH$_3$,6-CH$_3$***). δ_C (62.9 MHz) : 194.8 (***CO***), 101.04 (***C-2***), 68.4 (***C-4,C-6***), 53.1 (***CH***N_2), 39.2 (***CH$_3$-4, CH$_3$-6***), 26.6 (***CH$_3$-2***), 21.6 (***C-5***). *m/z* (ES^+) : 221.1 ($M+Na^+$, 100%).

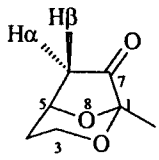
2-Diazoacetyl-2,4,6-trimethyl-1,3-dioxane (13) :[2]



Following the procedure described by Wardrop,[2] a solution of acid **(9)** (0.51 g, 2.9 mmol) and Et_3N (0.48 ml, 3.5 mmol, 1.2eq) in anhydrous CH_2Cl_2 (10 ml) was cooled to -20°C, and isobutylchloroformate (0.45 ml, 3.5 mmol, 1.2eq) was added dropwise *via* syringe at -20°C. After stirring for 5 min, an excess of an ethereal solution of diazomethane was added *via* syringe and the reaction mixture allowed to warm to room temperature 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 ethanoic acid was added. The resulting mixture was extracted with EtOAc and the organic extracts were washed with ammonium chloride (NH_4Cl), sodium bicarbonate ($NaHCO_3$) and brine (NaCl). The combined organic extracts were then dried over $MgSO_4$, filtrated and concentrated *in vacuo*. The resulting residue was purified by chromatography (EtOAc/Petrol : 1/1) to provide **(13)** as a yellow oil. (0.48 g, 84%).

Analytical data were identical in all respects with that obtained from previous procedure.

1-Methyl-2,8-dioxabicyclo[3.2.1]octan-7-one (14) :[2]

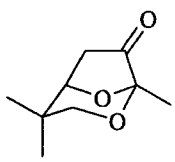


$Rh_2(OAc)_4$ (35 mg, 2 mol%) in anhydrous CH_2Cl_2 (25 ml) was added to a flame-dried flask under nitrogen. A solution of diazoketone **(11)** (670 mg, 3.94 mmol) in anhydrous CH_2Cl_2 (25 ml) was then added over 24 hours, at room temperature using a syringe pump. Once the reaction was complete, the reaction mixture was filtered. The filtrate was washed with saturated sodium bicarbonate ($NaHCO_3$), dried over $MgSO_4$, filtered and

concentrated *in vacuo*. The resulting residue was then purified by chromatography on alumina (EtOAc/Petrol : 1/9) to give **(14)** as a colorless oil. (0.16 g, 28%).

ν_{max} (thin film) : 2960, 2920, 2850, 1765 (***C=O***) *(lit.[2] 1760 cm^{-1})*, 1390, 1260 cm^{-1}. δ_H (250 MHz) : 4.8-4.7 (1H, m, ***5-H***), 3.97-3.93 (2H, m, 2×***3-H***), 2.72 (1H, dd, J=18.1, 7.6 Hz, ***6-H$_\alpha$***), 2.5-2.4 (1H, m, ***4-H$_{eq}$*** or ***4-H$_{ax}$***), 2.27 (1H, d, J=18.1 Hz, ***6-H$_\beta$***), 1.43-1.35 (1H, m, ***4-H$_{eq}$*** or ***4-H$_{ax}$***), 1.29 (3H, s, ***1-CH$_3$***). δ_C (62.9 MHz) : 211.0 (***CO***), 98.2 (***C-1***), 71.5 (***C-5***), 60.6 (***C-6***), 39.5 (***C-3***), 29.1 (***C-4***), 18.5 (***CH$_3$***). *m/z* (ES$^+$) : 165.1 (M+Na$^+$, 100%).

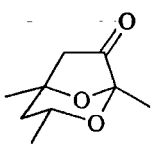
1,4,4-Trimethyl-2,8-dioxabicyclo[3.2.1]octan-7-one (15) :[2]



Following the same procedure as described above, a solution of diazoketone **(12)** (680 mg, 3.4 mmol) in anhydrous CH_2Cl_2 (25 ml) was added to a solution of $Rh_2(OAc)_4$ (3 mg, 2 mol%) in anhydrous CH_2Cl_2 (25 ml). After an identical work-up, the resulting residue was purified by chromatography on alumina (EtOAc/Petrol : 1/9) to give **(15)** as a colorless oil. (0.21 g, 37%).

ν_{max} (thin film) : 2962, 2868, 1768 (***C=O***) *(lit.[2] 1767 cm^{-1})*, 1476, 1394 cm^{-1}. δ_H (250 MHz) : 4.15 (1H, dd, J= 7.5, 1.5 Hz, ***5-H***), 3.67 (1H, d, J= 12.1 Hz, ***3-H$_{ax}$***), 3.45 (1H, dd, J= 12.1, 1.5 Hz, ***3-H$_{eq}$***), 2.57 (1H, dd, J= 18.3, 7.5 Hz, ***6-H$_\alpha$***), 2.35 (1H, d, J= 18.3 Hz, ***6-H$_\beta$***), 1.38 (3H, s, ***1-CH$_3$***), 1.26 (3H, s, ***4-CH$_3$***), 0.75 (3H, s, ***4-CH$_3$***). δ_C (62.9 MHz) : 211.2 (***CO***), 97.7 (***C-1***), 80.1 (***C-5***), 71.5 (***C-8***), 37.3 (***C-3***), 32.8 (***C-4***), 24.4 (***CH$_3$-4***), 21.7 (***CH$_3$-4***), 17.9 (***CH$_3$***). *m/z* (ES$^+$) : 193.2 (M+Na$^+$, 100%).

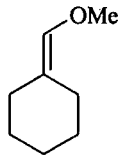
1,3,5-Trimethyl-2,8-dioxabicyclo[3.2.1]octan-7-one (16) :



Following the same procedure as described above, a solution of diazoketone **(13)** (0.16 g, 0.8 mmol) in anhydrous CH_2Cl_2 (25 ml) was added to a solution of $Rh_2(OAc)_4$ (7.2 mg, 2 mol%) in anhydrous CH_2Cl_2 (25 ml). After an identical work-up, the resulting residue was purified by chromatography on alumina (EtOAc/Petrol : 1/9) to give **(16)** as a colorless oil. (0.05 g, 38%).

ν_{max} (thin film) : 2973, 2870, 1766 (***C=O***) *(lit.[2] 1762 cm^{-1})*, 1470, 1375 cm^{-1}. δ_H (250 MHz) : 4.00-3.95 (1H, m, ***3-H***), 2.33 (2H, s, 2×***6-H***), 1.67 (1H, d, J= 11.0 Hz, ***4-H$_{ax}$***), 1.57 (1H, dd, J= 11.0, 3.9 Hz, ***4-H$_{eq}$***), 1.46 (3H, s, ***1-CH$_3$***), 1.38 (3H, s, ***5-CH$_3$***), 1.26 (3H, d, J= 6.2 Hz, ***3-CH$_3$***). δ_C (62.9 MHz) : 211.0 (***CO***), 97.5 (***C-1***), 80.6 (***C-5***), 71.0 (***C-8***), 37.0 (***C-3***), 32.3 (***C-4***), 24.0 (***CH$_3$-3***), 21.5 (***CH$_3$-5***), 17.5 (***CH$_3$***). *m/z* (ES$^+$) : 192.1 (M+Na$^+$, 100%).

Methoxymethylene-cyclohexane (17) :



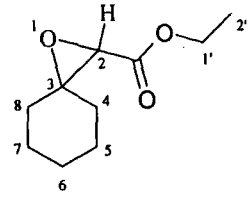
To a solution of methoxymethyl triphenyl phosphonium chloride (2.62 g, 7.65 mmol, 1.5 eq) in THF (50 ml), nBuLi (4.8 ml, 7.65 mmol, 1.5 eq) was added at 0°C and the reaction stirred at that temperature for 2 hours. The cylohexanone (0.53 ml, 5.10 mmol, 1eq) in solution in THF (5 ml) was added at 0°C, the reaction was allowed to warm up to room temperature and stirred at room temperature overnight. Aqueous ammonium chloride (NH_4Cl) was added to the reaction mixture, which was extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether/EtOAc : 95:5 then 9:1) to give the methoxymethylene cyclohexane **(17)** as a colorless oil (0.42 g, 65%).

ν_{max} (ATR) : (*lit.*[8]) 3054 (***CH*** alkene), 2955, 2930, 2869, 2822 (***CH*** alkane), 1479, 1435, 1192, 1119 (***CO***) cm^{-1}. δ_H (300 MHz) : 5.75 (1H, s, ***Alkene-H***), 3.50 (3H, s, ***OCH$_3$***), 2.20-

8/ Rousseau, G.; LePerchec, P.; Coria, J. M. *Synthesis* **1978**, 67.

2.05 (2H, m, 2×***CH*** cyclohexane), 1.93-1.8 (2H, m, 2×***CH*** cyclohexane), 1.6-1.4 (6H, m, 3×CH_2 cyclohexane). δ_C (75.4 MHz) : 134.5 (***CH*** alkene), 118.5 (***C*** alkene), 53.6 (OCH_3), 33.6 (1×CH_2 cyclohexane), 31.2 (2×CH_2 cyclohexane), 31.0 (2×CH_2 cyclohexane). *m/z* (CI) : 127 ($M+H^+$, 100 %), 112 (12%).

1-Oxa-spiro-[2,5]octane-2-carboxylic acid ethyl ester (19) :

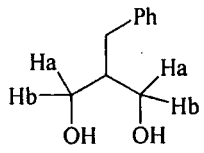


To a solution of sodium ethoxide (0.28 g, 4.1 mmol, 1.2 eq) in DCM at -78°C, ethyl bromoacetate (0.46 ml, 4.1 mmol, 1.2 eq) was added and the reaction mixture stirred at -78°C for 3 hours. The cyclohexanone (0.53 ml, 5.1 mmol, 1.5 eq) in solution in CH_2Cl_2 was then added and the reaction mixture slowly warmed up from -78°C to 0°C and stirred at 0°C overnight. Brine was added to the reaction mixture, which was then extracted with Et_2O. The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether neat then petroleum ether/EtOAc : 9/1) and the oxa-spiro-octane derivative **(19)** was obtained as an yellow oil (0.56 g, 89%).

δ_H (200 MHz) : 4.22 (3H, q, J= 7.1 Hz, OCH_2CH_3), 3.30 (1H, s, ***CH*** epoxide), 1.8-1.4 (10H, m, 5×CH_2 cyclohexane), 1.17 (3H, t, J= 7.1 Hz, OCH_2CH_3), (*lit.*[9] *J= 7.2Hz*). δ_C (50.3 MHz) : 168.2 (***C=O***), 64.6 (***C-2***), 61.1 (***C-3***), 59.3 (***C-1'***), 34.7 (***C-8***), 28.5 (***C-4***), 25.1 (*C-5*), 24.9 (***C-7***), 24.6 (***C-6***), 14.1 (***C-2'***). *m/z* (CI) : 184 ($[M]^+$, 2%), 138 (10%), 127 (86%), 111 ($[M-COOC_2H_5]^+$, 100%), 99 (70%), 81 (96%), 67 (90%).

9/ Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Eur.J.Org.Chem.* **2002**, 9, 1562.

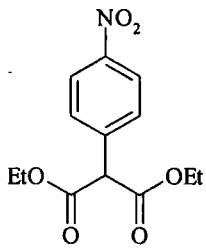
2-Benzyl-1,3-propane diol (20) :



A cooled solution of lithium aluminium hydride (10 g, 0.264 mol) in Et_2O (250 ml) at 0°C was treated dropwise with a solution of benzyl diethyl malonate (15.5 ml, 66 mmol) in Et_2O (80 ml). After stirring for 3h at room temperature, the reaction mixture was cooled in an external ice bath and treated successively by the dropwise addition of 10 ml of H_2O, 10 ml of aqNaOH 15 % and 30 ml of H_2O. The mixture was then filtered and washed with EtOAc and the filtrate concentrated *in vacuo*. The crude residue was then purified by chromatography on silica gel (cyclohexane/EtOAc, 1:1) to give alcohol **(20)** as a pale brown solid (8.7 g, 79%).

m.p. : 65-68°C (*lit.*[10] *67°C*). ν_{max} (ATR) : 3440-2980 (***OH H-bonded***), 1260, 1037, 744, 699 cm^{-1}. δ_H (400 MHz) : 7.35-7.25 (2H, m, ***Ar-H***), 7.25-7.20 (3H, m, ***Ar-H***), 3.87 (2H, dd, J= 10.5, 3.5 Hz, ***1-H_a, 3-H_a***), 3.75 (2H, dd, J= 10.5, 6.8 Hz, ***1-H_b, 3-H_b***), 2.70 (2H, d, J= 7.8 Hz, ***CH_2Ph***), 2.31 (2H, bs, 2×***OH***), 2.15 (1H, m, ***2-H***). δ_C (100.5 MHz) : 140,0 (***C-1'***), 129.1, 128.6, 126.3 (5×***CH***-Ar), 65.7 (***C-1,C-3***), 44.0 (***C-2***), 34.4 (***CH_2***Ph). *m/z* (ES^+) : 189.1 ($M+Na^+$, 100 %). HRMS (ES^+) found : 189.0890 ($C_{10}H_{14}O_2Na$ requires 189.0891).

2-(4'-Nitrophenyl)diethyl malonate (21) :

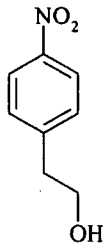


10/ Lee, J.; Lee, J.; Kim, J.; Kim, S. Y.; Chun, M. W.; Cho, H.; Hwang, S. W.; Oh, U.; Park, Y. H.; Marquez, V. E.; Beheshti, M.; Szabo, T.; Blumberg, P. M. *Bioorg.Med.Chem.* **2001**, 9, 19.

A cooled solution of sodium hydride (1.9 g, 75 mmol, 2.1 eq) in dry THF (50 ml) at 0°C was treated dropwise by slow addition of diethyl malonate (10.6 ml, 70 mmol, 2 eq). After complete addition, 1-fluoro-4-nitrobenzene was added (3.8 g, 35 mmol) and the reaction mixture was refluxed for 2 days at 60°C. A saturated solution of NH_4Cl was then added and the mixture was extracted with EtOAc. The organic extracts were then washed with a saturated solution of NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then purified by distillation under reduced pressure (8×10^{-1}mbar) to remove excess of diethylmalonate (b.p. 35°C) and unreacted 1-fluoro-4-nitro-benzene (b.p. 40°C) to give the title substituted diethyl malonate **(21)** as a brownish solid (4.8 g, 50%).

m.p. : 50-52°C. ν_{max} (ATR) : 3010, 2928, 1738 (***C=O***), 1525 + 1347 (***NO_2***), 1143, 858, 725 cm^{-1}. δ_H (400 MHz) : 8.20 (2H, d, J= 8.8 Hz, 2×***3'-H***), 7.60 (2H, d, J= 8.8 Hz, 2×***2'-H***), 4.74 (1H, s, ***2-H***), 4.22 (4H, m, J= 7.2 Hz, 2×***OCH_2***), 1.25 (6H, t, J= 7.2 Hz, 2×***CH_3***). δ_C (100.5 MHz) : 167.0 (2×***CO***), 148.0 (***C-1'***), 140.0 (***C-4'***), 130.6 (2×***C-2'***), 124.0 (2×***C-3'***), 62.4 (2×***OCH_2***), 57.8 (***C-2***), 34.2 (2×***CH_3***). *m/z* (ES^+) : 304 ($M+Na^+$, 100%), 336 ($M+Na^+$+MeOH, 18%). HRMS (ES^+) : 304.0819 ($C_{13}H_{15}NO_6Na$ requires 304.0797). Anal. [found : C 55.80, H 5.49, N 4.83 %, $C_{13}H_{15}NO_6$ requires C 55.51, H 5.37, N 4.98 %].

2-(4'-Nitrophenyl)ethanol (22) :

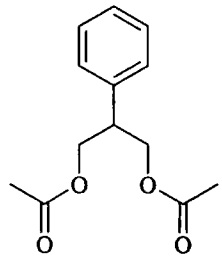


$NaBH_4$ (0.155 g, 3.5 mmol, 5 eq) was added dropwise to a solution of diethylmalonate **(21)** (0.20 g, 0.7 mmol) in THF (3 ml) at 0°C. MeOH (0.12 mL, 1/5 volume THF) was then slowly added to the refluxing mixture. The reaction was followed by GC. After 16h, the reaction was quenched with NH_4Cl, extracted with CH_2Cl_2 and dried over $MgSO_4$.

After evaporation of the solvent, the residue was purified by chromatography (CH_2Cl_2/MeOH, 30:1) and gave compound **(22)** as a colorless oil (0.60 g, 51%).

ν_{max} (ATR) : 3596-3146 (***OH***), 2948-2880, 1598, 1510+1341 (***NO_2***), 1107, 1041, 854, 745, 692 cm^{-1}. δ_H (400 MHz) : (*lit.*[11]) 8.18 (2H, d, J= 8.7 Hz, 2×***3'-H***), 7.42 (2H, d, J= 8.7 Hz, 2×***2'-H***), 3.95 (2H, t, J= 6.5 Hz, 2×***1-H***), 3.00 (2H, t, J= 6.5 Hz, 2×***2-H***), 1.62 (1H, bs, ***OH***). δ_C (100.5 MHz) : 147.0 (***C-1'***), 141.0 (***C-4'***), 130.0 (2×***C-2'***), 124.0 (2×***C-3'***), 62.8 (***C-1***), 39.0 (***C-2***). *m/z* (CI) : 185 ($M+NH_4^+$, 8%), 155 (37%), 138 ($M+H^+$-NO, 50%), 137 ($M+H^+$-CH_2OH, 100%), 119 (42%), 110 ($M+H^+$-NO-CO, 20%), 94 (10%).

2-phenylpropane-1,3-diacetate (23) :



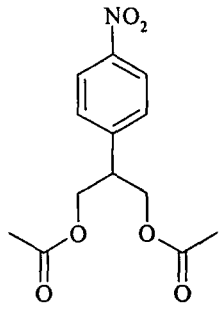
To a solution of commercially available 2-phenylpropan-1,3-diol (22 g, 0.145 mol) in CH_2Cl_2 (250 ml), Et_3N (201.5 ml, 1.451 mol, 10 eq) and a catalytic amount of DMAP (3.53 g, 29 mmol, 0.2 eq) were added at room temperature and the reaction stirred for 30 mins. Acetic anhydride (54.5 ml, 0.580 mol, 4 eq) was added dropwise, and the reaction mixture was stirred at room temperature and followed by TLC. The reaction mixture was washed with brine and the aqueous layer extracted twice with CH_2Cl_2. The organic extracts were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified by chromatography (cyclohexane/EtOAc, 9:1 then 8:2) and gave the diacetate **(23)** as a colorless oil (27.4 g, 80%).

ν_{max} (ATR) : 3000, 2961, 2950, 1734 (***C=O***), 1365, 1217, 1033, 762, 700 cm^{-1}. δ_H (400 MHz) : (*lit.*[12]) 7.30-7.15 (5H, m, ***Ar-H***), 4.27 (4H, d, J= 6.6 Hz, 2×***1-H***,2×***3-H***), 3.26 (1H, p, J= 6.6 Hz, ***2-H***), 1.95 (6H, s, 2×***CH_3***). δ_C (100.5 MHz) : 171.7 (2×***CO***), 138.6 (***C-1'***),

11/ Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. J.Org.Chem. **1973**, 38, 2786.
12/ Rumbero, A.; Borreguero, I.; Sinisterra, J. V.; Alcantara, A. R. *Tetrahedron* **1999**, 55, 14947.

129.0, 128.3, 127.8 (5×***CH-Ar***), 65.0 (***C-1***, ***C-3***), 44.0 (***C-2***), 21.7 (2×CH_3). *m/z* (ES^+) : 259 ($M+Na^+$, 100%), 177 (M^+-$OCOCH_3$, 97%).

2-(4'-Nitrophenyl)propyl-1,3-diacetate (24) :

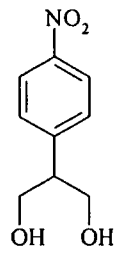


To a solution of **(23)** (27.4 g, 0.116 mol) in $CHCl_3$, ammonium nitrate (10.2 g, 0.128 mol, 1.1 eq) and trifluoroacetic anhydride (97.4 g, 0.464 mol, 4 eq) were added at 0°C. The reaction was stirred at that temperature for 2 hours and left to warm up to room temperature overnight. The crude mixture was poured into ice-water and extracted with $CHCl_3$. The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petrol/EtOAc, 9:1) to give the title product **(24)** as a pale yellow oil (21.2 g, 65%).

ν_{max} (ATR) : 3000, 2961, 2950, 1738 (***C=O***), 1368, 1525 + 1345 (***NO_2***), 1219, 1035, 725, 700 cm^{-1}. δ_H (400 MHz) : (*lit.*[13]) 8.20 (2H, d, J= 8.9 Hz, 2×***3'-H***), 7.43 (2H, d, J= 8.9 Hz, 2×***2'-H***), 4.35 (4H, d, J= 6.6 Hz, 2×***1-H***,2×***3-H***), 3.45 (1H, p, J= 6.6 Hz, ***2-H***), 2.02 (6H, s, 2×***CH_3***). δ_C (100.5 MHz) : 170.7 (2×***CO***), 146.0 (***C-1'***), 140.6 (***C-4'***), 130.6 (2×***C-2'***), 124.0 (2×***C-3'***), 64.0 (***C-1***,***C-3***), 42.0 (***C-2***), 22.2 (2×***CH_3***). *m/z* (ES^+) : 259 ($M+Na^+$, 100%), 177 (M^+-$OCOCH_3$, 97%).

13/ Hu, J.; Mattern, D. L. *J.Org.Chem.* **2000**, 65, 2277.

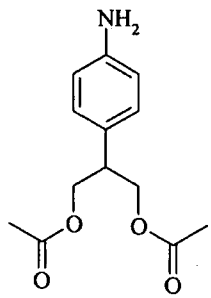
2-(4'-Nitrophenyl)-1,3-propanediol (25) :



The compound **(24)** (21.2 g, 75 mmol) was added to a solution of NaOMe (75.5 ml, 2M sol., 0.15 mol) at room temperature. After 30 mins, the reaction mixture was carefully concentrated and brine and $CHCl_3$ were added. The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was recrystallized from cyclohexane to give the diol **(25)** as a white solid (11.2 g, 76%).

m.p. : 83-86°C. ν_{max} (ATR) : 3500-3008 (***OH*** broad), 1513+1345(***NO₂***), 1024, 853, 751, 699 cm^{-1}. δ_H (400 MHz) : 8.2 (2H, d, J= 8.8 Hz, 2×***3'-H***), 7.45 (2H, d, J= 8.8 Hz, 2×***2'-H***), 4.05 (2H, dd, J= 10.6, 6.8 Hz, ***1-H$_a$,3-H$_a$***), 4.00 (2H, dd, J= 10.6, 5.6 Hz, ***1-H$_b$,3-H$_b$***), 3.20 (1H, tt, J= 6.8, 5.6 Hz, ***2-H***), 1.90 (2H, bs, 2×***OH***). δ_C (100.5 MHz) : 147.8 (***C-1'***), 147.2 (***C-4'***), 129.6 (2×***C-2'***), 124.2 (2×***C-3'***), 65.8 (***C-1,C-3***), 50.0 (***C-2***). *m/z* (ES^+) : 197 (M^+, 100%). Anal. (*lit.*[10]) [found : C 54.51, H 5.57, N 6.84 %, $C_9H_{11}NO_4$ requires C 54.82, H 5.62, N 7.10 %].

2-(4'-Aminophenyl)propyl-1,3-diacetate (26) :

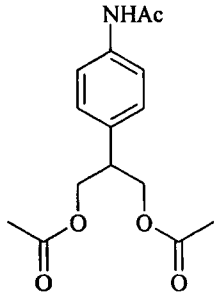


To a solution of **(24)** (5.6 g, 19.9 mmol) in dry EtOH (25 ml) was added $PtO_2.xH_2O$ 79 % (0.127 g, 0.44 mmol). A hydrogen gas source was attached to the reaction flask under atmospheric pressure. The reaction mixture was stirred for 12 h at room temperature.

Once finished, nitrogen gas was bubbled through the reaction mixture several times. The catalyst was removed by filtration through celite. After evaporation of the solvent, the residue was purified by chromatography to give **(26)** as a yellowish solid (4.5 g, 89%).

m.p. : 73-75°C (*lit.*[14] *73-75°C*). ν_{max} (thin film) : 3230, 3356 ***(NH$_2$)***, 1729 ***(C=O)*** cm^{-1}. δ_H (300 MHz) : 7.00 (2H, d, J= 8.4 Hz, 2×***3'-H***), 6.63 (2H, d, J= 8.4 Hz, 2×***2'-H***), 4.26 (4H, d, J= 6.9 Hz, 2×***1-H***, 2×***3-H***), 3.64 (2H, bs, ***NH$_2$***), 3.19 (1H, p, J= 6.9 Hz, ***2-H***), 2.01 (6H, s, 2×CO***CH$_3$***). δ_C (75.4 MHz) : 170.9 (2×***CO***), 145.6 (***C-1'***); 128.5 (**C-4'**), 128.0 (2×***C-2'***), 115.4 (2×***C-3'***), 64.9 (***C-1,C-3***), 42.9 (***C-2***), 20.8 (2xCO***CH$_3$***). *m/z* (ES^+): 274 $(M+Na)^+$. HRMS (ES^+) found : 274.1072 ($C_{13}H_{17}NO_4Na$ requires 274.1055).

2-(4'-Acetamidophenyl)propyl-1,3-diacetate (27) :



To a solution of **(26)** (3.9 g, 15.4 mmol) in dry CH_2Cl_2 (30 ml), Et_3N (5.4 ml, 38.6 mmol, 2.5eq) was added. Acetyl chloride (1.2 ml, 16.9 mmol, 1.1eq) was added dropwise. The reaction mixture was stirred for 12 h at room temperature. After completion, 10 ml H_2O were added to the reaction mixture and the two phases were separated. The aqueous phase was re-extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography to give **(27)** (4.3 g, 95%).

m.p. : 99-102°C (*lit.*[11] *99-102°C*). ν_{max} (thin film) : 1735 (***C=O***), 1686 (NH***C=O***) cm^{-1}. δ_H (500 MHz, CD_3OD) : 7.46 (2H, d, J= 8.5 Hz, 2×***3'-H***), 7.19 (2H, d, J= 8.5 Hz, 2×***2'-H***), 4.30 (4H, d, J= 6.5 Hz, 2×***1-H***, 2×***3-H***), 3.28 (1H, p, J= 6.5 Hz, ***2-H***), 2.03 (6H, s, 3×CO***CH$_3$***). δ_C (126 MHz, CD_3OD) : 170.8 (2×O***CO***CH_3), 168.2 (NH***CO***CH_3), 137.2 (***C-***

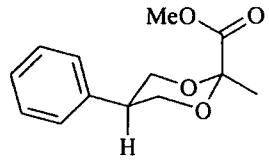
14/ Guanti, J.; Narisano, E.; Podgorski, T.; Thea, S.; Williams, A. *Tetrahedron* **1990**, 46, 7081.

then concentrated *in vacuo* to 1/3 of its initial volume and extracted with CH_2Cl_2. The organic extract was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude NMR shows the presence of two isomers. The residue was then purified by flash column chromatography (cyclohexane/EtOAc : 9/1).

2-Carboxymethyl-2-methyl-5-phenyl-[1,3]-dioxane (29,30) :

Following the general procedure, methyl pyruvate (6 ml, 66 mmol) and boron trifluoride diethyletherate ($BF_3.OEt_2$, 8.1 ml, 66 mmol) were combined with 2-phenyl-1,3-propanediol (5 g, 33 mmol) to afford a 8:2 mixture of isomeric ester acetals. Separation by flash column chromatography (cyclohexane/EtOAc : 9/1) afforded the major title ester acetal **(29)** (Ph in equatorial position) as a white crystalline solid (5.16 g, 83%) and the minor ester acetal **(30)** (Ph in axial position) as a white crystalline solid (1.0 g, 6%) after recrystallisation from cyclohexane.

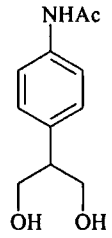
Major isomer **(29)** :



m.p. : 65-67°C. ν_{max} (ATR) : 2923-2845, 1724 (***C=O***), 1103, 1078, 1034, 724, 659 cm^{-1}. δ_H (400 MHz) : 7.35-7.25 (3H, m, ***Ar-H***), 7.15-7.10 (2H, m, ***Ar-H***), 4.10 (2H, dd, J= 11.7, 4.8 Hz, ***4-H$_{eq}$,6-H$_{eq}$***), 3.95 (3H, s, O***CH$_3$***), 3.95 (2H, t, J= 11.7 Hz, ***4-H$_{ax}$,6-H$_{ax}$***), 3.30-3.20 (1H, m, ***5-H***), 1.60 (3H, s, ***2-CH$_3$***). δ_C (100.5 MHz) : 171.0 (***CO***), 137.1 (***C-1'***), 128.7+127.55+127.5 (5×***CH-Ar***), 98.1 (***C-2***), 68.1 (***C-4,C-6***), 52.6 (***CH$_3$***O), 39.9 (***C-5***), 26.0 (***CH$_3$***). *m/z* (ES^+) : 259 ($M+Na^+$, 100%). Anal. [found : C 66.06, H 6.89 %, required for $C_{13}H_{16}O_4$: C 66.07, H 6.84 %].

1'), 134.2 (***C-4'***), 128.5 (2×***C-2'***), 120.1 (2×***C-3'***), 64.8 (***C-1,C-3***), 43.3 (***C-2***), 24.5 (NHCO***CH₃***), 20.8 (2×CO***CH₃***). *m/z* (ES^+) : 316 $(M+Na)^+$. HRMS (ES^+) found : 316.1152 ($C_{15}H_{19}NO_5Na$ requires 316.1161).

2-(4'-Acetamidophenyl)-1,3-propanediol (28) :



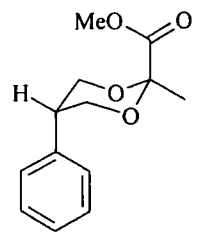
Sodium methoxide (1M in MeOH, 13.7 ml, 2 eq.) was added to a solution of **(27)** (2.0 g, 6.83 mmol) in dry MeOH (10 ml). The reaction mixture was stirred for 40 min at room temperature. After completion, the reaction mixture was carefully concentrated *in vacuo* and brine and $CHCl_3$ were added. The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound **(28)** was obtained as a white solid (1.38 g, 97%).

m.p. : 96-99°C. ν_{max} (thin film) : 3266-3120 (broad ***OH***), 1635 (amide), 1602, 1545, 1514, 823 cm^{-1}. δ_H (500 MHz, CD_3OD) : 7.46 (2H, d, J= 8.5 Hz, 2×***3'-H***), 7.19 (2H, d, J= 8.5 Hz, 2×***2'-H***), 3.86 (2H, dd, J= 11.0, 6.5 Hz, 1×***1-Ha***,1×***3-Ha***), 3.77 (2H, dd, J= 11.0, 6.5 Hz, 1×***1-Hb***,1×***3***-Hb), 2.90 (1H, m, 2-H), 2.09 (3H, s, NHCO***CH₃***). δ_C (126 MHz, CD_3OD) : 171.3 (NH***CO***Me), 138.1 (***C-4'***), 137.9 (***C-1'***), 129.6 (2×***C-2'***), 121.4 (2×***C-3'***), 64.6 (***C-1,C-3***), 51.7 (***C-2***), 24.2 (NHCO***CH₃***). *m/z* (ES^+) : 232 $(M+Na^+)$. HRMS (ES^+) found : 232.0942 ($C_{11}H_{15}NO_3Na$ requires 232.0944).

General procedure for ester acetal synthesis from methyl pyruvate :

Methyl pyruvate (2 eq.) and $BF_3.OEt_2$ (2 eq.) were added dropwise to a solution of diol (1eq) in dry CH_3CN at room temperature and the reaction mixture was stirred at room temperature overnight. A saturated solution of sodium bicarbonate ($NaHCO_3$) was then added and the resulting mixture was left to stir for an additional 30 mins. The mixture was

Minor isomer **(30)** :



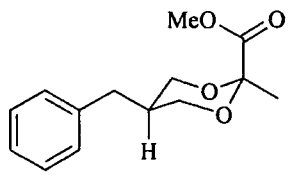
m.p. : 55-57°C. δ_H (400 MHz) : 7.45-7.40 (2H, m, ***Ar-H***), 7.35-7.20 (3H, m, ***Ar-H***), 4.25 (2H, dd, J= 12.1, 3.3 Hz, ***4-H_{eq},6-H_{eq}***); 4.10 (2H, dd, J= 12.1, 2.0 Hz, ***4-H_{ax},6-H_{ax}***), 3.80 (3H, s, O***CH_3***), 2.80-2.70 (1H, m, ***5-H***), 1.60 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 170.3 (***CO***), 141.1 (***C-1'***), 127.9+127.5+126.2 (5×***Ar-CH***), 97.6 (***C-2***); 66.3 (***C-4,C-6***), 52.1 (***CH_3***O), 37.9 (***C-5***), 24.1 (***CH_3***). 291 (M+Na+MeOH, 22%), 259 ($M+Na^+$, 100%). Anal. [found : C 66.02, H 6.87 %, required for $C_{13}H_{16}O_4$: C 66.07, H 6.84 %].

5-Benzyl-2-carboxymethyl-2-methyl-[1,3]-dioxane (31,32) :

Following the general procedure, methyl pyruvate (6.8 ml, 75 mmol) and boron trifluoride diethyletherate ($BF_3.OEt_2$, 9.2 ml, 75 mmol) were combined with 2-benzyl-1,3-propanediol (6.2 g, 37 mmol) to afford a 7:3 mixture of isomeric ester acetals. Flash column chromatography (cyclohexane/EtOAc: 95/5 then 9/1) afforded the title ester acetals **(31,32)** as an inseparable mixture (7:3 ratio, 7.9 g, 85 %).

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

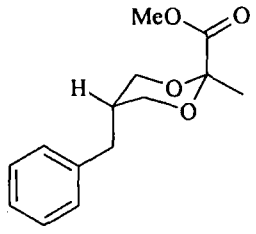
Major isomer **(31)** :



ν_{max} (ATR) : 3030-2853, 1741 (***C=O***), 1261, 1216, 1187, 1139, 1113, 1033, 760, 735, 699, 675 cm^{-1}. δ_H (400 MHz) : 7.35-7.20 (3H, m, ***Ar-H***), 7.10 (2H, d, J= 7.4 Hz, ***Ar-H***), 3.83 (3H, s, O***CH_3***), 3.80 (2H, dd, J= 11.5, 4.4 Hz, ***4-H_{eq},6-H_{eq}***), 3.50 (2H, t, J= 11.5 Hz, ***4-H_{ax},6-H_{ax}***), 2.40-2.30 (3H, m, ***5-H,CH_2***Ph), 1.50 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 171.2

(***CO***), 138.0 (***C-1'***), 128.75+128.7+126.6 (5×***Ar-CH***), 98.4 (***C-2***), 68.2 (***C-4,C-6***), 52.7 (***CH***$_3$O), 35.1 (***C-5***), 34.8 (***CH***$_2$Ph), 26.1 (***CH***$_3$). *m/z* (EI) : 251 ($M+H^+$, 2%), 235 (M^+-Me, 6%), 191 (M^+-COOMe, 90%), 131 (100%), 117 (46%), 91 ($PhCH_2^+$, 94%), 65 (40%). *m/z* (ES^+) : 273 ($M+Na^+$, 100%), 305 ($M+Na^+$+MeOH, 11%). HRMS (ES^+) found : 273.1077 ($C_{14}H_{18}O_4Na$ requires 273.1103).

Minor isomer **(32)** :

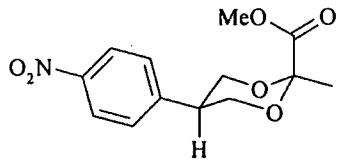


δ_H (400 MHz) : 7.35-7.20 (5H, m, ***Ar-H***), 3.95-3.90 (2H, m, ***4-H$_{eq}$,6-H$_{eq}$***), 3.81 (3H, s, O***CH***$_3$), 3.78 (2H, d, J= 11.0 Hz, ***4-H$_{ax}$,6-H$_{ax}$***), 3.00 (2H, d, J= 8.0 Hz, ***CH***$_2$Ph), 1.70-1.60 (1H, m, ***5-H***), 1.57 (3H, s, ***CH***$_3$). δ_C (100.5 MHz) : 171.3 (***CO***), 140.2 (***C-1'***), 129.4+129.4+126.3 (5×***Ar-CH***), 98.7 (***C-2***), 66.0 (***C-4,C-6***), 52.7 (***CH***$_3$O), 35.4 (***C-5***), 35.3 (***CH***$_2$Ph), 26.0 (***CH***$_3$). *m/z* (EI) : 235 (M^+-Me, 6%), 191 (M^+-COOMe, 88%), 131 (100%), 117 (30%), 91 ($PhCH_2^+$, 90%), 65 (28%). HRMS (ES^+) found : 273.1095 ($C_{14}H_{18}O_4Na$ requires 273.1097).

2-Carboxymethyl-2-methyl-5-(4'-nitrophenyl)-[1,3]-dioxane (33,34) :

Following the general procedure, methyl pyruvate (3.33 ml, 36.5 mmol) and boron trifluoride diethyletherate ($BF_3.OEt_2$, 4.5 ml, 36.5 mmol) were combined with 2-(4'-nitrophenyl)-1,3-propanediol (3.6 g, 18.3 mmol) to afford a 7:3 mixture of isomeric ester acetals. Purification by flash column chromatography (cyclohexane/EtOAc: 9/1) afforded the major title ester acetal **(33)** (aryl group in equatorial position) as a white crystalline solid (0.64 g, 12%) and a mixture of the two isomeric ester acetals **(33,34)** (4'-nitroPh in equatorial and axial position) (3.43 g, 72%), total yield 84%.

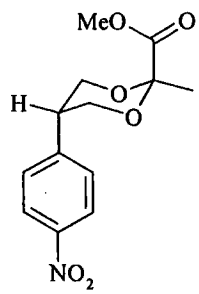
Major isomer **(33)** :



m.p. : 119-121°C. ν_{max} (ATR) : 2930, 2928, 2853, 1743 (***C=O***), 1514+1350 (***NO_2***), 1142, 1053, 906, 726 cm^{-1}. δ_H (400 MHz) : 8.10 (2H, d, J= 8.5 Hz, 2×***3'-H***), 7.30 (2H, d, J= 8.5 Hz, 2×***2'-H***), 4.10 (2H, dd, J= 11.2, 4.6 Hz, ***4-H_{eq},6-H_{eq}***), 3.90 (2H, t, J= 11.2 Hz, ***4-H_{ax},6-H_{ax}***), 3.85 (3H, s, O***CH_3***), 3.40 (1H, dd, J= 11.1, 4.7 Hz, ***5-H***), 1.60 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 170.5 (***CO***), 148.0 (***C-1'***), 145.0 (***C-4'***), 128.7 (2×***C-2'***), 124.2 (2×***C-3'***), 98.1 (***C-2***), 67.9 (***C-4,C-6***), 53.2 (***CH_3***O), 40.1 (***C-5***), 26.0 (***CH_3***). *m/z* (ES^+) : 304 ($M+Na^+$, 100%). HRMS (ES^+) found : 304.0808 ($C_{13}H_{15}NO_6Na$ requires 304.0797).

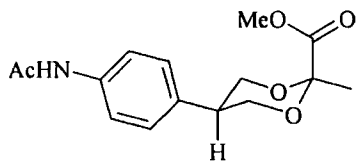
Minor isomer **(34)** :

A small sample of pure isomer obtained was used for analysis.



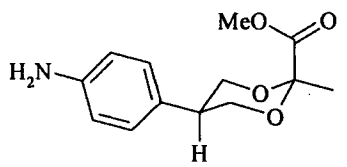
m.p.. : 78-80°C. ν_{max} (ATR) : 2940, 2932, 2860, 1742 (***C=O***), 1516+1346 (***NO_2***), 1127, 1031, 909, 727 cm^{-1}. δ_H (400 MHz) : 8.12 (2H, d, J= 8.8 Hz, 2×***3'-H***), 7.65 (2H, d, J= 8.8 Hz, 2×***2'-H***), 4.28 (2H, dd, J= 12.4, 3.5 Hz, ***4-H_{ax},6-H_{ax}***), 4.07 (2H, m, ***4-H_{eq},6-H_{eq}***), 3.85 (3H, s, O***CH_3***), 2.78 (1H, bs, ***5-H***), 1.58 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 170.6 (***CO***), 150.1 (***C-1'***), 146.9 (***C-4'***), 129.8 (2×***C-2'***), 124.0 (2×***C-3'***), 98.3 (***C-2***), 66.5 (***C-4,C-6***), 53.1 (***CH_3***O), 38.2 (***C-5***), 26.0 (***CH_3***). *m/z* (ES^+) : 304 ($M+Na^+$, 100%). HRMS (ES^+) found : 304.0788 ($C_{13}H_{15}NO_6Na$ requires 304.0792).

5-(4'-acetamidophenyl)-2-carboxymethyl-2-methyl-[1,3]-dioxane (35) :



Following the general procedure, methyl pyruvate (3.3 ml, 36.5 mmol) and boron trifluoride diethyletherate ($BF_3.OEt_2$, 4.5 ml, 36.5 mmol) were combined with 2-(4'-acetamidophenyl)-1,3-propanediol (3.6 g, 18.3 mmol) to afford a 7:3 mixture of crude isomeric ester acetals. Purification by flash column chromatography (cyclohexane/EtOAc: 9/1) affored the title ester acetals as a non-separable mixture (7:3 ratio, 2.33 g, 45%).

Alternatively, to a solution of **(33)** (4.8 g, 17.1 mmol) in dry toluene (40 ml) was added $PtO_2.xH_2O$ (0.32 g, 1.10 mmol). A hydrogen gas source was attached to the reaction flask under atmospheric pressure. The reaction mixture was stirred for 48 h at room temperature. Nitrogen gas was bubbled through the reaction mixture several times and the mixture filtered through celite to remove the catalyst. After evaporation of the solvent, the residue was was purified by chromatography to give 5-(4'-aminophenyl)-2-carboxymethyl-2-methyl-[1,3]-dioxane **(36)** (3.83 g, 89%) as a pale yellow solid.



m.p. : 79-82°C. ν_{max} (thin film) : 3476, 3402 (***NH₂***), 1742 (***C=O***), 1143 cm^{-1}. δ_H (300 MHz) : 6.92 (2H, d, J= 8.4 Hz, 2×***3'-H***), 6.66 (2H, d, J= 8.4 Hz, 2×***2'-H***), 4.04 (2H, dd, J= 12.0, 6.0 Hz, ***4-H$_{eq}$,6-H$_{eq}$***), 3.88 (3H, s, COO***CH₃***); 3.82 (2H, t, J= 12 Hz, ***4-H$_{ax}$,6-H$_{ax}$***), 3.13 (1H, m, ***5-H***), 1.575 (3H, s, ***CH₃***). δ_C (75.4 MHz) : 171.5 (***CO***Me), 146.0 (***C-4'***), 128.5 (2×***C-2'***), 127.0 (***C-1'***), 116.0 (2×***C-3'***), 99.2 (***C-2***), 68.3 (***C-4,C-6***), 42.5 (COO***CH₃***), 39.0 (***C-5***), 26.2 (***CH₃***). *m/z* (ES^+) : 274 ($M+Na^+$, 100%), 252 ($M+H^+$, 40%). HRMS (ES^+) found : 274.1045 ($C_{13}H_{17}NO_4Na$ requires 274.1050).

To a solution of **(36)** (4.2 g, 16.7 mmol) in dry DCM (30 ml), triethylamine (5.82 ml, 41.8 mmol, 2.5eq) and acetyl chloride (1.43 ml, 20.1 mmol, 1.2 eq.) were added at room temperature. After 12 h, H_2O was added to the reaction mixture. After separation of the two phases, the aqueous phase was re-extracted with ethyl acetate twice. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography (petroleum ether/EtOAc : 9/1). Recrystallization from cyclohexane yielded the ester acetal **(35)** (4.31 g, 88%) as a pale yellow solid.

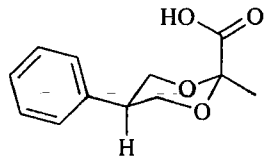
m.p.: 107-111°C. ν_{max} (thin film) : 3318 (***NH***), 1742 (***C=O***), 1687 (***amide***), 1144 cm^{-1}. δ_H (300 MHz) : 7.43 (2H, d, J= 8.4 Hz, 2×***3'-H***), 7.20 (1H, bs, MeCO***NH***), 7.07 (2H, d, J= 8.4 Hz, 2×***2'-H***), 4.05 (2H, dd, J= 12.0, 4.5 Hz, ***4-H_{eq},6-H_{eq}***), 3.88 (3H, s, COO***CH_3***), 3.85 (2H, t, J= 12 Hz, ***4-H_{ax},6-H_{ax}***), 3.21 (1H, m, ***5-H***), 2.16 (3H, s, NHCO***CH_3***), 1.58 (3H, s, ***CH_3***). δ_C (62.9 MHz) : 171.5 (***CO***OMe), 168.5 (NH***CO***Me), 137.5 (***C-4'***), 133.8 (***C-1'***), 128.2 (2×***C-2'***), 120.5 (2×***C-3'***), 99.1 (***C-2***), 68.2 (***C-4,C-6***), 42.7 (COO***Me***), 39.8 (***C-5***), 26.4 (***CH_3***), 25.0 (NHCO***CH_3***). *m/z* (ES^+) : 316 ($M+Na^+$, 100%), 294 ($M+H^+$, 60%). HRMS (ES^+) found : 316.1148 ($C_{15}H_{19}NO_5Na$ requires 316.1155).

General procedure for acid acetal synthesis :

Sodium hydroxide pellets (NaOH, 4.5 eq) were added to a solution of ester in THF/H_2O (1:1) and the reaction mixture stirred at room temperature overnight. After cooling to 0°C, the reaction mixture was acidified to pH 1 with an ice cold 5M solution of aqueous HCl and quickly extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

2-Carboxy-2-methyl-5-phenyl-[1,3]dioxane (37,38) :

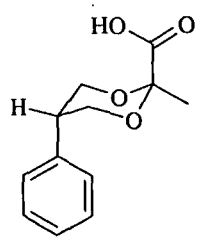
Major isomer **(37)**:



Following the general procedure, sodium hydroxide pellets (NaOH, 7.25 g, 0.18 mol) were added to a solution of **(29)** (9.5 g, 40.2 mmol) in THF/H_2O (1:1, 50 ml). Recrystallisation from cyclohexane afforded the title acid acetal **(37)** (7.03 g, 80%).

m.p. : 132-135°C. ν_{max} (ATR) : 3260-2840 (***OH***), 1735 (***C=O***), 1121, 1104, 746, 697 cm^{-1}. δ_H (400 MHz) : 8.2 (1H, s, CO***OH***), 7.35-7.22 (3H, m, ***Ar-H***), 7.15 (2H, d, J= 6.6 Hz, ***Ar-H***), 4.15 (2H, dd, J= 11.7, 4.5 Hz, ***4-H_{eq},6-H_{eq}***), 4.00 (2H, t, J= 11.7 Hz, ***4-H_{ax},6-H_{ax}***), 3.30 (1H, m, ***5-H***), 1.68 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 175.0 (***CO***), 137.6 (***C-1'***), 129.1+127.8 (5×***Ar-CH***), 98.1 (***C-2***), 68.6 (***C-4,C-6***), 40.1 (***C-5***), 26.0 (***CH_3***). Anal. [found : C 66.81, H 6.38 %, required for $C_{12}H_{14}O_4$: C 66.85, H 6.36 %].

Minor isomer **(38)**:



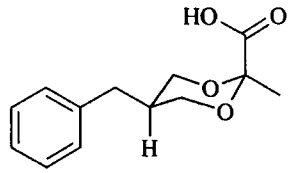
Following the general procedure, sodium hydroxide pellets (NaOH, 0.54 g, 13.4 mmol) were added to a solution of **(30)** (0.7 g, 2.98 mmol) in THF/H_2O (1:1, 5 mL). Recrystallisation from cyclohexane afforded of the title acid acetal **(38)** (0.4 g, 67 %) as a white solid.

m.p. : 120-122°C. ν_{max} (ATR) : 3260-2840 (***OH***), 1735 (***C=O***),1121, 1104, 746, 697 cm^{-1}. δ_H (400 MHz) : 8.2 (1H, s, CO***OH***), 7.40-7.30 (3H, m, ***Ar-H***), 7.25 (2H, d, J= 6.6 Hz, ***Ar-H***), 4.30 (2H, dd, J= 12.0, 3.6 Hz, ***4-H_{eq},6-H_{eq}***), 4.15 (2H, dd, J= 12.0, 3.5 Hz, ***4-H_{ax},6-H_{ax}***), 2.85 (1H, m, ***5-H***); 1.70 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 173.0 (***CO***), 139.9 (***C-1'***), 127.6+127.0+126.0 (5×***Ar-CH***), 96.7 (***C-2***), 65.8 (***C-4,C-6***), 37.7 (***C-5***), 22.8 (***CH_3***). *m/z* (ES^+) : 245.1 ($M+Na^+$, 100%). HRMS (ES^+) found : 245.0771 ($C_{12}H_{14}O_4Na$ requires 245.0790).

5-Benzyl-2-carboxy-2-methyl-[1,3]dioxane (39,40) :

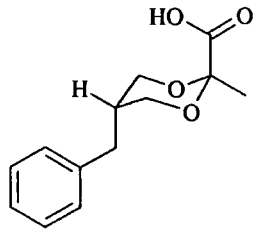
Following the general procedure, sodium hydroxide pellets (NaOH, 6.4 g, 0.16 mol) were added to a solution of an isomeric misxture of **(31,32)** (7:3 ratio) (8.5 g, 36.0 mmol) in THF/H_2O (1:1, 75 ml). After purification by chromatography, the 2 isomers were not separable and the title acid acetals **(39,40)** (6.04 g, 80%) were obtained as a colorless oil. Recrystallisation from cyclohexane afforded the major isomer **(39)** (3.55 g) as a white solid. The mother liquors contained a mixture (1:3) ratio of **(39)** and **(40)** (2.49 g).

Major isomer **(39)** :



m.p. : 99-101°C. ν_{max} (ATR) : 3200-2700 (CO***OH***), 1718 (***C=O***), 1142, 1032, 750, 672 cm^{-1}. δ_H (400 MHz) : 8.1 (1H, s, CO***OH***), 7.30-7.23 (2H, m, ***Ar-H***), 7.23-7.20 (1H, m, ***Ar-H***), 7.20-7.05 (2H, m, ***Ar-H***), 3.98 (2H, dd, J= 11.5, 4.2 Hz, ***4-H_{eq},6-H_{eq}***), 3.58 (2H, dd, J= 11.5, 10.8 Hz, ***4-H_{ax},6-H_{ax}***), 2.40-2.30 (3H, m, ***5-H,CH_2***Ph), 1.60 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 174.0 (***CO***), 137.9 (***C-1'***), 129.2+128.8+126.7 (5×***Ar-CH***), 98.2 (***C-2***), 68.3 (***C-4,C-6***), 35.1 (***C-5***), 34.8 (***CH_2***Ph), 25.9 (***CH_3***). *m/z* (ES^+) : 259.1 ($M+Na^+$, 100%). Anal. [found : C 65.94, H 6.84 %, required for $C_{13}H_{16}O_4$: C 66.08, H 6.84 %].

Minor isomer **(40) :** (as a mixture with the major isomer)



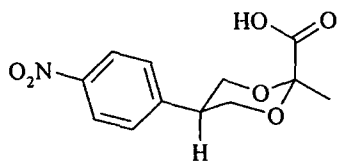
δ_H (400 MHz) : 7.95 (1H, s, CO***OH***), 7.40-7.30 (2H, m, ***Ar-H***), 7.30-7.20 (2H, m, ***Ar-H***), 7.15-7.05 (1H, m, ***Ar-H***), 4.04 (2H, dd, J= 12.2, 2.8 Hz, ***4-H_{eq},6-H_{eq}***), 3.84 (2H, dd, J= 12.2, 2.6 Hz, ***4-H_{ax},6-H_{ax}***), 3.05 (2H, d, J= 7.8 Hz, ***CH_2***Ph), 1.70-1.60 (1H, m, ***5-H***), 1.68

(3H, s, ***CH₃***). δ_C (100.5 MHz) : 175.2 (***CO***), 139.9 (***C-1'***), 129.3+128.6+126.6 (5×***Ar-CH***), 98.4 (***C-2***), 66.0 (***C-4,C-6***), 35.2 (***C-5***), 35.1 (***CH₂***Ph), 25.6 (***CH₃***). *m/z* (ES^+) : 259.1 ($M+Na^+$, 100%). HRMS (ES^+) found : 259.0937 ($C_{13}H_{16}O_4Na$ requires 259.0946).

2-Carboxy-2-methyl-5-(4'-nitrophenyl)-[1,3]dioxane (41,42) :

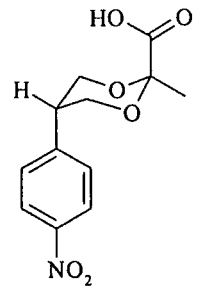
Following the general procedure, sodium hydroxide pellets (NaOH, 2.8 g, 69 mmol) were added to a solution of an isomeric mixture of **(33,34)** (7:3 ratio) (4.33 g, 15.4 mmol) in THF/H_2O (1:1, 30 ml). After purification by chromatography, the two isomers were not separable and the title acid acetals **(41,42)** (3.54 g, 86%) were obtained as a colorless oil. Recrystallisation from cyclohexane afforded the major isomer **(41)** (2.0 g) as a white solid. The mother liquors contained a mixture (3:7) ratio of **(41,42)** (1.54 g).

Major isomer **(41)** :



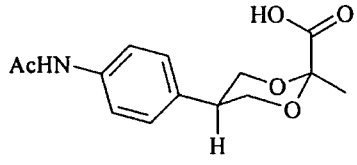
m.p. : 156-158°C. ν_{max} (ATR) : 3635-3058 (CO***OH***), 3058-2883, 1741 (***C=O***), 1520+1348 (***NO₂***), 1142, 1050, 891, 847, 752, 670 cm^{-1}. δ_H (400 MHz) : 8.19 (2H, d, J= 8.9 Hz, 2×***3'-H***), 8.0 (CO***OH***), 7.35 (2H, d, J= 8.9 Hz, 2×***2'-H***), 4.16 (2H, dd, J=11.2, 4.8 Hz, ***4-H$_{eq}$,6-H$_{eq}$***), 4.04 (2H, t, J= 11.2 Hz, ***4-H$_{ax}$,6-H$_{ax}$***), 3.40 (1H, dd, J= 11.2, 4.8 Hz, ***5-H***), 1.68 (3H, s, ***CH₃***). δ_C (100.5 MHz) : 174.0 (***CO***), 147.5 (***C-1'***), 145.0 (***C-4'***), 129.0 (2×***C-2'***), 124.5 (2×***C-3'***), 98.0 (***C-2***), 68.0 (***C-4,C-6***), 40.5 (***C-5***), 27.2 (***CH₃***). *m/z* (ES^+) : 259.1 ($M+Na^+$, 100%). HRMS (ES^+): 322.0887 ($C_{13}H_{17}NO_7Na$ requires 322.0903). Anal. [found : C 65.94, H 6.84 %, required for $C_{13}H_{16}O_4$: C 66.08, H 6.84 %].

Minor isomer (42) : (as a mixture with the major isomer)



δ_H (400 MHz) : 8.25 (2H, d, J= 8.5Hz, 2×***3'-H***), 8.1 (CO***OH***), 7.75 (2H, d, J= 8.5 Hz, 2×***2'-H***), 4.45 (2H, dd, J= 12.3, 3.4 Hz, ***4-H_{ax},6-H_{ax}***), 4.20 (2H, m, ***4-H_{eq},6-H_{eq}***), 2.90 (1H, m, ***5-H***), 1.71 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 174.0 (***CO***), 149.5 (***C-1'***), 147.2 (***C-4'***), 129.5 (2×***C-2'***), 124.0 (2×***C-3'***), 99.0 (***C-2***), 67.0 (***C-4,C-6***), 38.5 (***C-5***), 26.0 (***CH_3***). *m/z* (ES^+) : 259.1 ($M+Na^+$, 100%).

5-(4'-Acetamidophenyl)-2-Carboxy-2-methyl-[1,3]dioxane (43) :



Following the general procedure, sodium hydroxide pellets (NaOH, 2.65 g, 66.1 mmol) were added to a solution of **(35)** (4.3 g, 14.7 mmol) in THF/H_2O (1:1, 30 ml). After purification by chromatography, the acid acetal **(43)** (3.82 g, 93%) was obtained as a white solid.

m.p. : 160-164°C. ν_{max} (thin film) : 3710-2700 (***NH+COOH***), 1761 (***C=O***), 1680 (NH***CO***), 1109 cm^{-1}. δ_H (300 MHz) : 7.47 (2H, d, J= 8.4 Hz, 2×***3'-H***), 7.3- (1H, bs, MeCO***NH***), 7.10 (2H, d, J= 8.4 Hz, 2×***2'-H***), 4.08 (2H, dd, J= 11.4, 3.9 Hz, ***4-H_{eq},6-H_{eq}***), 3.91 (2H, t, J= 11.4 Hz, ***4-H_{ax},6-H_{ax}***), 3.22 (1H, m, ***5-H***), 2.19 (3H, s, NHCO***CH_3***), 1.65 (3H, s, ***CH_3***). δ_C (75.4 MHz) : 173.6 (***CO***OH), 168.9 (NH***CO***CH_3), 144.1 (***C-4'***), 133.2 (***C-1'***), 128.4 (2×***C-2'***), 120.6 (2×***C-3'***), 98.1 (***C-2***), 68.4 (***C-4,C-6***), 39.5 (***C-5***), 26.1

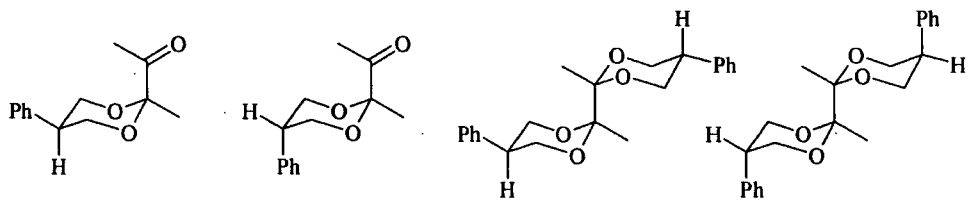
(***CH*$_3$**), 24.8 (NHCO***CH*$_3$**). *m/z* (ES^+): 302 ($M+Na^+$, 100%), 280 ($M+H^+$, 55%). HRMS (ES^+) found : 280.1184 ($C_{14}H_{18}O_5$ requires 280.1180).

N-methyl-N-nitroso-*p*-toluenesulfonamide preparation :

Following the protocol of DeBoer and Wacker, *p*-toluene sulfonyl chloride (56.25 g, 0.295 mol) were slowly added to methylamine (CH_3NH_2, 40% in H_2O, 70 ml, 0.81 mol, 1.5 eq.) at room temperature. The reaction mixture was heated to 80-90°C with rigorous stirring and 15 ml of aqueous NaOH solution (prepared by dissolving 21.88 g of NaOH pellets in 22 ml of H_2O) were added. Further *p*-toluene sulfonyl chloride (31.25 g, 0.164 mol) was added followed by 7.5 ml of aqueous NaOH solution. Finally, a third batch of *p*-toluene sulfonyl chloride (12.5 g, 0.066 mol) was added followed by the remainder of the NaOH solution. The sides of the flask were washed with a small amount of H_2O and the reaction was heated to 100°C and stirred at that temperature for 15 mins. The reaction mixture was poured into glacial acetic acid (500 ml) and the flask washed with further glacial acetic acid (80 ml). The reaction mixture was cooled with an ice bath and a solution of sodium nitrite in water (38.75 g of $NaNO_2$ in 78 ml of H_2O) was added over 1 hour. The reaction mixture was stirred at 10°C for 20 mins and a yellow precipitate of N-methyl-N-nitroso-*p*-toluenesulfonamide was formed. The precipitate was collected by filtration and washed three times with water (3×100 ml) to remove any acetic acid. The product was obtained as a shiny yellow solid (76.6 g, 68%).

Diazotransfer method :

2-Ethanone-2-methyl-5-phenyl-1,3-dioxane (44,45) and dimers (46,47) :



To a solution of 2-phenylpropane-1,3-diol (3.85 g, 25.3 mmol) and butan-1,4-dione (2 ml, 23.0 mmol, 1.1 eq) in benzene (100 ml), *p*-TsOH (*p*-toluene sulfonic acid, 219 mg, 1.15 mmol, 5 mol%) was added. The reaction mixture was stirred at reflux overnight using a Dean-Stark trap to collect the water formed during the reaction. After cooling to room

temperature, the solvent was removed by evaporation. Brine and CH_2Cl_2 were added to the residue. After separation, the organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The GC analysis of the residue showed the presence of four compounds. The GC/MS identified those compounds as being a mixture of the desired methyl ketone (45 %, two isomers **(44,45)** in a 3:2 ratio, m/z: 238, $[M+NH_4]^+$, 100%) and dimerization products (30 %, 2 isomers **(46,47)** in a 9:1 ratio, m/z: 372 [M+NH4]+, 10%). After purification by chromatography (petroleum ether/EtOAc : 98:2 then 9:1), the methyl ketones **(44,45)** were obtained as a non separable mixture (3:2 ratio, 2.27 g, 45%) and the dimers **(46,47)** were obtained as a non separable mixture (9:1 ratio, 2.33 g, 30%).

Methyl ketones **(44,45)** :

ν_{max} (ATR) : 2990-2850, 1725 (***CO***), 1495, 1355, 1188, 1135, 1048, 1026, 879, 755, 699 cm^{-1}.δ_H (500 MHz) : 7.42-7.20 (8H, m, Ar-CH), 7.15-7.05 (2H, m, ***Ar-CH***), 4.17-3.98 (6H, m, ***4-H$_{eq}$***(major),***6-H$_{eq}$***(major), 2×***4-H***(minor), 2×***6-H***(minor)), 3.80 (2H, bt, J= 11.6 Hz, ***4-H$_{ax}$***(major),***6-H$_{ax}$***(major)), 3.34-3.10 (1H, m, ***5-H***(major)), 3.01-2.86 (1H, m, ***5-H***(minor)), 2.30 (3H, s, CO***CH$_3$***(major)), 2.29 (3H, s, CO***CH$_3$***(minor)), 1.53 (3H, s, ***CH$_3$***(minor)), 1.47 (3H, s, ***CH$_3$***(major)). δ_C (125.7 MHz): 208.3 (***CO***(major)), 206.5 (***CO***(minor)),140.0 (***C-1'***(minor)), 137.2 (***C-1'***(major)), 128.7 + 128.6 + 127.8 + 127.55 + 127.5 + 127.1 (10×***Ar-CH***), 100.7 (***C-2***(major)), 99.7 (***C-2***(minor)), 67.8 (***C-4***(major),***C-6***(major)), 66.0 (***C-4***(minor),***C-6***(minor)), 40.3 (***C-5***(major)), 39.6 (***C-5***(minor)), 25.3 (CO***CH$_3$***(major)), 24.6 (***CH$_3$***(major)), 24.4 (CO***CH$_3$***(minor)), 19.7 (***CH$_3$***(minor)). *m/z* (CI) : 238 ($M+NH_4^+$, 100%), 221 ($M+H^+$, 10%).

Dimers **(46,47)** :

2,2'-Dimethyl-5,5'-diphenyl-[2,2']bi[[1,3]dioxanyl]

δ_H (500 MHz) : 7.40-7.14 (20H, m, ***Ar-CH***), 4.15-4.01 (16H, m, (2×***4-H***,2×***6-H***,2×***4'-H***,2×***6'-H***)(major), (2×***4-H***,2×***6-H***,2×***4'-H***,2×***6'-H***)(minor)), 3.29-3.17 (4H, m, (***5-H***,***5'-H***)(major), (***5-H***,***5'-H***)(minor)), 1.73 (12H, s, (***2-CH$_3$***,***2'-CH$_3$***)(major), (***2-CH$_3$***,***2'-CH$_3$***)(minor)). δ_C (125.7 MHz) : 138.0 (4×***C-IV^{aire}***-Ar), 128.7+127.7+127.4 (20×***CH***-Ar), 100.5 (2×***C-2***,2×***C-2'***), 65.2 (***C-4***(minor),***C-4'***(minor),***C-6***(minor),***C-6'***(minor)), 60.4 (***C-4***(major),***C-4'***(major),***C-6***(major),***C-6'***(major)), 41.3 (2×***C-5***,2×***C-5'***), 21.0 (2×***2-CH$_3$***,2×***2'-CH$_3$***). *m/z* (CI) : 372 ($M+NH_4^+$, 15%), 355 (M+H+, 10%), 238

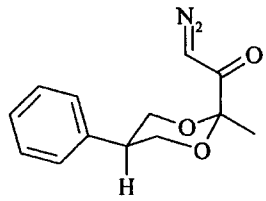
(monomer+NH_4^+, 60%), 221 (monomer+H+, 22%), 205 (65%), 189 (30%), 177 (15%), 119 (30%), 72 (100%).

General procedure for diazoketone synthesis :

A solution of carboxylic acid (1eq) and triethylamine (1.5 eq) in anhydrous CH_2Cl_2 was cooled at -15°C and isobutyl chloroformate (1.2 eq) was added dropwise at the same temperature. After 2h-3h (reaction followed by TLC), an excess of an ethereal solution of diazomethane (2.2eq) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. When the reaction was complete, argon was bubbled through the solution with vigorous stirring and a small amount of dilute acetic acid was added to remove the excess of diazomethane. The resulting mixture was successively washed with ammonium chloride (NH_4Cl), sodium bicarbonate ($NaHCO_3$) and brine. The organic phase was then dried over magnesium sulfate ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography on silica gel.

2-Diazoacetyl-2-methyl-5-phenyl-1,3-dioxane (49,50) :

Major isomer **(49)** :

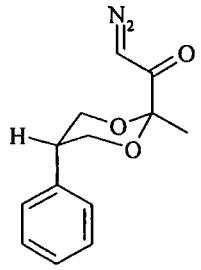


Following the general procedure, Et_3N (6.6 ml, 48 mmol) and iBuOCOCl (4.9 ml, 38 mmol) were added to a solution of acid **(37)** (4.33 g, 15.4 mmol) in CH_2Cl_2 at -20°C. After 2 hours, an excess of diazomethane (CH_2N_2, 215.3 ml, 70.4 mmol) was added. The reaction was allowed to warm to room temperature and stirred overnight. Purification by flash chromatography (Petrol/EtOAc, 9:1 then 8:2) gave the diazoketone **(49)** (6.32 g, 80%) as a yellow solid.

m.p. : 78-82°C. ν_{max} (ATR) : 3101, 2955-2868, 2107 (***C=N=N***), 1654 (***CO***), 1338, 1189, 1131, 1025, 829, 767, 702 cm^{-1}. δ_H (400 MHz) : 7.32-7.26 (3H, m, ***Ar-CH***), 7.15-7.10 (2H, m, ***Ar-CH***), 5.80 (1H, s, ***CH***N_2), 4.05 (2H, dd, J= 11.6, 4.5 Hz, ***4-H$_{eq}$,6-H$_{eq}$***), 3.93

(2H, t, J= 11.6 Hz, ***4-H_{ax},6-H_{ax}***), 3.20 (1H, dd, J= 4.5, 11.6 Hz, ***5-H***), 1.50 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 192.4 (***CO***); 135.6 (***C-1'***), 127.2+126.1+126 (5×***Ar-CH***), 98.6 (***C-2***), 66.3 (***C-4,C-6***), 52.3 (***CH***N_2), 38.7 (***C-5***), 24.6 (***CH_3***). *m/z* (ES^+) : 269.1 ($M+Na^+$, 100%). Anal. [found : C 63.31, H 5.74, N 11.37 % required for $C_{13}H_{14}N_2O_3$: C 63.39, H 5.74, N 11.38 %].

Minor isomer **(50)** :

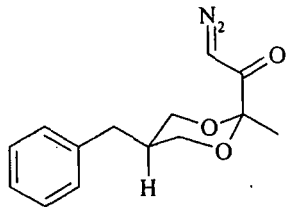


Following the general procedure, Et_3N (0.35 ml, 2.5 mmol) and iBuOCOCl (0.28 ml, 2.2 mmol) were added to a solution of acid **(38)** (0.4 g, 1.8 mmol) in CH_2Cl_2 at -20°C. After 2 hours, an excess of diazomethane (CH_2N_2, 12.1 ml, 4.0 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. Purification by flash chromatography (Petrol/EtOAc, 9:1 then 8:2) gave the diazoketone **(50)** (0.36 g, 82%) as a yellow solid.

m.p. : 68-70°C. ν_{max} (ATR) : 3093, 3023-2906, 2843, 2105 (***C=N=N***), 1650 (***CO***), 1337, 1191, 1130, 1025, 880, 827, 764, 701 cm^{-1}. δ_H (400 MHz) : 7.38-7.35 (2H, m, ***Ar-CH***), 7.30-7.20 (3H, m, ***Ar-CH***), 5.75 (1H, s, ***CH***N_2), 4.18 (2H, dd, J= 11.8, 3.8 Hz, ***4-H_{eq},6-H_{eq}***), 4.08 (2H, dd, J= 11.8, 4.4 Hz, ***4-H_{ax},6-H_{ax}***), 2.73 (1H, dd, J= 4.4, 3.8 Hz, ***5-CH***), 1.50 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 193.4 (***CO***); 140.8 (***C-1'***), 128.6+128+127 (5×***Ar-CH***), 99.8 (***C-2***), 66.3 (***C-4,C-6***), 53.3 (***CH***N_2), 39.1 (***C-5***), 22.8 (***CH_3***). *m/z* (ES^+) : 269.1 ($M+Na^+$, 100%). HRMS (ES^+) found : 269.0890 ($C_{13}H_{14}N_2O_3Na$ requires 269.0902).

5-Benzyl-2-diazoacetyl-2-methyl-1,3-dioxane (51,52) :

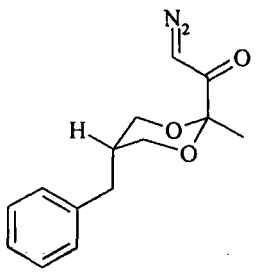
Major isomer **(51) :**



Following the general procedure, Et_3N (0.45 ml, 3.3 mmol) and iBuOCOCl (0.36 ml, 2.8 mmol) were added to a solution of acid **(39)** (0.55 g, 2.3 mmol) in CH_2Cl_2 at -20°C. After 2 hours, an excess of diazomethane (CH_2N_2, 15.5 ml, 5.06 mmol) was added. The reaction was allowed to warm to room temperature and stirred overnight. Purification by flash chromatography (Petrol/EtOAc, 9:1 then 8:2) gave the diazoketone **(51)** (0.50 g, 85%) as a yellow solid.

m.p. : 63-65°C. ν_{max} (ATR) : 3131, 2974-2871, 2107 (***C=N=N***); 1626 (***C=O***), 1335, 1131, 1023, 829, 730, 700, 670 cm^{-1}. δ_H (400 MHz) : 7.32-7.28 (2H, m, ***Ar-CH***), 7.23-7.10 (3H, m, ***Ar-CH***), 5.70 (1H, s, ***CH***N_2), 3.85 (2H, dd, J= 11.6, 4.5 Hz, ***4-H_{eq},6-H_{eq}***), 3.52 (2H, t, J= 11.6 Hz, ***4-H_{ax},6-H_{ax}***), 2.40-2.30 (3H, m, ***5-H,CH_2***Ph), 1.40 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 194.4 (***CO***), 138.0 (***C-1'***), 128.9+128.8+126.7 (5×***Ar-CH***), 100.7 (***C-2***), 67.8 (***C-4,C-6***), 53.8 (***CH***N_2), 35.2 (***C-5***), 34.9 (***CH_2***), 26.1 (***CH_3***). *m/z* (ES^+) : 283.1 ($M+Na^+$, 100%). Anal. [found : C 64.22, H 6.29, N 10.44 % required for $C_{14}H_{16}N_2O_3$: C 64.59, H 6.21, N 10.76 %].

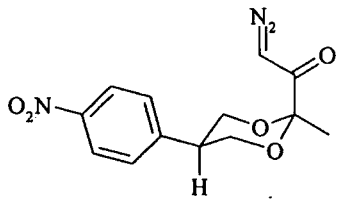
Minor isomer **(52) :**



Following the general procedure, Et_3N (0.45 ml, 3.3 mmol) and iBuOCOCl (0.36 mL, 2.8 mmol) were added to a solution of the mixed acids **(39)** and **(40)** (1:3 ratio) (0.55 g, 2.3 mmol) in CH_2Cl_2 at -20°C. After 2 hours, an excess of diazomethane (CH_2N_2, 15.5 ml, 5.06 mmol) was added. The reaction was allowed to warm to room temperature and stirred overnight. Purification by flash chromatography (Petrol/EtOAc, 9:1 then 8:2) gave a mixture of the diazoketones **(51,52)** (0.47 g, 80%) in a (1:3) ratio as a yellow solid.
The analytical data for the minor isomer were deduced by comparison of the data of the mixture with the analytical data of the pure major isomer.

δ_H (400 MHz) : 7.32-7.28 (2H, m, ***Ar-CH***), 7.25-7.20 (3H, m, ***Ar-CH***), 5.70 (1H, s, ***CHN$_2$***), 3.95 (2H, dd, J= 12.0, 2.6 Hz, ***4-H$_{eq}$,6-H$_{eq}$***), 3.72 (2H, dd, J= 12.0, 2.5 Hz, ***4-CH$_{ax}$,6-CH$_{ax}$***), 2.95 (2H, d, J= 8.2 Hz, ***CH$_2$***Ph), 1.65 (1H, m, ***5-H***), 1.44 (3H, s, ***CH$_3$***). δ_C (100.5 MHz) : 194.3 (***CO***), 140.0 (***C-1'***), 129.3+128.6+126.4 (5×***Ar-CH***), 100.6 (***C-2***), 65.6 (***C-4,C-6***), 53.6 (***CH***N_2), 35.4 (***C-5***), 35.0 (***CH$_2$***Ph), 27.0 (***CH$_3$***). *m/z* (ES^+) : 283.1 ($M+Na^+$, 100%). HRMS (ES^+) : 283.1060 ($C_{14}H_{16}N_2O_3Na$ requires 283.1059).

2-Diazoacetyl-2-methyl-5-(4'-nitrophenyl)-1,3-dioxane (53,54) :
Major isomer **(53)** :

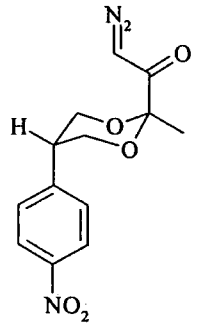


Following the general procedure, Et_3N (1.60 ml, 11.2 mmol) and iBuOCOCl (1.20 ml, 9.5 mmol) were added to a solution of acid **(41)** (2.0 g, 7.5 mmol) in CH_2Cl_2 at -20°C. After 2 hours, an excess of diazomethane (CH_2N_2, 50.5 ml, 16.5 mmol) was added. The reaction was allowed to warm to room temperature and stirred overnight. Purification by flash chromatography (Petrol/EtOAc, 9:1 then 8:2) gave the diazoketone **(53)** (1.64 g, 75%) as a yellow solid.

m.p. : 138-140°C. ν_{max} (ATR) : 3117, 2983-2867, 2114 (***C=N=N***), 1638(***C=O***), 1520+1343 (***NO$_2$***), 1188, 1138, 1027, 852, 828, 754, 700, 640 cm^{-1}. δ_H (400 MHz) : 8.10

(2H, d, J= 8.7 Hz, 2×***3'-H***), 7.26 (2H, d, J= 8.7 Hz, 2×***2'-H***), 5.71 (1H, s, ***CH***N_2), 4.00 (2H, dd, J= 11.7, 4.6 Hz, ***4-*** H_{eq}***,6-*** H_{eq}), 3.90 (2H, t, J= 11.7 Hz, ***4-*** H_{ax}***,6-*** H_{ax}), 3.29 (1H, dd, J= 11.7, 4.6 Hz, ***5-H***), 1.40 (3H, s, ***CH***$_3$). δ_C (100.5 MHz) : 193.5 (***CO***); 158.0 (***C-1'***), 145.5 (***C-4'***), 129.0 (2×***C-2'***), 124.5 (2×***C-3'***), 101.0 (***C-2***), 67.0 (***C-4,C-6***), 55.0 (***CH***N_2), 40.5 (***C-5***), 26.2 (***CH***$_3$). *m/z* (ES^+) : 314.1 ($M+Na^+$, 100%). HRMS (ES^+) found : 314.0757 ($C_{13}H_{13}N_3O_5Na$ requires 314.0753). Anal. [found : C 53.59, H 4.58, N 14.28 % required for $C_{13}H_{13}N_3O_5$: C 53.61, H 4.50, N 14.43 %].

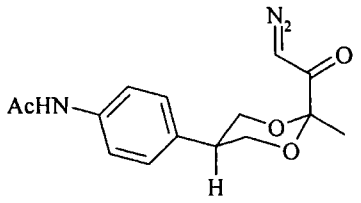
Minor isomer **(54)** :



Following the general procedure, Et_3N (0.55 ml, 3.9 mmol) and iBuOCOCl (0.44 ml, 3.5 mmol) were added to a mixture of acids **(41)** and **(42)** in a (3:7) ratio (2.0 g, 7.5 mmol) in CH_2Cl_2 at -20°C. After 2 hours, an excess of diazomethane (CH_2N_2, 50.5 ml, 16.5 mmol) was added. The reaction was allowed to warm to room temperature and stirred overnight. Purification by flash chromatography (Petrol/EtOAc, 9:1 then 8:2) gave the diazoketone **(54)** (0.37 g, 70%) as a yellow solid.

m.p. : 114-116°C. ν_{max} (ATR) : 3120, 2980-2862, 2114 (***C=N=N***), 1645 (***C=O***), 1508+1337 (***NO***$_2$), 1198, 1102, 1030, 851, 827, 754, 700, 640 cm^{-1}. δ_H (400 MHz) : 8.26 (2H, d, J= 8.8 Hz, ***3'-H***), 7.74 (2H, d, J= 8.8 Hz, ***2'-H***), 5.81 (1H, s, ***CH***N_2), 4.35 (2H, dd, J= 12.5, 3.6 Hz, ***4-*** H_{ax}***,6-*** H_{ax}), 4.16-4.10 (2H, dd, J= 12.5, 3.7 Hz, ***4-*** H_{eq}***,6-*** H_{eq}), 2.84 (1H, m, ***5-H***), 1.55 (3H, s, ***CH***$_3$). δ_C (100.5 MHz) : 193.0 (***CO***); 149.5 (***C-1'***), 147.0 (***C-4'***), 129.5 (2×***C-2'***), 124.0 (2×***C-3'***), 101.5 (***C-2***), 66.0 (***C-4,C-6***), 54.5 (***CH***N_2), 38.5 (***C-5***), 25.5 (***CH***$_3$). *m/z* (ES^+) : 314.1 ($M+Na^+$, 100%). Anal. [found : C 53.58, H 4.65, N 14.62 % required for $C_{13}H_{13}N_3O_5$: C 53.61, H 4.50, N 14.43 %].

5-(4'-Acetamidophenyl)-2-diazoacetyl-2-methyl-1,3-dioxane (55) :



Following the general procedure, Et_3N (1.2 ml, 8.6 mmol) and iBuOCOCl (1.12 ml, 8.6 mmol) were added to the acid **(43)** (2.0 g, 7.2 mmol) in CH_2Cl_2 at -20°C. After 2 hours, an excess of diazomethane (CH_2N_2, 50.5 ml, 16.5 mmol) was added. The reaction was allowed to warm to room temperature and stirred overnight. After work up, purification by flash chromatography (Petrol/EtOAc, 9:1 then 8:2) gave the diazoketone **(55)** (1.72 g, 79%) as a yellow solid.

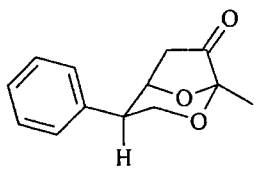
m.p. : 162-163°C. ν_{max} (thin film): 3054 (***NH***), 2988, 2116 (***C=N=N***), 1654 (NH***CO***) cm^{-1}. δ_H (300 MHz) : 7.43 (2H, d, J= 8.4 Hz, 2×***3'-H***), 7.15 (1H, bs, MeCO***NH***), 7.07 (2H, d, J= 8.4 Hz, 2×***2'-H***), 5.77 (1H, s, ***CH***N_2), 4.03 (2H, dd, J= 11.4, 4.5 Hz, ***4-H$_{eq}$,6-H$_{eq}$***), 3.88 (2H, t, J= 11.4 Hz, ***4-H$_{ax}$,6-H$_{ax}$***), 3.19 (1H, m, ***5-H***), 2.16 (3H, s, NHCO***CH$_3$***), 1.50 (3H, s, ***CH$_3$***). δ_C (75.4 MHz) : 194.1 (***CO***CHN_2), 168.9 (NH***CO***Me), 137.5 (***C-4'***), 133.7 (***C-1'***), 128.4 (2×***C-2'***), 120.6 (2×***C-3'***), 100.4 (***C-2***), 68.1 (***C-4,C-6***), 54.2 (***CH***N_2), 39.8 (***C-5***), 26.3 (***CH$_3$***), 24.7 (NHCO***Me***). *m/z* (ES^+) : 326.1 ($M+Na^+$). HRMS (ES^+) found : 326.1105 ($C_{15}H_{17}N_3O_4Na$ requires 326.1111).

General procedure for C-H insertion step :

To a solution of rhodium acetate dimer, $Rh_2(OAc)_4$, in CH_2Cl_2 (1 mmol/L, 2 mol%), was added dropwise a solution of diazoketone in CH_2Cl_2 (100 mmol/L) over 24h *via* a syringe pump at room temperature. When the addition was complete, silica gel was added and the reaction mixture was concentrated *in vacuo*. The residue was then immediately purified by flash chromatography.

1-Methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one (56, 57) :

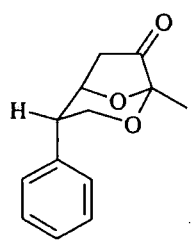
Major isomer **(56)** :



Following the general procedure, the diazoketone **(49)** (0.615 g, 2.5 mmol) in solution in CH_2Cl_2 (25 ml) was added to a solution of $Rh_2(OAc)_4$ (22.1 mg, 0.5 mmol) in CH_2Cl_2 (50 ml). After purification by chromatography (cyclohexane/EtOAc : 9/1), the C-H insertion product **(56)** (0.245 g, 45%) was obtained as a white solid.

m.p.: 78-80°C. ν_{max} (ATR) : 3000-2838, 1763 (***C=O***), 1259, 1183, 1086, 1021, 862, 799, 759, 699, 668 cm^{-1}. δ_H (400 MHz) : 7.35-7.15 (3H, m, ***Ar-CH***), 7.07 (2H, d, J= 7.0 Hz, ***Ar-CH***), 4.83 (1H, dd, J= 7.1, 3.3 Hz, ***5-H***), 4.25-4.15 (2H, m, ***3-H_{ax}***, ***3-H_{eq}***), 3.80 (1H, ddd, J= 10.2, 7.7, 3.3 Hz, ***4-H***), 2.50 (1H, dd, J= 18.7, 7.1 Hz, ***6-H_{α}***), 2.35 (1H, d, J= 18.7 Hz, ***6-H_{β}***), 1.4 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 210.7 (***CO***), 136.3 (***C-1'***), 129.1+127.6+127.2 (5×***Ar-CH***), 98.2 (***C-1***), 76.1 (***C-5***), 64.1 (***C-3***), 42.2 (***C-6***), 36.4 (***C-4***), 18.1 (***CH_3***). *m/z* (CI, NH_3) : 236 ($[MH+NH_3]^+$, 50%), 219 ($[MH]^+$, 100%), 201 (25%), 187 (62%), 173 (60%), 157 (9%), 130 (62%), 117 (19%), 104 ($[PhCHCH_2]^+$, 34%), 91 ($[PhCH]^+$, 17%), 77 ($[Ph]^+$, 12%). HRMS (ES^+) : 218.0965 ($C_{13}H_{14}O_3$ requires 218.0941).

Minor isomer **(57)** :

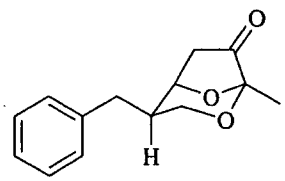


Following the general procedure, the diazoketone **(50)** (0.615 g, 2.5 mmol) in solution in CH_2Cl_2 (25 ml) was added to a solution of $Rh_2(OAc)_4$ (22.1 mg, 0.5 mmol) in CH_2Cl_2 (50

ml). After purification by chromatography (cyclohexane/EtOAc : 9/1), the C-H insertion product **(57)** was obtained as a non separable mixture with an unknown by-product.
The relevant peaks of the product, selected from the NMR of the mixture, are reported below.

δ_H (400 MHz) : 7.40-7.23 (5H, m, ***Ar-CH***), 4.77 (1H, d, J= 7.4 Hz, ***5-H***), 4.40 (2H, m, ***3-H_{ax}, 3-H_{eq}***), 3.37 (1H, m, ***4-H***), 2.90 (1H, dd, J= 18.3, 7.4 Hz, ***6-H_α***), 2.48 (1H, d, J= 18.3 Hz, ***6-H_β***), 1.45 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 211.0 (***CO***), 138.4 (***C-1'***), 128.9+128.5+127.7 (5×***Ar-CH***), 98.6 (***C-1***), 76.9 (***C-5***), 64.8 (***C-3***), 43.7 (***C-4***), 40.9 (***C-6***), 18.6 (***CH_3***).

4-Benzyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-7-one (58) :

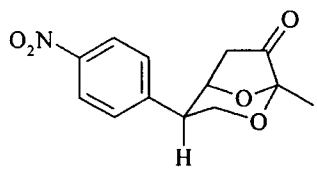


Following the general procedure, the diazoketone **(51)** (0.23 g, 0.885 mmol) in solution in CH_2Cl_2 (8.85 ml) was added to a solution of $Rh_2(OAc)_4$ (7.8 mg, 0.018 mmol) in CH_2Cl_2 (18 ml). After purification by chromatography (cyclohexane/EtOAc : 9/1), the C-H insertion product **(58)** (0.10 g, 50%) was obtained as a white solid.

m.p : 80-82°C. ν_{max} (ATR) : 3062, 3000-2842, 1752 (***C=O***), 1180, 1095, 1020, 858, 742, 702, 550 cm^{-1}. δ_H (400 MHz) : 7.3-7.25 (2H, m, ***3'-H***), 7.22-7.15 (1H, m, ***4'-H***), 7.12 (2H, d, J= 7.2 Hz, ***2'-H***), 4.55 (1H, ddd, J= 7.5, 3.4, 1.0 Hz, ***5-H***), 3.88 (1H, ddd, J= 12.1, 5.8, 1.0 Hz, ***3-H_{eq}***), 3.63 (1H, t, J= 12.1 Hz, ***3-H_{ax}***), 2.85-2.80 (1H, m, ***4-H***), 2.63 (1H, dd, J= 18.4, 7.5 Hz, ***6-H_α***), 2.48 (1H, d, J= 18.4 Hz, ***6-H_β***), 2.38 (2H, d, J= 8.1 Hz, ***CH_2***Ph), 1.35 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 211.0 (***CO***), 137.4 (***C-1'***), 128.9+128.6+126.8 (5×***Ar-CH***), 98.0 (***C-1***), 74.5 (***C-5***), 66.0 (***C-3***), 38.8 (***C-4***), 35.9 (***C-6***), 34.8 (***CH_2***Ph), 18.2 (***CH_3***). ***m/z*** (CI, NH_3) : 250 ([M+NH_4^+], 29%), 233 ([MH^+], 100%), 217 (12%), 203 (20%), 187 (10%), 144 (25%), 129 (10%), 91 ([PhCH]$^+$, 18%), 77 ([Ph]$^+$, 5%). HRMS (ES^+) found : 287.1223 ($C_{15}H_{20}O_4Na$ requires 287.1259).

1-Methyl-4-(4'-nitrophenyl)-2,8-dioxabicyclo[3.2.1]octan-7-one (59,60) :

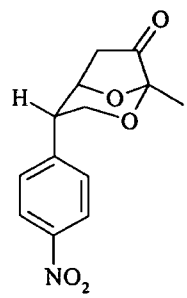
Major isomer **(59)** :



Following the general procedure, the diazoketone **(53)** (0.7275 g, 2.5 mmol) in solution in 25 mL in CH_2Cl_2 was added to a solution of Rh_2OAc_4 (20.1 mg, 0.05 mmol) in 50 mL of CH_2Cl_2. After purification by chromatography (cyclohexane/EtOAc : 9/1), the C-H insertion product **(59)** (0.13 g, 20 %) was obtained as a white solid.

m.p : 148-150°C. ν_{max} (ATR) : 3000-2833, 1771 (***C=O***), 1517+1347 (***NO₂***), 1183, 1091, 853, 745, 697, 668 cm^{-1}. δ_H (400 MHz) : 8.22 (2H, d, J= 8.8 Hz, 2×***3'-H***), 7.33 (2H, d, J= 8.8 Hz, 2×***2'-H***), 4.98 (1H, dd, J= 7.5, 3.3 Hz, ***5-H***), 4.33-4.20 (2H, m, ***3-H_{ax},3-H_{eq}***), 3.93 (1H, ddd, J= 10.9, 6.5, 3.3 Hz , ***4-H***), 2.67 (1H, dd, J= 18.5, 7.5 Hz, ***6-H_α***), 2.35 (1H, d, J= 18.5 Hz, ***6-H_β***), 1.47 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 210.0 (***CO***), 147.2 (***C-1'***), 143.8 (***C-4'***), 128.0 (2×***C-2'***), 124.3 (2×***C-3'***), 98.0 (***C-1***), 75.5 (***C-5***), 64.0 (***C-3***), 42.0 (***C-4***), 36.3 (***C-6***), 18.0 (***CH_3***). m/z (ES^+) : 286 ($M+Na^+$, 5%).

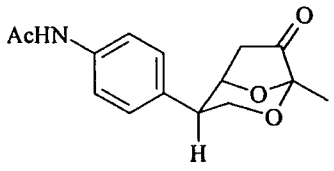
Minor isomer **(60) :**



Following the general procedure, the diazoketone **(54)** (0.7275 g, 2.5 mmol) in solution in CH_2Cl_2 (25 ml) was added to a solution of $Rh_2(OAc)_4$ (20.1 mg, 0.05 mmol) in CH_2Cl_2 (50 ml). After purification by chromatography (cyclohexane/EtOAc : 9/1), the C-H insertion product **(60)** (65.7 mg, 10%) was obtained as a white solid.

m.p : 143-145°C. ν_{max} (ATR) : 2960-2855, 1769 (***C=O***), 1517+1347 (***NO₂***), 1184, 1092, 853, 745, 722, 697, 668 cm^{-1}. δ_H (400 MHz) : 8.17 (2H, d, J= 8.8 Hz, 2×***3'-H***), 7.70 (2H, d, J= 8.8 Hz, 2×***2'-H***), 4.69 (1H, d, J= 7.5 Hz, ***5-H***), 4.34 (1H, dd, J= 12.8, 4.3 Hz, ***3-H$_{ax}$***), 4.09 (1H, d, J= 12.8 Hz, ***3-H$_{eq}$***), 2.87 (1H, dd, J= 18.0, 7.5 Hz, ***6-H$_{\alpha}$***), 2.74 (1H, d, J= 4.3 Hz, ***4-H***), 2.43 (1H, d, J= 18.0 Hz, ***6-H$_{\beta}$***), 1.37 (3H, s, ***CH₃***). δ_C (100.5 MHz) : 210.1 (***CO***), 149.8 (***C-1'***), 147.5 (***C-4'***), 128.9 (2×***C-2'***), 124.0 (2×***C-3'***), 99.2 (***C-1***), 75.8 (***C-5***), 64.5 (***C-3***), 43.5 (***C-4***), 40.5 (***C-6***), 18.5 (***CH₃***). *m/z* (CI, NH_3) : 281 ([M+NH_4^+], 15%), 264 ([MH^+], 50%), 234 (85%), 218 ([MH-NO_2]$^+$, 10%), 148 (45%), 134 (50%), 120 (100%). HRMS (ES^+) found : 304.0793 ($C_{13}H_{15}O_6Na$ requires 304.0792).

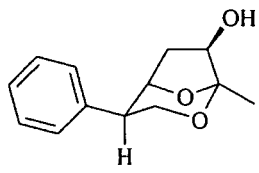
4-(4'-Acetamidophenyl)-1-methyl-2,8-dioxabicyclo[3.2.1]octan-7-one (61) :



Following the general procedure, the diazoketone **(55)** (0.303 g, 1.0 mmol) in solution in CH_2Cl_2 (10 ml) was added to a solution of $Rh_2(OAc)_4$ (10.0 mg, 0.02 mmol) in CH_2Cl_2 (20 ml). After purification by chromatography (cyclohexane/EtOAc : 9/1), the C-H insertion product **(61)** (81.4 mg, 30%) was obtained as a colorless oil.

ν_{max} (thin film): 3336 (***NH***), 1764 (***C=O***), 1654 (NH***CO***), 1601, 1182, 821 cm^{-1}. δ_H (500 MHz): 7.48 (2H, d, J= 8.5 Hz, 2×***3'-H***), 7.14 (1H, bs, ***NH***COMe), 7.08 (2H, d, J= 8.5 Hz, 2×***2'-H***), 4.86 (1H, dd, J= 7.5, 3.5 Hz, ***5-H***), 4.18-4.05 (2H, m, ***3-H$_{ax}$***, ***3-H$_{eq}$***), 3.76 (1H, dt, J= 9.0, 3.5 Hz, ***4-H***), 2.52 (1H, dd, J= 18.5, 7.5 Hz, ***6-H$_{\alpha}$***), 2.39 (1H, d, J= 18.5 Hz, ***6-H$_{\beta}$***), 2.18 (3H, s, NHCO***CH₃***), 1.42 (3H, s, ***CH₃***). δ_C (126 MHz): 210.5 (***C-7***), 168.9 (NH***CO***Me), 137.5 (***C-4'***), 133.7 (***C-1'***), 128.2 (2×***C-2'***), 120.1 (2×***C-3'***), 98.4 (***C-1***), 76.2 (***C-5***), 64.1 (***C-3***), 42.1 (***C-4***), 36.2 (***C-6***), 24.8 (NHCO***Me***), 18.3 (***CH₃***). *m/z* (ES^+): 298 (M+Na^+, 100%). HRMS (ES^+) found : 298.1051 ($C_{15}H_{17}NO_4Na$ requires 298.1050).

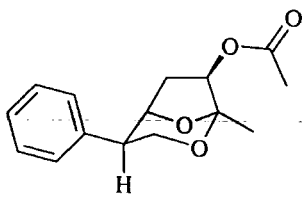
1-Methyl-4-phenyl-2,8-dioxabicyclo-[3.2.1]octan-7-ol (63) :



$NaBH_4$ (25 mg, 0.66 mmol) was added to a solution of ketone **(56)** (120 mg, 0.55 mmol) in MeOH (20 ml) at room temperature and the reaction mixture stirred at room temperature overnight. After extraction with CH_2Cl_2, the organic layer was successively washed with a saturated solution of ammonium chloride (NH_4Cl) and brine (NaCl). The organic extracts were dried over magnesium sulfate ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography on silica gel (cyclohexane/EtOAc, 8/2 then 7/3) to give the alcohol **(63)** as a white crystalline solid (105 mg, 87%).

m.p. : 109-112°C. ν_{max} (ATR) : 3600-3150 (broad ***OH***), 2995-2900, 1387, 1160, 1113, 1043, 755, 700 cm^{-1}. δ_H (400 MHz) : 7.37-7.22 (3H, m, ***Ar-CH***), 7.15 (2H, d, J=7.2 Hz, ***Ar-CH***), 4.60-4.50 (2H, m, ***5-H+3-H$_{ax}$***), 4.20-4.15 (2H, m, ***7-H+3-H$_{eq}$***), 3.55 (1H, ddd, J= 12.0, 5.5, 3.3 Hz, ***4-H***), 2.47 (1H, ddd, J= 13.5, 10.8, 7.8 Hz, ***6-H$_{\alpha}$***), 2.10 (1H, bs, ***OH***), 1.85 (1H, dd, J= 13.5, 3.9 Hz, ***6-H$_{\beta}$***), 1.48 (3H, s, ***CH$_3$***). δ_C (100.5 MHz) : 137.6 (***C-1'***), 128.9+127.5+127.3 (5×***Ar-CH***), 102.9 (***C-1***), 78.7 (***C-5***), 75.5 (***C-7***), 64.1 (***C-3***), 42.5 (***C-4***), 33.4 (***C-6***), 22.2 (***CH$_3$***). *m/z* (CI, NH_3) : 238 ($[MH+NH_3]^+$, 21%), 221 ($[MH]^+$, 100%), 204 (16%), 189 (10%), 160 (4%), 118 (2%), 104 ($[PhCHCH_2]^+$, 60%), 91 ($[PhCH]^+$, 6%), 77 ($[Ph]^+$, 2%). *m/z* (ES^+) : 243.1 ($M+Na^+$, 100%). HRMS (ES^+) found : 243.0967 ($C_{13}H_{16}O_3Na$ requires 243.0997).

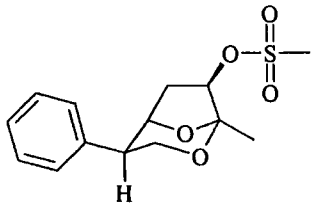
1-Methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]oct-7-yl acetate (64) :



To a solution of the alcohol **(63)** (100 mg, 0.45 mmol) in CH_2Cl_2 (10 ml), triethylamine (Et_3N, 0.32 ml, 2.3 mmol, 5 eq) and a catalytic amount of dimethylaminopyridine (DMAP, 5.6 mg, 0.045 mmol, 0.1 eq) were added at room temperature and the reaction was stirred for 30 mins. Acetic anhydride (Ac_2O, 0.08 ml, 0.9 mmol, 2 eq) was added dropwise, and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was washed with brine and the aqueous layer extracted twice with CH_2Cl_2. The organic extracts were then dried over magnesium sulfate ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 9:1 then 8:2) to give the acetate protected product **(64)** as a colorless oil (0.09 g, 75%).

ν_{max} (ATR) : 3000-2950, 1735 (***C=O***), 1385, 1180, 1110, 750, 699 cm^{-1}. δ_H (400 MHz) : 7.4-7.35 (2H, m, 2×***3'-H***), 7.3-7.2 (1H, m, ***4'-H***), 7.07 (2H, d, J= 7.0 Hz, 2×***2'-H***), 5.07 (1H, dd, J= 11.2, 3.9 Hz, ***7-H***), 4.62 (1H, ddd, J= 7.5, 3.0, 1.3 Hz, ***5-H***), 4.45 (1H, t, J= 11.7 Hz, ***3-H$_{ax}$***), 4.18 (1H, ddd, J= 11.7, 5.8, 1.3 Hz, ***3-H$_{eq}$***), 3.55 (1H, ddd, J= 11.7, 5.8, 3.0 Hz, ***4-H***), 2.65 (1H, ddd, J= 14.0, 11.2, 7.5 Hz, ***6-H$_{\alpha}$***), 1.85 (1H, dd, J= 14.0, 3.9 Hz, ***6-H$_{\beta}$***), 2.20 (3H, s, ***CH$_3$***CO), 1.50 (3H, s, ***CH$_3$***). δ_C (100.5 MHz) : 169.7 (***CO***), 136.4 (***C-1'***), 127.8 (2×***C-2'***), 127.4 (2×***C-3'***), 126.2 (***C-4'***), 101.1 (***C-1***), 77.1 (***C-7***), 74.5 (***C-5***), 62.7 (***C-3***), 41.1 (***C-4***), 30.3 (***C-6***), 21.7 (***CH$_3$***), 20.0 (***CH$_3$***CO). *m/z* (ES^+) : 285.1 (M+Na, 100%).

1-Methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]oct-7-yl methane sulfonate (65) :

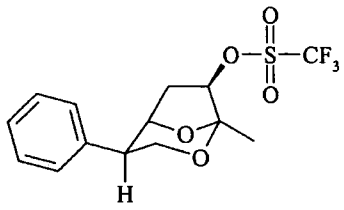


To a solution of the alcohol **(63)** (150 mg, 0.68 mmol) in CH_2Cl_2 (10 ml), triethylamine (Et_3N, 0.2 ml, 1.36 mmol, 2 eq) was added at 0°C and the mixture was stirred for 30 mins. Methane sulfonyl chloride ($MeSO_2Cl$, 0.08 ml, 1.02 mmol, 1.5 eq) was then added at 0°C and the reaction mixture was stirred at room temperature for 3.5 hours. A saturated solution of brine (NaCl) was then added and the organic phase separated from the

aqueous one, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The mesylate product **(65)** was obtained as a white solid (0.20 g, 98%) and used without further purification.

m.p. : 123-125°C. ν_{max} (ATR) : 3037-2955, 2165, 2150, 1999, 1391, 1346, 1166, 1105, 1058, 1035, 1009, 985, 954, 889, 856, 765, 700 cm^{-1}. δ_H (400 MHz) : 7.33-7.26 (2H, t, J= 8.1 Hz, ***3'-H***), 7.26-7.11 (1H, t, J= 8.1 Hz, ***4'-H***), 7.11 (2H, d, J=8.1 Hz, ***2'-H***), 4.84 (1H, dd, J= 11.0, 3.5 Hz, ***7-H***), 4.59 (1H, td, J= 7.6, 1.3 Hz, ***5-H***), 4.40 (1H, t, J= 12.0 Hz, ***3-H_{ax}***), 4.17 (1H, ddd, J= 12.0, 5.6, 1.3 Hz, ***3-H_{eq}***), 3.54 (1H, ddd, J= 12.0, 5.6, 3.4 Hz, ***4-H***), 3.12 (3H, s, SO_2***CH_3***), 2.61 (1H, ddd, J= 14.3, 11.0, 7.6 Hz, ***6-H_α***), 2.10 (1H, dd, J= 14.3, 3.5 Hz, ***6-H_β***), 1.53 (3H, s, ***CH_3***). δ_C (100.5 MHz) : 137.0 (***C-1'***), 129.2 (2×***C-3'***), 127.6 (***C-4'***), 127.5 (2×***C-2'***), 101.8 (***C-1***), 80.2 (***C-7***), 78.6 (***C-5***), 63.9 (***C-3***), 42.1 (***C-4***), 38.7 (SO_2***CH_3***), 31.3 (***C-6***), 22.5 (***CH_3***). *m/z* (ES^+) : 353.1 (M+Na+MeOH, 100%), HRMS (ES^+) found : 321.0798 ($C_{14}H_{18}O_5SNa$ requires 321.0773).

1-Methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]oct-7-yl trifluoromethane sulfonate (66) :

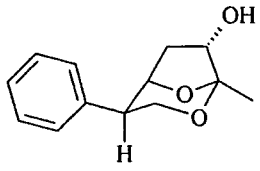


To a solution of the alcohol **(63)** (190 mg, 0.72 mmol) in CH_2Cl_2 (10 ml), trifluoromethane sulfonic anhydride (Tf_2O, 0.38 ml, 2.15 mmol, 3 eq) and 2,6-lutidine (0.25 ml, 2.15 mmol, 3 eq) were added at room temperature and the reaction mixture was stirred for 6 hours. A saturated solution of brine (NaCl) was then added. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The triflate product **(66)** was obtained (202 mg, 80%) and used without further purification.

ν_{max} (ATR) : 3116-2864, 1414+1202 (***OSO_2***), 1246, 1141, 1070, 1038, 949, 893, 758, 699, 621, 605, 579, 511 cm^{-1}. δ_H (400 MHz) : 7.35 (2H, t, J= 8.0 Hz, 2×***3'-H***), 7.28 (1H, t, J= 8.0 Hz, ***4'-H***), 7.12 (2H, d, J= 8.0 Hz, 2×***2'-H***), 5.00 (1H, dd, J= 11.1, 3.8 Hz, ***7-H***), 4.63 (1H, ddd, J= 7.5, 3.1, 1.5 Hz, ***5-H***), 4.37 (1H, t, J= 11.8 Hz, ***3-H_{ax}***), 4.23 (1H, ddd, J= 11.8, 5.9, 1.5 Hz, ***3-H_{eq}***), 3.60 (1H, ddd, J= 11.8, 5.9, 3.1 Hz, ***4-H***), 2.61 (1H, ddd, J=

14.6, 11.1, 7.5 Hz, ***6-H$_\alpha$***), 2.12 (1H, dd, J= 14.6, 3.8 Hz, ***6-H$_\beta$***), 1.55 (3H, s, ***CH$_3$***). δ_F (282.2 MHz) : -74.78. δ_C (100.5 MHz) : 136.6 (***C-1'***), 129.2 (2×***C-3'***), 127.7 (***C-4'***), 127.2 (2×***C-2'***), 119.0 (q, J= 320 Hz, ***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 (***CH$_3$***). *m/z* (ES^-) : 149.3 (OSO_2CF_3, 100%).

1-Methyl-4-phenyl-2,8-dioxabicyclo-[3.2.1]octan-7-ol (67) :



Potassium hydroxide (KOH, 24 mg, 0.43 mmol, 2eq) was added to a solution of the triflate derivative **(66)** (0.215 mmol) in DMF (10 ml). 18-crown-6 (114 mg, 0.43 mmol, 2 eq) was then added and the reaction mixture heated to reflux for 16 hours. An ice-cooled solution of saturated ammonium chloride was added, the mixture was extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc : 7:3) and the alcohol **(67)** was obtained as a colorless oil (28 mg, 60 %).

ν_{max} (ATR) : 3680-3197 (broad ***OH***), 3025-2867, 1387, 1162, 1116, 1066, 880, 756, 699 cm^{-1}. δ_H (500 MHz) : 7.37-7.29 (3H, m, ***Ar-CH***), 7.10 (2H, d, J= 7.6 Hz, ***Ar-CH***), 4.72 (1H, dd, J= 7.5, 3.0, 1.1 Hz, ***5-H***), 4.35 (1H, dd, J= 7.5, 2.8 Hz, ***7-H***), 4.12 (1H, ddd, J= 11.6, 5.3, 1.1 Hz, ***3-H$_{eq}$***), 3.98 (1H, t, J= 11.6 Hz, ***3-H$_{ax}$***), 3.43 (1H, ddd, J= 11.6, 5.3, 3.0 Hz, ***4-H***), 2.47 (1H, dd, J= 14.1, 7.5 Hz, ***6-H$_\beta$***), 1.81 (1H, ddd, J= 14.1, 7.5, 2.8 Hz, ***6-H$_\alpha$***), 1.56 (1H, bs, ***OH***), 1.52 (3H, s, ***CH$_3$***). δ_C (125.7 MHz) : 137.0 (***C-1'***), 129.0+127.4+127.3 (5×***Ar-CH***), 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 (***CH$_3$***). *m/z* (ES^+) : 243.1 ($M+Na^+$, 100%). HRMS (ES^+) found : 243.0995 ($C_{13}H_{16}O_3Na$ requires 243.0997).

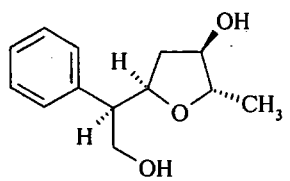
5-(2'-Hydroxy-1'-phenylethyl)-2-methyl-tetrahydrofuran-3-ol (68,69) :

To a solution of the acetal **(63)** (35 mg, 0.16 mmol) in CH_2Cl_2 (15 ml), triethylsilane (Et_3SiH, 0.04 ml, 0.24 mmol, 1.5 eq) was added at -78°C followed by the dropwise

addition of a solution of titanium tetrachloride ($TiCl_4$) in CH_2Cl_2 (1M, 0.02 ml, 0.192 mmol, 1.2 eq). The reaction mixture was stirred at -78°C. After 6 hours, the reaction mixture was quenched with ice cold 1N HCl and extracted with CH_2Cl_2. The combined organic extracts were dried over magnesium sulfate ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue, containing a mixture of two tetrahydrofuran isomers **(68)** and **(69)** in a 6:4 ratio, was purified by flash chromatography (cylcohexane/EtOAc : 9:1) and the tetrahydrofurans **(68)** and **(69)** were obtained as a non separable mixture (23 mg, 65%).

When boron trifluoride diethyletherate ($BF_3.Et_2O$, 0.025 ml, 0.192 mmol, 1.2 eq) was used as Lewis-acid, a solution of sodium bicarbonate ($NaHCO_3$) was added after completion (6 hours) and the resulting mixture was stirred for 30 mins. The reaction mixture was then concentrated to one-third of its initial volume, washed with brine and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The cude residue, containing a mixture of the tetrahydrofurans **(68)** and **(69)** in a 7:3 ratio, was purified by flash chromatography (cyclohexane/EtOAc : 9/1) and the tetrahydrofurans **(68)** and **(69)** were obtained as a non separable mixture (21 mg, 60%).
However, during the purification a small sample of the major isomer was obtained. This sample was used for analytical data.

Major isomer **(68)** :

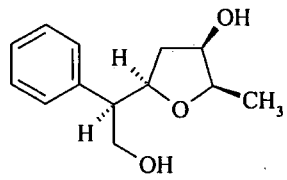


ν_{max} (ATR) : 3630-3124 (broad ***OH***), 3018-2818, 2189, 2148, 2036, 1997, 1970, 1460, 1070, 780, 700 cm^{-1}. δ_H (500 MHz) : 7.36-7.26 (5H, m, ***Ar-CH***), 4.50 (1H, td, J= 7.6, 4.4 Hz, ***5-H***), 4.06 (1H, dd, J= 11.0, 7.3 Hz, ***2'-H***), 3.97 (1H, dd, J= 11.0, 6.4 Hz, ***2'-H***), 3.93-3.87 (1H, m, ***3-H***), 3.85 (1H, qd, J= 6.5, 3.6 Hz, ***2-H***), 3.05 (1H, ddd, J= 7.3, 6.4, 4.4 Hz, ***1'-H***), 2.30 (1H, ddd, J= 13.3, 7.6, 6.6 Hz, ***4-H$_\alpha$***), 2.00 (2H, bs, 2×***OH***), 1.75 (1H, ddd, J= 13.3, 7.6, 4.7 Hz, ***4-H$_\beta$***), 1.12 (3H, d, J= 6.5 Hz, ***CH$_3$***). δ_C (125.7 MHz) : 139.0 (***C-a***),

129.5+129.0+127.6 (5×***Ar-CH***), 81.9 (***C-2***), 77.8 (***C-5***), 77.6 (***C-3***), 64.7 (***C-2'***), 51.9 (***C-1'***), 37.1 (***C-4***), 18.3 (***CH_3***). *m/z* (ES^+) : 245.1 (M+Na, 100%). HRMS (ES^+) found : 245.1152 ($C_{13}H_{18}O_3Na$ requires 245.1154).

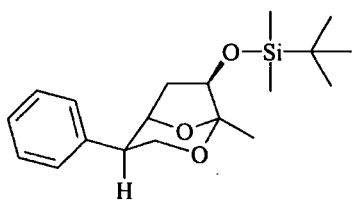
Minor isomer **(69) :**

as an inseparable mixture with the major. The NMR data were deduced by comparison of the NMR of the mixture with the NMR of the major compound.



δ_H (500 MHz) : 7.36-7.26 (5H, m, ***Ar-CH***), 4.32 (1H, ddd, J= 8.5, 6.8, 3.4 Hz, ***5-H***), 4.09 (1H, dd, J= 11.3, 7.8 Hz, ***2'-H***), 4.06 (1H, dd, J= 11.3, 6.5 Hz, ***2'-H***), 3.96-3.93 (1H, m, ***3-H***), 3.68 (1H, qd, J= 6.3, 3.1 Hz, ***2-H***), 3.12 (1H, ddd, J= 7.8, 6.5, 3.4 Hz, ***1'-H***), 2.30 (1H, ddd, J= 13.3, 8.5, 6.7 Hz, ***4-H_α***), 2.00 (2H, bs, 2×***OH***), 1.75 (1H, ddd, J= 13.3, 6.8, 4.7 Hz, ***4-H_β***), 1.23 (3H, d, J= 6.3 Hz, ***CH_3***). δ_C (125.7 MHz) : 138.6 (***C-a***), 129.5+129.0+127.8 (5×***Ar-CH***), 79.2 (***C-2***), 78.7 (***C-5***), 73.5 (***C-3***), 64.6 (***C-2'***), 51.3 (***C-1'***), 38.2 (***C-4***), 14.0 (***CH_3***).

***t*-Butyldimethyl-(1-methyl-4-phenyl-2,8-dioxa-bicyclo[3.2.1]oct-7-yloxy)-silane (70) :**



To a solution of the alcohol **(63)** (50 mg, 0.23 mmol) in CH_2Cl_2 (15 ml), 2,6-lutidine (0.053 ml, 0.46 mmol, 2 eq) and *tert*-butyldimethylsilyl triflate (TBDMSOTf, 0.12 ml, 0.68 mmol, 3 eq) were added dropwise at room temperature. The reaction was stirred at room temperature overnight. After evaporation of the solvent, the residue was purified by

chromatography (cyclohexane/EtOAc : 95/5 then 9/1) and the TBDMS protected alcohol **(70)** was obtained as a colorless oil (46 mg, 60%).

ν_{max} (ATR) : 3015-2940, 1260, 1100, 1090, 1070, 1010, 787, 750, 700 cm^{-1}. δ_H (400 MHz) : 7.25-7.2 (2H, m, 2×***3'-H***), 7.2-7.15 (1H, m, ***4'-H***), 7.04 (2H, d, J= 8.3 Hz, 2×***2'-H***), 4.70 (1H, t, J= 11.2 Hz, ***3-H_{ax}***), 4.50 (1H, ddd, J= 7.4, 3.2, 1.5 Hz, ***5-H***), 4.10-3.95 (2H, m, ***3-H_{eq}+7-H***), 3.50 (1H, ddd, J= 11.2, 5.5, 3.2 Hz, ***4-H***), 2.40 (1H, ddd, J= 13.2, 10.8, 7.4 Hz, ***6-H_{α}***), 1.70 (1H, dd, J= 13.2, 3.6 Hz, ***6-H_{β}***), 1.31 (3H, s, ***CH_3***), 0.95 (9H, s, SiC***$(CH_3)_3$***), 0.12+0.10 (6H, 2×s, Si***$(CH_3)_2$***). δ_C (100.5 MHz) : 138.2 (***C-1'***), 128.9 (2×***C-2'***), 127.5 (2×***C-3'***), 127.0 (***C-4'***), 102.6 (***C-1***), 78.8 (***C-5***), 75.7 (***C-7***), 63.4 (***C-3***), 42.3 (***C-4***), 34.8 (***C-6***), 26.0 (3×***CH_3***), 22.2 (***CH_3***), 18.2 (***C***$(CH_3)_3$), -4.2 (Si***$(CH_3)_2$***). *m/z* (ES^+) : 357.1 (M+Na, 100%). HRMS (ES^+) found : 357.1848 ($C_{19}H_{30}O_3SiNa$ requires 357.1862).

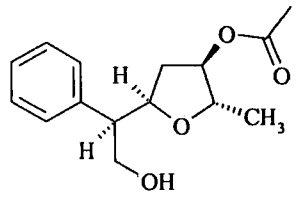
5-(2'-hydroxy-1'-phenyl-ethyl)-2-methyl-tetrahydrofuran-3-yl acetate (71,72) :

To a solution of the acetate **(64)** (40 mg, 0.153 mmol) in CH_2Cl_2 (15 ml), triethylsilane (Et_3SiH, 0.04 ml, 0.24 mmol, 1.5 eq) was added at -78°C followed by the dropwise addition of a solution of titanium tetrachloride ($TiCl_4$) in CH_2Cl_2 (1M, 0.019 ml, 0.184 mmol, 1.2 eq). The reaction mixture was stirred at -78°C. After 6 hours, the reaction mixture was quenched with ice cold 1N HCl and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue, containing a mixture of two tetrahydrofuran isomers **(71)** and **(72)** in a 6:4 ratio, was purified by flash chromatography (cylcohexane/EtOAc : 9:1) and the tetrahydrofurans **(71)** and **(72)** were obtained as a non-separable mixture (29 mg, 85%).

When boron trifluoride diethyletherate ($BF_3.Et_2O$, 0.024 ml, 0.184 mmol, 1.2 eq) was used as Lewis-acid, a solution of sodium bicarbonate ($NaHCO_3$) was added after completion (8 hours) and the resulting mixture was stirred for 30 mins. The reaction mixture was then concentrated to one-third of its initial volume, washed with brine and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The cude residue, containing a mixture of the tetrahydrofurans **(71)** and **(72)** in a 7:3 ratio, was purified by flash chromatography (cyclohexane/EtOAc : 9/1) and the tetrahydrofurans **(71)** and **(72)** were obtained as a non separable mixture (24 mg, 70%).

However a small sample of the pure major isomer was obtained during the purification. This sample was used for obtention of the analytical data. The NMR of the minor isomer was deduced by comparison of the NMR of the mixture with the NMR of the pure major isomer.

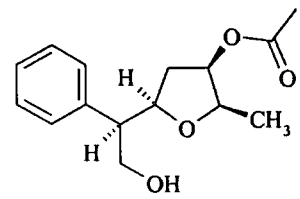
Major isomer **(71)** :



ν_{max} (ATR) : 3672-3022 (broad ***OH***), 2990-2813, 1726 (***C=O***), 1500, 1448, 1380 (OCO***CH***), 1050, 750, 700 cm^{-1}. δ_H (500 MHz) : 7.36-7.26 (5H, m, ***Ar-CH***), 4.80 (1H, dt, J= 7.5, 4.5 Hz, ***3-H***), 4.49 (1H, dt, J= 8.0, 6.5 Hz, ***5-H***), 4.06-4.00 (2H, m, ***2-H+2'-H***), 3.90 (1H, dd, J= 11.0, 6.5 Hz, ***2'-H***), 3.10 (1H, q, J= 6.5 Hz, ***1'-H***), 2.40 (1H, ddd, J= 13.6, 7.5, 6.5 Hz, ***4-H$_a$***), 1.95 (3H, s, CO***CH$_3$***), 1.80 (1H, ddd, J= 13.6, 8.0, 4.5 Hz, ***4-H$_\beta$***), 1.60 (2H, bs, 2×***OH***), 1.20 (3H, d, J= 6.4 Hz, ***CH$_3$***). δ_C (125.7 MHz) : 171.0 (***CO***), 139.0 (***C-a***), 129.5+129.0+127.6 (5×***Ar-CH***), 81.9 (***C-2***), 77.8 (***C-5***), 77.6 (***C-3***), 64.7 (***C-2'***), 51.9 (***C-1'***), 37.1 (***C-4***), 21.2 (***CH$_3$***CO), 18.3 (***CH$_3$***). *m/z* (ES^+) : 287.2 (M+Na, 100%). HRMS (ES^+) found : 287.1259 ($C_{15}H_{20}O_4Na$ requires 287.1259).

Minor isomer **(72)** :

as an inseparable mixture with the major. NMR data were deduced by comparison of the NMR of the mixture with the major isomer.



δ_H (500 MHz) : 7.35-7.24 (5H, m, ***Ar-CH***), 5.13 (1H, ddd, J= 7.1, 4.1, 2.7 Hz, ***3-H***), 4.26 (1H, td, J= 8.0, 6.1 Hz, ***5-H***), 4.16-4.00 (1H, m, ***2-H***), 3.93 (1H, dd, J= 11.0, 6.1 Hz, ***2'-***

H), 3.85 (1H, dd, J= 11.0, 6.1 Hz, ***2'-H***), 3.12 (1H, ddd, J= 6.1, 6.1, 6.1 Hz, ***1'-H***), 2.10 (1H, ddd, J= 14.5, 8.0, 7.1 Hz, ***4-H$_\alpha$***), 1.90 (3H, s, CO***CH$_3$***), 1.74 (1H, ddd, J= 14.5, 8.0, 4.1 Hz, ***4-H$_\beta$***), 1.60 (2H, bs, 2×***OH***), 1.18 (3H, d, J= 6.5 Hz, ***CH$_3$***). δ_C (125.7 MHz) : 170.8 (***CO***), 138.7 (***C-a***), 129.3+128.5+127.3 (5×***Ar-CH***), 79.1 (***C-2***), 78.0 (***C-5***), 75.1 (***C-3***), 64.4 (***C-2'***), 51.0 (***C-1'***), 36.0 (***C-4***), 21.0 (***CH$_3$***CO), 14.2 (***CH$_3$***).

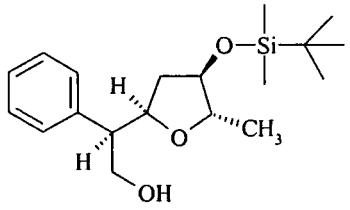
2-[4'-(*t*-Butyldimethylsilanyloxy)-5'-methyltetrahydrofuran-2'-yl]-2-phenylethanol (73,74) :

To a solution of the TBDMS protected alcohol **(70)** (70 mg, 0.21 mmol) in CH_2Cl_2 (15 ml), triethylsilane (Et_3SiH, 0.05 ml, 0.315 mmol, 1.5 eq) was added at -78°C followed by the dropwise addition of a solution of titanium tetrachloride ($TiCl_4$) in CH_2Cl_2 (1M, 0.030 ml, 0.252 mmol, 1.2 eq). The reaction mixture was stirred at -78°C. After 8 hours, the solvent was evaporated *in vacuo*. The crude residue, containing a mixture of two tetrahydrofuran isomers **(73)** and **(74)** in a 95:5 ratio, was purified by flash chromatography (cylcohexane/EtOAc : 9:1) and the tetrahydrofurans **(73)** and **(74)** were obtained as a non separable mixture (37 mg, 80%).

When boron trifluoride diethyletherate ($BF_3.Et_2O$, 0.031 ml, 0.252 mmol, 1.2 eq) was used as Lewis acid, a solution of sodium bicarbonate ($NaHCO_3$) was added after completion (9 hours) and the resulting mixture was stirred for 30 mins. The reaction mixture was then concentrated to one-third of its initial volume, washed with brine and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The cude residue, containing a mixture of the tetrahydrofurans **(73,74)** in a (95:5) ratio, was purified by flash chromatography (cyclohexane/EtOAc : 9/1) and the tetrahydrofurans **(73)** and **(74)** were obtained as a non separable mixture (32 mg, 70%).

Data of the major isomer were obtained on the mixture. Unfortunately, the NMR signals of the minor isomer were too weak and could not be reported.

Major isomer **(73)** :

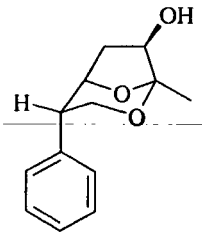


ν_{max} (ATR) : 3480-3000 (broad ***OH***) 2980-2850 (***CH***-OSi), 1245+835 (***Si-C***H_3), 1111, 1044, 881, 835, 730, 699, 667 cm^{-1}. δ_H (500 MHz) : 7.32-7.17 (5H, m, ***Ar-CH***), 4.44 (1H, ddd, J= 8.8, 6.5, 6.2 Hz, ***5-H***), 4.02 (1H, dd, J= 11.0, 6.2 Hz, ***2'-H***), 3.90-3.82 (2H, m, ***2'-H+3-H***), 3.66 (1H, p, J= 6.2 Hz, ***2-H***), 3.07 (1H, q, J= 6.2 Hz, ***1'-H***), 2.27 (1H, bs, ***OH***), 2.07 (1H, ddd, J= 12.4, 6.5, 6.2 Hz, ***4-H$_\alpha$***), 1.76 (1H, ddd, J= 12.4, 8.8, 6.8 Hz, ***4-H$_\beta$***), 1.13 (3H, d, J= 6.2 Hz, ***CH$_3$***), 0.86 (9H, s, SiC***(CH$_3$)$_3$***), 0.36+0.30 (6H, 2×s, Si***(CH$_3$)$_2$***). δ_C (125.7 MHz) : 139.5 (***C-a***), 129.0+128.7+127.1 (5×***Ar-CH***), 80.5 (***C-2***), 78.4 (C-5), 77.9 (C-3), 64.2 (C-2'), 51.7 (C-1'), 37.5 (C-4), 25.9 (SiC***(CH$_3$)$_3$***), 18.4 (CH_3), 18.2 (Si***C***$(CH_3)_3$), -4.5+-4.7 (Si***(CH$_3$)$_2$***). *m/z* (ES^+) : 359.2 (M+Na, 100%). HRMS (ES^+) found : 359.2024 ($C_{19}H_{32}O_3SiNa$ requires 359.2018).

General procedure for the reduction of the C-H insertion product :

Sodium borohydride ($NaBH_4$, 1.2 eq) was added to a solution of insertion product in MeOH at room temperature and the reaction mixture stirred at room temperature overnight. The reaction mixture was then extracted with CH_2Cl_2 and successively washed with a saturated solution of ammonium chloride (NH_4Cl) and brine (NaCl). The organic layer was then dried over magnesium sulfate ($MgSO_4$), filtered and concentrated *in vacuo*.

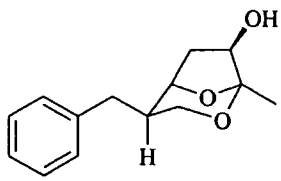
1-Methyl-4-phenyl-2,8-dioxabicyclo-[3.2.1]octan-7-ol (75) :



Following the general procedure, $NaBH_4$ (8.3 mg, 0.22 mmol, 1.2 eq) was added to a solution of the C-H insertion product **(57)** (as a mixture with an unknown product) (40 mg, 0.18 mmol) in MeOH (10 ml). The reaction was stirred overnight at room temperature. After work up, the residue was purified by chromatography to give the alcohol **(75)** as a non-separable mixture with an unknown product.

ν_{max} (ATR) : 3660-3006 (broad ***OH***), 3000-2800, 1384, 1266, 1186, 1120, 1076, 731, 699 cm^{-1}. δ_H (400 MHz) : 7.58-7.44 (3H, m, ***Ar-CH***), 7.40-7.32 (2H, m, ***Ar-CH***), 4.61 (1H, dd, J= 12.1, 5.2 Hz, ***3-H$_{ax}$***), 4.36 (1H, dd, J= 8.0, 3.7 Hz, ***7-H***), 4.20-4.03 (3H, m, ***5-H+4-H+3-H$_{eq}$***), 2.77 (1H, ddd, J= 13.7, 10.7, 8.0 Hz, ***6-H$_{\alpha}$***), 2.65 (1H, bs, ***OH***), 1.83 (1H, dd, J= 13.7, 3.7 Hz, ***6-H$_{\beta}$***), 1.47 (3H, s, ***CH$_3$***). δ_C (100.5 MHz) : 142.9 (***C-1'***), 128.6+128.5+126.8 (5×***Ar-CH***), 103.1 (***C-1***), 79.1 (***C-5***), 75.6 (***C-7***), 64.5 (***C-3***), 45.3 (***C-4***), 38.7 (***C-6***), 22.5 (***CH$_3$***). *m/z* (CI, NH_3) : 238 ($[MH+NH_3]^+$, 15%), 221 ($[MH]^+$, 49%), 204 ($[MH-OH]^+$, 100%), 187 (27%), 173 (20%), 104 ($[PhCHCH_2]^+$, 43%), 91 ($[PhCH]^+$, 7%), 77 ($[Ph]^+$, 12%). *m/z* (ES^+) : 275.1 (M+Na+MeOH, 100%). HRMS (ES^+) found : 275.1229 ($C_{14}H_{20}O_4Na$ requires 275.1259).

4-Benzyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-7-ol (76) :

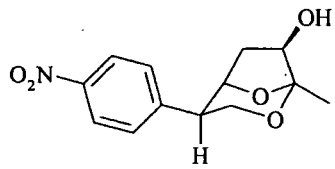


Following the general procedure, $NaBH_4$ (20 mg, 0.52 mmol, 1.2 eq) was added to a solution of the C-H insertion product **(58)** (100 mg, 0.43 mmol) in MeOH (20 ml). The reaction was stirred overnight at room temperature. After work up, the residue was purified by chromatography (cyclohexane/EtOAc, 8/2 then 7/3) to give the alcohol **(76)** as white solid (70 mg, 70%).

ν_{max} (ATR) : 3670-2950 (broad ***OH***), 1632, 1262, 1160, 1068, 1050, 745, 700 cm^{-1}. δ_H (400 MHz, $CDCl_3$) : 7.21 (2H, t, J= 7.2 Hz, 2×***3'-H***), 7.15 (1H, t, J= 7.2 Hz, ***4'-H***), 7.05 (2H, d, J= 7.2 Hz, 2×***2'-H***), 4.10 (1H, ddd, J= 7.7, 2.9, 1.4 Hz, ***5-H***), 4.05 (1H, dd, J=

11.0, 3.8 Hz, *7-H*), 3.83 (1H, t, J= 11.7 Hz, ***3-H$_{ax}$***), 3.77 (1H, ddd, J= 11.7, 5.8, 1.4 Hz, ***3-H$_{eq}$***), 2.52-2.45 (1H, m, *4-H*), 2.43 (1H, ddd, J= 13.6, 11.0, 7.7 Hz, ***6-H$_{\alpha}$***), 2.28 (2H, m, ***CH$_2$Ph***), 1.93 (1H, bs, ***OH***), 1.79 (1H, dd, J= 13.6, 3.8 Hz, ***6-H$_{\beta}$***), 1.31 (3H, s, ***CH$_3$***). δ_C (100.5 MHz, $CDCl_3$) : 138.2 (***C-1'***), 128.8 (2×***C-2'***,2×***C-3'***), 126.6 (***C-4'***), 102.7 (***C-1***), 77.1 (***C-5***), 75.4 (***C-7***), 65.7 (***C-3***), 38.9 (***C-4***), 35.0 (***CH$_2$Ph***), 32.7 (***C-6***), 22.2 (***CH$_3$***). *m/z* (ES^+) : 289.1 (M+Na+MeOH, 100%), 257.1 (M+Na, 39%). Elemental analysis [found : C 71.29, H 7.72 % required for $C_{14}H_{18}O_3$: C 71.76, H 7.72 %].

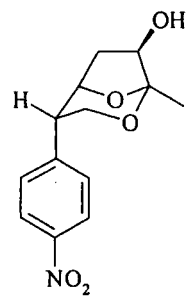
1-Methyl-4-(4'-nitrophenyl)-2,8-dioxabicyclo[3.2.1]octan-7-ol (77) :



Following the general procedure, $NaBH_4$ (22.5 mg, 0.59 mmol, 1.2 eq) was added to a solution of the C-H insertion product **(59)** (0.13 g, 0.49 mmol) in MeOH (25 ml). The reaction was stirred overnight at room temperature. After work up, the residue was purified by chromatography to give the alcohol **(77)** as a colorless oil (0.11 g, 84%).

ν_{max} (ATR) : 3540-3161 (broad ***OH***), 2968-2798, 1519+1384 (***NO$_2$***), 1199, 1107, 1008, 954, 806, 700 cm^{-1}. δ_H (400 MHz) : 8.19 (2H, d, J= 8.7 Hz, 2×***3'-H***), 7.32 (2H, d, J= 8.7 Hz, 2×***2'-H***), 4.62-4.54 (2H, m, ***5-H+3-H$_{ax}$***), 4.24-4.15 (2H, m, ***7-H+3-H$_{eq}$***), 3.62 (1H, ddd, J= 12.0, 5.3, 2.8 Hz, ***4-H***), 2.50 (1H, ddd, J= 13.9, 10.8, 7.7 Hz, ***6-H$_{\alpha}$***), 1.85 (1H, dd, J= 13.9, 3.6 Hz, ***6-H$_{\beta}$***), 1.84 (1H, bs, ***OH***), 1.47 (3H, s, ***CH$_3$***). δ_C (100.5 MHz) : 147.3 (***C-1'***), 145.2 (***C-4'***), 128.8 (2×***C-2'***), 124.1 (2×***C-3'***), 103.2 (***C-1***), 78.0 (***C-5***), 75.0 (***C-7***), 63.1 (***C-3***), 42.5 (***C-4***), 34.0 (***C-6***), 22.0 (***CH$_3$***). *m/z* (ES^+) : 288.1 (M+Na, 100%). HRMS (ES^+) found : 288.1570 ($C_{13}H_{15}O_5Na$ requires 288.0848).

1-Methyl-4-(*4'*-nitrophenyl)-2,8-dioxabicyclo[3.2.1]octan-7-ol (78) :



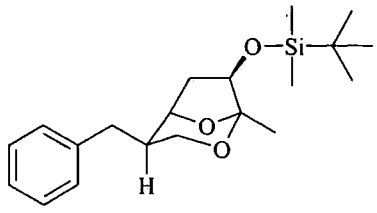
Following the general procedure, $NaBH_4$ (6.9 mg, 0.182 mmol, 1.2 eq) was added to a solution of the C-H insertion product **(60)** (as a mixture with an unknown product) (40 mg, 0.152 mmol) in MeOH (10 ml). The reaction was stirred overnight at room temperature. After work up, the residue was purified by chromatography to give the alcohol **(78)** as a colorless oil.

ν_{max} (ATR) : 3650-3165 (broad ***OH***), 3005-2842, 1517+1346 (***NO₂***), 1112, 1074, 1053, 910, 729, 705 cm^{-1}. δ_H (400 MHz) : 8.15 (2H, d, J= 8.6 Hz, 2×***3'-H***), 7.62 (2H, d, J= 8.6 Hz, 2×***2'-H***), 4.67 (1H, dd, J= 12.4, 4.7 Hz, ***3-H$_{ax}$***), 4.27 (1H, d, J= 8.1 Hz, ***5-H***), 4.13 (1H, dd, J= 10.7, 3.7 Hz, ***7-H***), 4.00 (1H, d, J= 12.4 Hz, ***3-H$_{eq}$***), 2.75 (1H, ddd, J= 13.6, 10.7, 8.1 Hz, ***6-H$_{\alpha}$***), 2.66 (1H, d, J= 4.7 Hz, ***4-H***), 1.80 (1H, dd, J= 13.6, 3.7 Hz, ***6-H$_{\beta}$***), 1.50 (1H, bs, ***OH***), 1.39 (3H, s, ***CH₃***). δ_C (100.5 MHz) : 150.8 (***C-1'***), 147.1 (***C-4'***), 129.5 (2×***C-2'***), 124.0 (2×***C-3'***), 103.5 (***C-1***), 78.5 (***C-5***), 75.7 (***C-7***), 64.0 (***C-3***), 44.3 (***C-4***), 38.2 (***C-6***), 22.5 (***CH₃***). *m/z* (ES^+) : 320.1 (M+Na+MeOH, 100%), HRMS (ES^+) found : 320.1098 ($C_{14}H_{19}NO_6Na$ requires 320.110).

General procedure for the silylation of the alcohol :

To a solution of the alcohol in dichloromethane (CH_2Cl_2), 2,6-lutidine (2 eq) and tert-butyldimethylsilyl triflate (TBDMSOTf, 3 eq) were added dropwise at room temperature. The reaction mixture was stirred at room temperature overnight. After evaporation of the solvent and without work up, the residue was purified by chromatography (cyclohexane/EtOAc, 95/5 then 9/1) and gave the TBDMS protected alcohol.

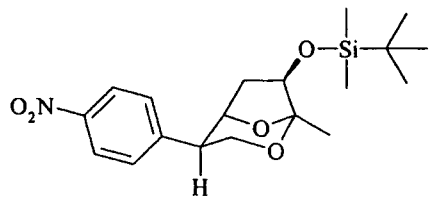
t-Butyldimethyl-(1-methyl-4-benzyl-2,8-dioxabicyclo[3.2.1]oct-7-yloxy)-silane (79)



Following the general procedure, 2,6-lutidine (0.053 ml, 0.46 mmol) and TBDMSOTf (0.12 ml, 0.68 mmol) were added to a solution of alcohol **(76)** (50 mg, 0.23 mmol) in MeOH (10 ml). After purification, the TBDMS protected alcohol **(79)** was obtained as a colorless oil (68 mg, 85%).

ν_{max} (ATR) : 3015-2813, 1250, 1134, 1098, 1054, 960, 880, 837, 778, 700, 670 cm^{-1}. δ_H (400 MHz) : 7.28 (2H, t, J= 7.0 Hz, 2×***3'-H***), 7.20 (1H, t, J=7.0 Hz, ***4'-H***), 7.11 (2H, d, J= 7.0 Hz, 2×***2'-H***), 4.15-4.10 (1H, m, ***5-H***), 4.10-4.05 (2H, m, ***7-H+3-H$_{ax}$***), 3.75 (1H, dd, J= 11.4, 5.7 Hz, ***3-H$_{eq}$***), 2.52 (1H, m, ***4-H***), 2.43 (1H, ddd, J= 13.0, 10.7, 7.7 Hz, ***6-H$_{\alpha}$***), 2.35-2.29 (2H, m, ***CH$_2$***Ph), 1.68 (1H, dd, J= 13.0, 3.5 Hz, ***6-H$_{\beta}$***), 1.32 (3H, s, ***CH$_3$***), 0.95 (9H, s, SiC***(CH$_3$)$_3$***), 0.12+0.11 (6H, 2×s, Si***(CH$_3$)$_2$***). δ_C (100.5 MHz) : 138.6 (***C-1'***), 128.8 (2×***C-2'***), 128.6 (2×***C-3'***), 126.4 (***C-4'***), 102.5 (***C-1***), 77.0 (***C-5***); 75.6 (***C-7***), 65.2 (***C-3***), 39.2 (***C-4***), 35.0 (***CH$_2$***Ph), 33.9 (C-6), 26.0 (3×***CH$_3$***), 22.5 (***CH$_3$***), 18.2 (***C***$(CH_3)_3$), -4.6+-4.7 (Si***(CH$_3$)$_2$***). ***m/z*** (ES^+) : 403.3 (M+Na+MeOH, 100%), 371.2 (M+Na, 21%). HRMS (ES^+) found : 403.2271 ($C_{21}H_{36}O_4SiNa$ requires 403.2281).

t-Butyldimethyl-(1-methyl-4-(*4'*-nitrophenyl)-2,8-dioxabicyclo[3.2.1]oct-7-yloxy)-silane (80) :

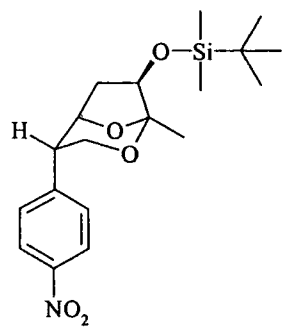


Following the general procedure, 2,6-lutidine (0.053 ml, 0.46 mmol) and TBDMSOTf (0.12 ml, 0.68 mmol) were added to a solution of alcohol **(77)** (50 mg, 0.23 mmol) in

MeOH (10 ml). After purification, the TBDMS protected alcohol **(80)** was obtained as a white solid (57 mg, 65%).

m.p.: 109–112°C. ν_{max} (ATR) : 3022-2818, 1511+1341 (***NO₂***), 1248, 1113, 1094, 1059, 962, 903, 837, 775, 748, 700, 669 cm^{-1}. δ_H (400 MHz) : 8.19 (2H, d, J= 8.8 Hz, 2×***3'-H***), 7.28 (1H, d, J=8.8 Hz, 2×***2'-H***), 4.70 (1H, t, J= 11.8 Hz, ***3-H$_{ax}$***), 4.53-4.48 (1H, m, ***5-H***), 4.15-4.08 (2H, m, ***7-H+3-H$_{eq}$***), 3.53 (1H, ddd, J= 11.8, 5.2, 3.0 Hz, ***4-H***), 2.43 (1H, ddd, J= 13.5, 11.0, 7.7 Hz, ***6-H$_{\alpha}$***), 1.58 (1H, dd, J= 13.5, 3.5 Hz, ***6-H$_{\beta}$***), 1.41 (3H, s, ***CH₃***), 0.89 (9H, s, SiC***(CH₃)₃***), 0.11+0.09 (6H, 2×s, Si***(CH₃)₂***). δ_C (100.5 MHz) : 146.7 (***C-1'***), 145.4 (***C-4'***), 128.2 (2×***C-2'***), 124.0 (2×***C-3'***), 103.0 (***C-1***), 78.1 (***C-5***); 75.5 (***C-7***), 62.9 (***C-3***), 39.2 (***C-4***), 35.0 (***CH₂***Ph), 33.9 (***C-6***), 26.0 (3×***CH₃***), 22.5 (***CH₃***), 18.2 (***C***$(CH_3)_3$), -4.6+-4.7 (Si***(CH₃)₂***). ***m/z*** (ES^+) : 434.1 (M+Na+MeOH, 100%). HRMS (ES^+) found : 434.1956 ($C_{20}H_{33}O_6SiNa$ requires 434.1975).

t-Butyldimethyl-(1-methyl-4-(4'-nitrophenyl)-2,8-dioxabicyclo[3.2.1]oct-7-yloxy)-silane (81) :



Following the general procedure, 2,6-lutidine (0.053 ml, 0.46 mmol) and TBDMSOTf (0.12 ml, 0.68 mmol) were added to a solution of alcohol **(78)** (50 mg, 0.23 mmol) in MeOH (10 ml). After purification, the TBDMS protected alcohol **(81)** was obtained as a colorless oil (52 mg, 60%).

ν_{max} (ATR) : 3018-2836, 1515+1350 (***NO₂***), 1259, 1115, 1090, 1050, 1030, 797, 705, 672 cm^{-1}. δ_H (400 MHz) : 8.20 (2H, d, J= 8.7 Hz, 2×***3'-H***), 7.72 (1H, d, J=8.7 Hz, 2×***2'-H***), 4.86 (1H, dd, J= 12.2, 4.4 Hz, ***3-H$_{ax}$***), 4.30 (1H, d, J= 7.7 Hz, ***5-H***), 4.14 (1H, dd, J= 10.6, 3.7 Hz, ***7-H***), 3.99 (1H, d, J= 12.2 Hz, ***3-H$_{eq}$***), 2.76 (1H, ddd, J= 13.1, 10.6, 7.7 Hz, ***6-H$_{\alpha}$***),

2.63 (1H, d, J= 4.4 Hz, ***4-H***), 1.76 (1H, dd, J= 13.1, 3.7 Hz, ***6-H$_\beta$***), 1.41 (3H, s, ***CH$_3$***), 0.95 (9H, s, SiC***(CH$_3$)$_3$***), 0.13 and 0.11 (6H, 2×s, Si***(CH$_3$)$_2$***). δ_C (100.5 MHz) : 151.2 (***C-1'***), 146.7 (***C-4'***), 129.4 (2×***C-2'***), 123.4 (2×***C-3'***), 103.2 (***C-1***), 78.2 (***C-5***); 75.2 (***C-7***), 63.2 (***C-3***), 44.2 (***C-4***), 39.2 (***C-6***), 25.7 (3×***CH$_3$***), 22.7 (***CH$_3$***), 17.7 (***C***(CH$_3$)$_3$), -4.6+-4.7 (Si***(CH$_3$)$_2$***). *m/z* (ES$^+$) : 434.1 (M+Na+MeOH, 100%). HRMS (ES$^+$) found : 434.2027 ($C_{20}H_{33}O_6SiNa$ requires 434.2036).

General procedure for reductive cleavage using $Et_3SiH/BF_3.Et_2O$:

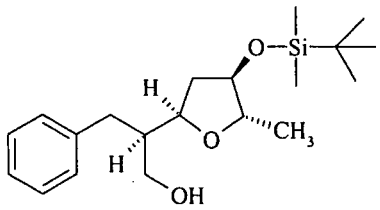
To a solution of the TBDMS protected alcohol **(79-81)** in CH_2Cl_2, triethyl silane (Et_3SiH, 1.5 eq) was added at -78°C. Boron trifluoride diethyletherate ($BF_3.OEt_2$, 1.2eq) was then added dropwise and the reaction mixture stirred at -78°C. After completion, a solution of saturated sodium bicarbonate ($NaHCO_3$) was added and the resulting mixture stirred for 30 mins. The reaction mixture was then concentrated *in vacuo* to one-third of its initial volume. The residue was washed with brine and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered, concentrated *in vacuo* and purified by column chromatography on silica gel.

2-[4'-(*t*-Butyldimethylsilanyloxy)-5'-methyltetrahydrofuran-2'-yl]-3-phenylpropan-1-ol (82,83) :

To a solution of the TBDMS protected alcohol **(79)** (40 mg, 0.11 mmol) in CH_2Cl_2 (10 ml), Et_3SiH (0.026 ml, 0.165 mmol) was added at -78°C followed by the dropwise addition of $BF_3.Et_2O$ (0.017 ml, 0.14 mmol). The reaction mixture was stirred at -78°C. After 8 hours, the solvent was evaporated, the residue was washed with brine and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue, containing a mixture of two isomers in 95:5 ratio, was purified by chromatography (cyclohexane/EtOAc : 9/1) and gave the tetrahydrofurans **(82)** and **(83)** as a non separable mixture (32 mg, 80%).

All data were obtained on the mixture. NMR peaks of the minor not well defined because sample too small; therefore, only the NMR peaks of the major are reported.

Major isomer **(82)** :



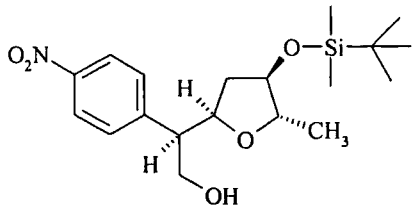
ν_{max} (ATR) : 3600-3098 (broad ***OH***) 3020-2856 (***CH***-OSi), 1259+835 (***Si-C***H_3), 1100, 1038, 907, 728, 699 cm^{-1}. δ_H (500 MHz) : 7.36-7.30 (2H, m, ***Ar-CH***), 7.25-7.21 (3H, m, ***Ar-CH***), 4.26 (1H, dt, J= 7.8, 5.2 Hz, ***5-H***), 4.03 (1H, q, J= 5.8 Hz, ***3-H***), 3.96 (1H, qd, J= 6.3, 5.8 Hz, ***2-H***), 3.70 (2H, d, J= 4.8 Hz, ***2'-H***), 2.74 (1H, dd, J= 13.6, 6.1 Hz, ***CH***Ph), 2.68 (1H, dd, J= 13.6, 8.8 Hz, ***CH***Ph), 2.28-2.18 (2H, m, ***1'-H+4-H$_a$***), 1.99 (1H, ddd, J= 13.0, 7.8, 5.8 Hz, ***4-H$_\beta$***), 1.19 (3H, d, J= 6.3 Hz, ***CH$_3$***), 0.96 (9H, s, SiC***(CH$_3$)$_3$***), 0.14+0.13 (6H, 2×s, Si***(CH$_3$)$_2$***). δ_C (125.7 MHz) : 140.4 (***C-a***), 129.2+128.6+126.2 (5×***Ar-CH***), 81.2 (***C-2***), 79.0 (***C-5***), 78.1 (*C-3*), 62.6 (**C-2'**), 45.7 (***C-1'***), 36.5 (***C-4***), 33.7 (***CH$_2$***Ph), 25.9 (SiC***(CH$_3$)$_3$***), 18.4 (***CH$_3$***), 18.2 (Si***C***$(CH_3)_3$), -4.6+-4.65 (Si***(CH$_3$)$_2$***). *m/z* (ES^+) : 373.2 (M+Na, 100%). HRMS (ES^+) found : 373.2175 ($C_{20}H_{34}O_3SiNa$ requires 373.2175).

2-[4'-(*t*-Butyldimethylsilanyloxy)-5'-methyltetrahydrofuran-2'-yl]-2-(*4'*-nitrophenyl)-ethanol (84,85) :

To a solution of the TBDMS protected alcohol **(80)** (0.15 g, 0.4 mmol) in CH_2Cl_2 (30 ml), Et_3SiH (0.095 ml, 0.6 mmol) was added at -78°C followed by the dropwise addition of $BF_3.Et_2O$ (0.031 ml, 0.48 mmol). The reaction mixture was stirred at -78°C. After 8 hours, the solvent was evaporated, the residue was washed with brine and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue, containing a mixture of 2 isomers in 97:3 ratio, was purified by chromatography (cyclohexane/EtOAc : 9/1) and gave the tetrahydrofurans **(84)** and **(85)** as a non separable mixture (0.12 g, 79%).

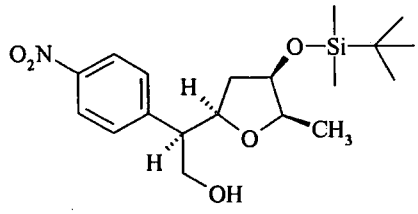
IR and GC were obtained on the mixture. A small sample of the major isomer was obtained during the purification. NMR data were obtained on the pure compound. NMR data of the minor isomer was deduced by comparison of the NMR of the mixture with the NMR ot the pure major isomer.

Major isomer **(84)** :



ν_{max} (ATR) : 3500-3000 (broad ***OH***) 2980-2850 (***CH***-OSi), 1257+835 (***Si-C***H_3), 1111, 1098, 1033, 774, 700, 669 cm^{-1}. δ_H (500 MHz) : 8.18 (2H, d, J= 8.5 Hz, 2×***3"-H***), 7.49 (2H, d, J= 8.5 Hz, 2×***2"-H***), 4.45 (1H, ddd, J= 6.8, 6.2, 6.0 Hz, ***5-H***), 4.01 (1H, dd, J= 11.2, 6.2 Hz, ***2'-H***), 3.95 (1H, dd, J= 11.2, 6.2 Hz, ***2'-H***), 3.91 (1H, dt, J= 7.6, 6.2 Hz, ***3-H***), 3.68 (1H, p, J= 6.2 Hz, ***2-H***), 3.15 (1H, q, J= 6.2 Hz, ***1'-H***), 2.19 (1H, ddd, J= 12.7, 6.2, 6.0 Hz, ***4-H***$_\alpha$), 2.01 (1H, bs, ***OH***), 1.70 (1H, ddd, J= 12.7, 7.6, 6.8 Hz, ***4-H***$_\beta$), 1.12 (3H, d, J= 6.2 Hz, ***CH***$_3$), 0.85 (9H, s, SiC***(CH***$_3$***)***$_3$), 0.04+0.03 (6H, 2×s, Si***(CH***$_3$***)***$_2$). δ_C (125.7 MHz) : 147.9 (***C-a***), 147.1 (***C-d***), 130.1 (2×***C-b***), 123.7 (2×***C-c***), 80.9 (***C-2***), 77.8 (***C-3***), 77.6 (***C-5***), 64.1 (***C-2'***), 52.0 (***C-1'***), 38.1 (***C-4***), 25.8 (SiC***(CH***$_3$***)***$_3$), 18.4 (***CH***$_3$), 18.1 (Si***C***$(CH_3)_3$). -4.6+-4.7 (Si(**CH**$_3$**)**$_2$). ***m/z*** (ES^+) : 404.2 (M+Na, 100%). HRMS (ES^+) found : 404.1853 ($C_{19}H_{31}NO_5SiNa$ requires 404.1869).

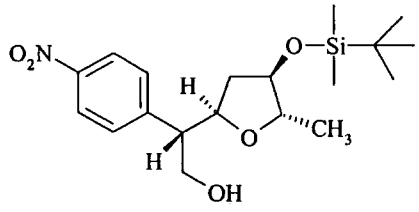
Minor isomer **(85)** :



δ_H (500 MHz) : 8.18 (2H, d, J= 8.5 Hz, 2×***3"-H***), 7.49 (2H, d, J= 8.5 Hz, 2×***2"-H***), 4.32-4.28 (1H, m, ***5-H***), 4.27-4.20 (2H, m, 2×***2'-H***), 4.20-4.15 (1H, m, ***3-H***), 3.76-3.71 (1H, m, ***2-H***), 3.25 (1H, td, J= 5.7, 5.7 Hz, ***1'-H***), 2.19 (1H, m, ***4-H***$_\alpha$), 2.01 (1H, bs, ***OH***), 1.70 (1H, m, ***4-H***$_\beta$), 1.18 (3H, d, J= 6.4 Hz, ***CH***$_3$), 0.84 (9H, s, SiC***(CH***$_3$***)***$_3$), 0.03+0.02 (6H, 2×s, Si***(CH***$_3$***)***$_2$). δ_C (125.7 MHz) : 147.8 (***C-a***), 147.0 (***C-d***), 130.0 (2×***C-b***), 123.6 (2×***C-c***), 79.3 (***C-2***), 78.7 (***C-3***), 73.5 (***C-5***), 64.1 (***C-2'***), 51.0 (***C-1'***), 38.7 (***C-4***), 25.7 (SiC***(CH***$_3$***)***$_3$), 14.8 (***CH***$_3$), 14.6 (Si***C***$(CH_3)_3$). -4.7+-4.8 (Si***(CH***$_3$***)***$_2$).

2-[4'-(*t*-Butyl-dimethylsilanyloxy)-5'-methyltetrahydrofuran-2'-yl]-2-(*4'*-nitrophenyl)-ethanol (86,87):

To a solution of the TBDMS protected alcohol **(81)** (5.8 mg, 0.0153 mmol) in CH_2Cl_2 (10 ml), Et_3SiH (0.0037 ml, 0.023 mmol) was added at -78°C followed by the dropwise addition of $BF_3.Et_2O$ (0.0023 ml, 0.0185 mmol). The reaction mixture was stirred at -78°C. After 8 hours, the solvent was evaporated, the residue was washed with brine and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue, containing a mixture of two isomers in 99:1 ratio, was purified by chromatography (cyclohexane/EtOAc : 9/1) and gave the tetrahydrofurans **(86)** and **(87)** as a colorless oil (5.0 mg, 86%).



ν_{max} (ATR) : 3500-3000 (broad ***OH***) 2980-2850 (***CH***-OSi), 1257+835 (***Si-C***H_3), 1111, 1098, 1033, 774, 700, 669 cm^{-1}. δ_H (500 MHz) : 8.18 (2H, d, J= 8.2 Hz, 2×***3"-H***), 7.37 (2H, d, J= 8.2 Hz, 2×***2"-H***), 4.46 (1H, dt, J= 8.0, 6.5 Hz, ***5-H***), 4.08 (1H, dd, J= 11.0, 8.1 Hz, ***2'-H***), 4.02 (1H, qd, J= 6.5, 6.0 Hz, ***2-H***), 3.90 (1H, q, J= 6.0 Hz, ***3-H***), 3.82 (1H, dd, J= 11.0, 4.3 Hz, ***2'-H***), 3.23 (1H, ddd, J= 8.1, 8.0, 4.3 Hz, ***1'-H***), 2.05 (1H, ddd, J= 13.3, 6.5, 6.0 Hz, ***4-H***$_a$), 1.65-1.50 (2H, m, ***4-H***$_\beta$***+OH***), 1.20 (3H, d, J= 6.5 Hz, ***CH***$_3$), 0.89 (9H, s, SiC***(CH***$_3$***)***$_3$), 0.07+0.06 (6H, 2×s, ***Si(CH***$_3$***)***$_2$). δ_C (125.7 MHz, $CDCl_3$) : 148.0 (***C-a***), 147.2 (***C-d***), 129.3 (2×***C-b***), 124.1 (2×***C-c***), 82.0 (***C-2***), 81.3 (***C-5***), 77.7 (***C-3***), 66.8 (***C-2'***), 52.9 (***C-1'***), 39.6 (***C-4***), 25.9 (SiC***(CH***$_3$***)***$_3$), 18.9 (***CH***$_3$), 18.2 (Si***C***$(CH_3)_3$). -4.6+-4.8 (Si***(CH***$_3$***)***$_2$). *m/z* (ES^+) : 404.2 (M+Na, 100%). HRMS (ES^+) found : 404.1853 ($C_{19}H_{31}NO_5SiNa$ requires 404.1869).

APPENDICES

APPENDIX A: CRYSTAL STRUCTURES OF THE ESTER ACETALS **(29,30,33)**

2-methyl-5-phenyl-[1,3]-dioxane-2-carboxylic acid methyl ether (29) :

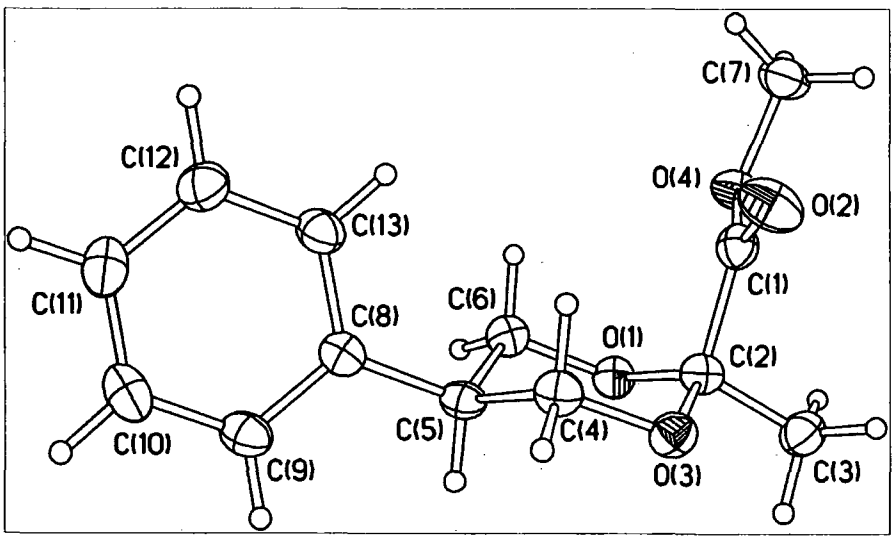


Table 1. Crystal data and structure refinement for 04srv026.

Identification code		
Empirical formula	C13 H16 O4	
Formula weight	236.26	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P2/n* (No.)	
Unit cell dimensions	a = 13.735(2) Å	α= 90°
	b = 6.1336(8) Å	β= 99.59(1)°
	c = 14.962(2) Å	γ = 90°
Volume	1242.9(3) $Å^3$	
Z	4	
Density (calculated)	1.263 g/cm^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	504	
Crystal size	0.27 × 0.05 × 0.02 mm^3	
θ range for data collection	1.86 to 27.49°.	
Index ranges	$-17 \leq h \leq 17, -7 \leq k \leq 7, -19 \leq l \leq 19$	
Reflections collected	14011	
Independent reflections	2848 [R(int) = 0.0850]	
Reflections with I>2σ(I)	1840	
Completeness to θ = 27.49°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2848 / 0 / 218	
Largest final shift/e.s.d. ratio	0.001	
Goodness-of-fit on F^2	0.935	
Final R indices [I>2σ(I)]	R1 = 0.0359, wR2 = 0.0779	
R indices (all data)	R1 = 0.0686, wR2 = 0.0893	
Largest diff. peak and hole	0.205 and -0.224 e.$Å^{-3}$	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for 04srv026. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	5204(1)	5798(1)	3850(1)	245(2)
O(2)	5858(1)	3826(2)	1824(1)	394(3)
O(3)	4860(1)	2397(1)	3162(1)	270(2)
O(4)	5867(1)	7241(2)	2356(1)	296(2)
C(1)	5621(1)	5140(2)	2343(1)	253(3)
C(2)	4918(1)	4662(2)	3028(1)	240(3)
C(3)	3898(1)	5462(3)	2633(1)	313(4)
C(4)	5759(1)	1461(2)	3649(1)	262(3)
C(5)	6065(1)	2609(2)	4552(1)	237(3)
C(6)	6117(1)	5042(2)	4366(1)	251(3)
C(7)	6392(1)	7957(3)	1646(1)	359(4)
C(8)	7018(1)	1706(2)	5064(1)	236(3)
C(9)	7015(1)	376(2)	5816(1)	296(3)
C(10)	7883(1)	-491(3)	6282(1)	359(4)
C(11)	8777(1)	-47(3)	6009(1)	347(4)
C(12)	8796(1)	1278(2)	5267(1)	333(4)
C(13)	7923(1)	2144(2)	4796(1)	294(3)

Table 3. Bond lengths [Å] and angles [°] for 04srv026.

O(1)-C(2)	1.4113(16)	C(4)-C(5)	1.520(2)
O(1)-C(6)	1.4355(16)	C(4)-H(41)	1.007(14)
O(2)-C(1)	1.2012(16)	C(4)-H(42)	0.985(15)
O(3)-C(2)	1.4074(16)	C(5)-C(8)	1.5089(19)
O(3)-C(4)	1.4439(17)	C(5)-C(6)	1.5217(19)
O(4)-C(1)	1.3310(16)	C(5)-H(5)	0.974(13)
O(4)-C(7)	1.4482(17)	C(6)-H(61)	0.981(14)
C(1)-C(2)	1.5500(19)	C(6)-H(62)	0.997(15)
C(2)-C(3)	1.508(2)	C(7)-H(71)	1.002(16)
C(3)-H(31)	0.981(16)	C(7)-H(72)	1.005(18)
C(3)-H(32)	0.991(17)	C(7)-H(73)	0.980(17)
C(3)-H(32)	0.986(17)		
C(8)-C(9)	1.390(2)	C(11)-C(12)	1.379(2)
C(8)-C(13)	1.3942(19)	C(11)-H(11)	0.950(16)
C(9)-C(10)	1.384(2)	C(12)-C(13)	1.391(2)
C(9)-H(9)	0.951(14)	C(12)-H(12)	0.991(16)
C(10)-C(11)	1.384(2)	C(13)-H(13)	0.984(15)
C(10)-H(10)	0.956(16)		
C(2)-O(1)-C(6)	113.58(10)	O(2)-C(1)-O(4)	124.33(13)
C(2)-O(3)-C(4)	113.59(10)	O(2)-C(1)-C(2)	124.51(13)
C(1)-O(4)-C(7)	116.02(11)		
O(4)-C(1)-C(2)	110.96(11)		
O(3)-C(2)-O(1)	112.16(11)		

O(3)-C(2)-C(3)	107.83(11)	C(5)-C(6)-H(61)	112.1(8)
O(1)-C(2)-C(3)	106.62(11)	O(1)-C(6)-H(62)	105.6(8)
O(3)-C(2)-C(1)	109.75(10)	C(5)-C(6)-H(62)	111.2(8)
O(1)-C(2)-C(1)	111.69(11)	H(61)-C(6)-H(62)	108.5(11)
C(3)-C(2)-C(1)	108.62(12)	O(4)-C(7)-H(71)	109.7(9)
C(2)-C(3)-H(31)	108.1(9)	O(4)-C(7)-H(72)	110.2(9)
C(2)-C(3)-H(32)	111.3(9)	H(71)-C(7)-H(72)	107.9(13)
H(31)-C(3)-H(32)	108.8(12)	O(4)-C(7)-H(73)	104.3(10)
C(2)-C(3)-H(32)	111.4(10)	H(71)-C(7)-H(73)	113.2(13)
H(31)-C(3)-H(32)	110.3(13)	H(72)-C(7)-H(73)	111.6(14)
H(32)-C(3)-H(32)	107.0(14)	C(9)-C(8)-C(13)	117.99(13)
O(3)-C(4)-C(5)	110.50(11)	C(9)-C(8)-C(5)	120.46(12)
O(3)-C(4)-H(41)	109.7(8)	C(13)-C(8)-C(5)	121.54(12)
C(5)-C(4)-H(41)	109.6(8)	C(10)-C(9)-C(8)	120.96(14)
O(3)-C(4)-H(42)	104.4(8)	C(10)-C(9)-H(9)	120.3(8)
C(5)-C(4)-H(42)	112.6(8)	C(8)-C(9)-H(9)	118.7(8)
H(41)-C(4)-H(42)	109.9(11)	C(11)-C(10)-C(9)	120.55(15)
C(8)-C(5)-C(4)	111.71(11)	C(11)-C(10)-H(10)	120.7(9)
C(8)-C(5)-C(6)	112.93(11)	C(9)-C(10)-H(10)	118.8(9)
C(4)-C(5)-C(6)	107.83(12)	C(12)-C(11)-C(10)	119.33(15)
C(8)-C(5)-H(5)	109.0(8)	C(12)-C(11)-H(11)	122.1(9)
C(4)-C(5)-H(5)	108.7(8)	C(10)-C(11)-H(11)	118.5(9)
C(6)-C(5)-H(5)	106.5(7)	C(11)-C(12)-C(13)	120.18(15)
O(1)-C(6)-C(5)	110.60(11)	C(11)-C(12)-H(12)	120.2(9)
O(1)-C(6)-H(61)	108.6(8)	C(13)-C(12)-H(12)	119.6(9)
C(12)-C(13)-C(8)	120.98(14)		
C(12)-C(13)-H(13)	118.8(9)		
C(8)-C(13)-H(13)	120.2(8)		

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^4$) for 04srv026. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	253(5)	239(5)	249(5)	-29(4)	57(4)	37(4)
O(2)	540(8)	330(6)	363(6)	-54(5)	220(5)	27(5)
O(3)	266(5)	226(5)	313(6)	-8(4)	38(4)	-26(4)
O(4)	337(6)	264(5)	311(6)	7(4)	123(4)	-30(4)
C(1)	246(7)	259(7)	248(7)	-9(6)	27(6)	30(6)
C(2)	251(7)	227(7)	249(7)	-19(6)	59(6)	-10(5)
C(3)	258(8)	338(9)	339(9)	4(7)	40(7)	0(6)
C(4)	287(8)	208(8)	294(8)	-4(6)	63(6)	1(6)
C(5)	241(7)	240(7)	253(7)	-4(6)	106(6)	11(6)
C(6)	260(8)	242(7)	256(8)	-31(6)	58(6)	5(6)
C(7)	358(9)	404(10)	343(10)	61(8)	138(8)	-18(7)
C(8)	268(8)	210(7)	240(7)	-27(6)	68(6)	16(5)
C(9)	328(9)	280(8)	306(8)	14(6)	127(7)	16(6)
C(10)	465(10)	335(9)	280(8)	67(7)	67(7)	55(7)
C(11)	346(9)	383(9)	293(9)	-14(7)	-5(7)	84(7)

C(12)	280(8)	379(9)	348(9)	-8(7)	79(7)	41(7)
C(13)	314(8)	311(8)	278(8)	34(7)	110(6)	44(6)

Table 5. Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 04srv026.

	x	y	z	U(iso)
H(31)	344(1)	499(2)	303(1)	37(4)
H(32)	368(1)	485(2)	202(1)	41(4)
H(32)	388(1)	706(3)	257(1)	50(5)
H(41)	630(1)	160(2)	327(1)	24(4)
H(42)	560(1)	-9(2)	372(1)	29(4)
H(5)	555(1)	241(2)	492(1)	18(3)
H(61)	665(1)	540(2)	404(1)	22(4)
H(62)	621(1)	590(2)	494(1)	29(4)
H(71)	603(1)	748(2)	104(1)	39(4)
H(72)	707(1)	728(3)	173(1)	49(5)
H(73)	643(1)	954(3)	172(1)	52(5)
H(9)	640(1)	6(2)	600(1)	26(4)
H(10)	785(1)	-142(3)	679(1)	40(4)
H(11)	936(1)	-65(2)	635(1)	35(4)
H(12)	943(1)	163(3)	507(1)	42(5)
H(13)	795(1)	306(2)	426(1)	34(4)

Table 6. Torsion angles [°] for 04srv026.

C(7)-O(4)-C(1)-O(2)	4.7(2)	C(4)-C(5)-C(8)-C(13)	72.88(17)
C(7)-O(4)-C(1)-C(2)	-170.50(12)	C(6)-C(5)-C(8)-C(13)	-48.87(17)
C(4)-O(3)-C(2)-O(1)	-55.24(14)		
C(4)-O(3)-C(2)-C(3)	-172.33(11)		
C(4)-O(3)-C(2)-C(1)	69.52(14)		
C(6)-O(1)-C(2)-O(3)	55.46(14)		
C(6)-O(1)-C(2)-C(3)	173.26(11)		
C(6)-O(1)-C(2)-C(1)	-68.23(14)		
O(2)-C(1)-C(2)-O(3)	18.94(19)		
O(4)-C(1)-C(2)-O(3)	-165.88(10)		
O(2)-C(1)-C(2)-O(1)	143.97(13)		
O(4)-C(1)-C(2)-O(1)	-40.85(15)		
O(2)-C(1)-C(2)-C(3)	-98.72(16)		
O(4)-C(1)-C(2)-C(3)	76.46(14)		
C(2)-O(3)-C(4)-C(5)	55.66(15)		
O(3)-C(4)-C(5)-C(8)	-178.42(11)		
O(3)-C(4)-C(5)-C(6)	-53.77(15)		
C(2)-O(1)-C(6)-C(5)	-55.93(14)		
C(8)-C(5)-C(6)-O(1)	177.96(11)		
C(4)-C(5)-C(6)-O(1)	54.04(15)		
C(4)-C(5)-C(8)-C(9)	-106.08(15)		
C(6)-C(5)-C(8)-C(9)	132.17(14)		

2-methyl-5-phenyl-[1,3]-dioxane-2-carboxylic acid methyl ether (30) :

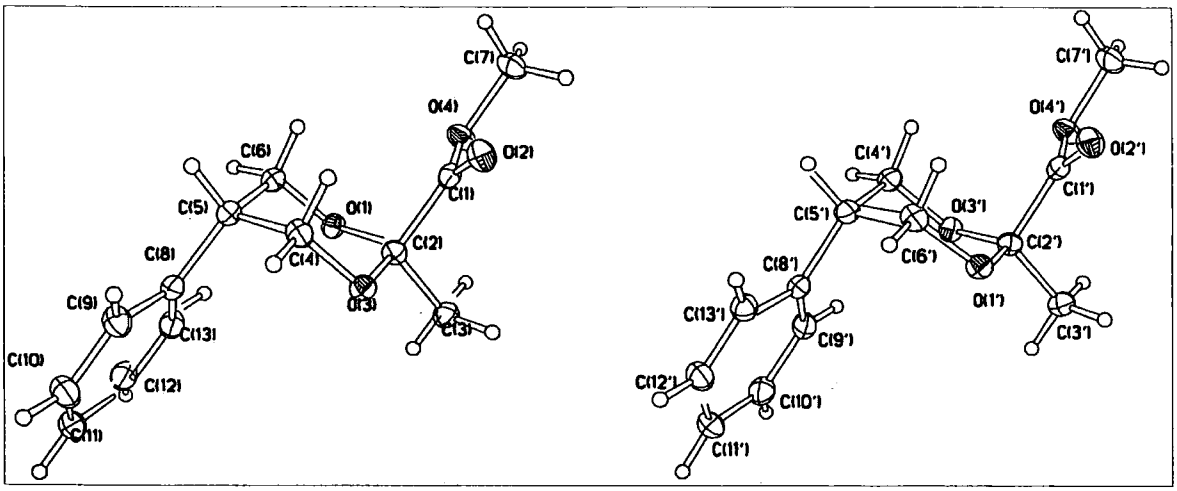


Table 1. Crystal data and structure refinement for 04srv044.

Identification code	amel garbi	
Empirical formula	C13 H16 O4	
Formula weight	236.26	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$ (No. 14, non-standard setting)	
Unit cell dimensions	a = 9.868(2) Å	α= 90°
	b = 23.056(8) Å	β= 97.87(1)°
	c = 10.382(5) Å	γ = 90°
Volume	2339.8(15) $Å^3$	
Z	8	
Density (calculated)	1.341 g/cm^3	
Absorption coefficient	0.099 mm^{-1}	
F(000)	1008	
Crystal size	0.34 × 0.26 × 0.18 mm^3	
θ range for data collection	2.1 to 27.5°.	
Index ranges	$-12 \le h \le 12, -29 \le k \le 29, -13 \le l \le 13$	
Reflections collected	23926	
Independent reflections	5369 [R(int) = 0.0472]	
Reflections with $I>2\sigma(I)$	3917	
Completeness to θ = 27.5°	100.0 %	
Absorption correction	N/A	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5369 / 0 / 435	
Largest final shift/e.s.d. ratio	0.003	
Goodness-of-fit on F^2	0.934	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0356, wR2 = 0.0924	
R indices (all data)	R1 = 0.0507, wR2 = 0.0979	
Largest diff. peak and hole	0.351 and -0.232 $e.Å^{-3}$	

Table 2. Atomic coordinates ($\times 10^5$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for 04srv044. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	78933(7)	22096(3)	48356(7)	175(2)
O(2)	80027(8)	11630(3)	24043(7)	233(2)
O(3)	66840(7)	13396(3)	45495(7)	174(2)
O(4)	86900(8)	20925(3)	24604(7)	226(2)
C(1)	80053(11)	16415(4)	28597(10)	173(2)
C(2)	71481(11)	18313(4)	39384(10)	162(2)
C(3)	59033(12)	21592(5)	33141(12)	204(2)
C(4)	77690(12)	10199(5)	53079(11)	188(2)
C(5)	85733(11)	14089(5)	63333(10)	177(2)
C(6)	90334(11)	19316(5)	56097(11)	193(2)
C(7)	95149(13)	19674(6)	14397(12)	258(3)
C(8)	77628(11)	15424(5)	74395(10)	180(2)
C(9)	74307(12)	10852(5)	82249(11)	228(3)
C(10)	66575(13)	11760(6)	92272(12)	270(3)
C(11)	61945(13)	17273(6)	94620(11)	275(3)
C(12)	65345(12)	21855(5)	87137(11)	260(3)
C(13)	73134(12)	20959(5)	77101(11)	217(2)
O(1')	81850(8)	87681(3)	53060(7)	185(2)
O(2')	69351(8)	86075(3)	75047(7)	233(2)
O(3')	70523(7)	96603(3)	50799(7)	178(2)
O(4')	62415(8)	95385(3)	74146(7)	228(2)
C(1')	69225(11)	90827(4)	70308(10)	175(2)
C(2')	77774(11)	92655(4)	59451(10)	169(2)
C(3')	90627(12)	95678(5)	65586(12)	220(3)
C(4')	58758(11)	94065(5)	43079(11)	193(2)
C(5')	62988(11)	88921(5)	35380(10)	179(2)
C(6')	70675(12)	84772(5)	45333(11)	198(2)
C(7')	54024(13)	94267(6)	84315(12)	267(3)
C(8')	71329(11)	90375(5)	24551(10)	178(2)
C(13')	76670(12)	95863(5)	22659(11)	223(2)
C(12')	84404(12)	96831(5)	12608(11)	267(3)
C(11')	87127(13)	92355(6)	4476(11)	286(3)
C(10')	81765(12)	86888(5)	6201(11)	258(3)
C(9')	73866(12)	85939(5)	16034(11)	211(2)

Table 3. Bond lengths [Å] and angles [°] for 04srv044.

O(1)-C(2)	1.4078(12)
O(1)-C(6)	1.4404(13)
O(2)-C(1)	1.2002(13)
O(3)-C(2)	1.4061(12)
O(3)-C(4)	1.4418(13)
O(4)-C(1)	1.3366(13)
O(4)-C(7)	1.4509(14)
C(1)-C(2)	1.5558(15)
C(2)-C(3)	1.5108(15)
C(4)-C(5)	1.5284(15)
C(5)-C(8)	1.5182(16)
C(5)-C(6)	1.5220(15)
C(8)-C(13)	1.3924(15)
C(8)-C(9)	1.3988(16)
C(9)-C(10)	1.3878(17)
C(10)-C(11)	1.3836(18)
C(11)-C(12)	1.3797(18)
C(12)-C(13)	1.3922(17)
O(1')-C(2')	1.4108(13)
O(1')-C(6')	1.4377(13)
O(2')-C(1')	1.2004(13)
O(3')-C(2')	1.4041(12)
O(3')-C(4')	1.4415(13)
O(4')-C(1')	1.3371(13)
O(4')-C(7')	1.4513(15)
C(1')-C(2')	1.5557(16)
C(2')-C(3')	1.5096(15)
C(4')-C(5')	1.5202(15)
C(5')-C(8')	1.5190(16)
C(5')-C(6')	1.5309(16)
C(8')-C(13')	1.3949(15)
C(8')-C(9')	1.3967(15)
C(13')-C(12')	1.3926(17)
C(12')-C(11')	1.3827(18)
C(11')-C(10')	1.3881(18)
C(10')-C(9')	1.3841(17)

C(2)-O(1)-C(6)	113.00(8)
C(2)-O(3)-C(4)	113.28(8)
C(1)-O(4)-C(7)	115.45(9)
O(2)-C(1)-O(4)	124.54(10)
O(2)-C(1)-C(2)	124.76(10)
O(4)-C(1)-C(2)	110.62(9)
O(3)-C(2)-O(1)	111.96(8)
O(3)-C(2)-C(3)	107.53(9)
O(1)-C(2)-C(3)	107.10(9)
O(3)-C(2)-C(1)	109.93(8)
O(1)-C(2)-C(1)	111.37(8)
C(3)-C(2)-C(1)	108.80(9)
O(3)-C(4)-C(5)	110.87(9)
C(8)-C(5)-C(6)	115.88(9)
C(8)-C(5)-C(4)	111.64(9)
C(6)-C(5)-C(4)	106.41(9)
O(1)-C(6)-C(5)	111.39(9)
C(13)-C(8)-C(9)	117.81(11)
C(13)-C(8)-C(5)	123.63(10)
C(9)-C(8)-C(5)	118.56(10)
C(10)-C(9)-C(8)	121.34(11)
C(11)-C(10)-C(9)	119.96(11)
C(12)-C(11)-C(10)	119.51(12)
C(11)-C(12)-C(13)	120.64(11)
C(12)-C(13)-C(8)	120.71(11)
C(2')-O(1')-C(6')	113.29(8)
C(2')-O(3')-C(4')	113.18(8)
C(1')-O(4')-C(7')	115.93(9)
O(2')-C(1')-O(4')	124.93(10)
O(2')-C(1')-C(2')	124.61(10)
O(4')-C(1')-C(2')	110.34(9)
O(3')-C(2')-O(1')	112.29(9)
O(3')-C(2')-C(3')	107.20(9)
O(1')-C(2')-C(3')	107.25(9)
O(3')-C(2')-C(1')	111.08(9)
O(1')-C(2')-C(1')	109.77(8)
C(3')-C(2')-C(1')	109.09(9)
O(3')-C(4')-C(5')	110.54(9)
C(8')-C(5')-C(4')	115.64(9)
C(8')-C(5')-C(6')	111.65(9)
C(4')-C(5')-C(6')	106.20(9)
O(1')-C(6')-C(5')	110.88(9)
C(13')-C(8')-C(9')	118.11(11)
C(13')-C(8')-C(5')	123.91(10)
C(9')-C(8')-C(5')	117.99(10)
C(12')-C(13')-C(8')	120.48(11)
C(11')-C(12')-C(13')	120.68(11)
C(12')-C(11')-C(10')	119.31(12)
C(9')-C(10')-C(11')	120.12(11)
C(10')-C(9')-C(8')	121.27(11)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^4$) for 04srv044. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	186(4)	163(4)	170(4)	-5(3)	4(3)	-13(3)
O(2)	281(5)	226(4)	196(4)	-32(3)	42(3)	0(3)
O(3)	167(4)	160(4)	195(4)	21(3)	24(3)	-18(3)
O(4)	232(4)	250(4)	215(4)	-5(3)	102(3)	-36(3)
C(1)	149(5)	212(6)	152(5)	20(4)	-7(4)	3(4)
C(2)	167(5)	150(5)	170(5)	-3(4)	28(4)	-22(4)
C(3)	187(6)	213(6)	208(6)	22(5)	15(5)	6(5)
C(4)	218(6)	173(5)	179(5)	13(4)	47(5)	30(4)
C(5)	159(5)	202(5)	169(5)	16(4)	14(4)	26(4)
C(6)	155(5)	232(6)	190(5)	-7(5)	8(4)	-14(4)
C(7)	236(6)	342(7)	215(6)	-3(5)	105(5)	-31(5)
C(8)	150(5)	233(6)	151(5)	-13(4)	-2(4)	1(4)
C(9)	261(6)	222(6)	204(6)	-3(5)	43(5)	16(5)
C(10)	286(7)	338(7)	195(6)	18(5)	62(5)	-45(5)
C(11)	227(6)	434(7)	169(6)	-55(5)	42(5)	27(5)
C(12)	260(7)	300(6)	209(6)	-57(5)	-6(5)	87(5)
C(13)	225(6)	230(6)	187(6)	-3(5)	-3(5)	25(5)
O(1')	183(4)	168(4)	208(4)	-25(3)	34(3)	28(3)
O(2')	289(5)	202(4)	208(4)	30(3)	33(3)	-6(3)
O(3')	195(4)	151(4)	184(4)	9(3)	16(3)	12(3)
O(4')	244(4)	236(4)	222(4)	16(3)	99(3)	47(3)
C(1')	147(5)	194(5)	176(5)	-10(4)	-4(4)	-3(4)
C(2')	162(5)	156(5)	192(5)	0(4)	38(4)	18(4)
C(3')	182(6)	225(6)	251(6)	-13(5)	27(5)	-11(5)
C(4')	154(6)	222(6)	199(6)	18(5)	14(5)	21(4)
C(5')	158(5)	192(5)	187(5)	-15(4)	23(4)	-18(4)
C(6')	237(6)	163(5)	199(6)	-7(4)	44(5)	-15(5)
C(7')	245(7)	350(7)	226(6)	12(5)	105(5)	35(6)
C(8')	144(5)	220(5)	164(5)	8(4)	3(4)	12(4)
C(13')	223(6)	245(6)	195(6)	-12(5)	9(5)	-23(5)
C(12')	253(6)	316(7)	226(6)	37(5)	12(5)	-101(5)
C(11')	241(7)	439(8)	187(6)	32(5)	66(5)	-29(5)
C(10')	261(7)	319(7)	196(6)	-27(5)	44(5)	50(5)
C(9')	210(6)	223(6)	195(6)	2(5)	11(5)	22(5)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 04srv044.

	x	y	z	U(iso)
H(31)	5363(14)	2295(6)	3987(13)	34(4)
H(32)	5348(12)	1918(5)	2707(12)	24(3)
H(33)	6175(12)	2505(5)	2888(12)	24(3)
H(41)	8386(12)	863(5)	4713(11)	19(3)
H(42)	7304(11)	705(5)	5699(11)	18(3)
H(5)	9382(12)	1200(5)	6701(11)	19(3)
H(61)	9438(12)	2236(5)	6195(11)	21(3)
H(62)	9716(12)	1802(5)	5047(12)	22(3)
H(71)	10303(14)	1716(6)	1805(13)	35(4)
H(72)	9864(14)	2345(6)	1212(12)	32(4)
H(73)	8979(14)	1784(6)	709(14)	38(4)
H(9)	7753(12)	690(5)	8081(11)	25(3)
H(10)	6467(14)	860(5)	9775(13)	34(4)
H(11)	5629(14)	1804(5)	10141(13)	35(4)
H(12)	6241(13)	2587(6)	8874(12)	34(4)
H(13)	7558(12)	2419(5)	7205(12)	20(3)
H(31')	8861(13)	9898(5)	7033(12)	28(3)
H(32')	9587(13)	9706(5)	5879(13)	33(4)
H(33')	9626(13)	9300(6)	7104(12)	28(3)
H(41')	5438(11)	9717(5)	3751(11)	17(3)
H(42')	5213(12)	9285(5)	4867(11)	18(3)
H(5')	5475(12)	8700(5)	3159(11)	15(3)
H(61')	6428(12)	8325(5)	5118(11)	19(3)
H(62')	7498(11)	8156(5)	4105(11)	17(3)
H(71')	5941(15)	9234(6)	9164(15)	45(4)
H(72')	4584(14)	9189(6)	8067(13)	38(4)
H(73')	5096(14)	9818(6)	8666(13)	37(4)
H(13')	7503(12)	9895(5)	2817(12)	24(3)
H(12')	8734(13)	10076(5)	1124(12)	27(3)
H(11')	9260(14)	9310(6)	-259(14)	38(4)
H(10')	8329(13)	8385(5)	54(13)	31(4)
H(9')	6996(12)	8215(5)	1712(12)	25(3)

Table 6. Torsion angles [°] for 04srv044.

C(7)-O(4)-C(1)-O(2)	-2.57(15)
C(7)-O(4)-C(1)-C(2)	-179.27(9)
C(4)-O(3)-C(2)-O(1)	-56.20(11)
C(4)-O(3)-C(2)-C(3)	-173.58(8)
C(4)-O(3)-C(2)-C(1)	68.13(10)
C(6)-O(1)-C(2)-O(3)	55.88(11)
C(6)-O(1)-C(2)-C(3)	173.51(9)
C(6)-O(1)-C(2)-C(1)	-67.65(10)
O(2)-C(1)-C(2)-O(3)	16.42(14)
O(4)-C(1)-C(2)-O(3)	-166.88(8)
O(2)-C(1)-C(2)-O(1)	141.09(10)
O(4)-C(1)-C(2)-O(1)	-42.21(11)
O(2)-C(1)-C(2)-C(3)	-101.08(12)
O(4)-C(1)-C(2)-C(3)	75.61(11)
C(2)-O(3)-C(4)-C(5)	56.82(11)
O(3)-C(4)-C(5)-C(8)	73.23(11)
O(3)-C(4)-C(5)-C(6)	-54.10(11)
C(2)-O(1)-C(6)-C(5)	-56.68(12)
C(8)-C(5)-C(6)-O(1)	-70.51(12)
C(4)-C(5)-C(6)-O(1)	54.24(11)
C(6)-C(5)-C(8)-C(13)	7.21(15)
C(4)-C(5)-C(8)-C(13)	-114.82(12)
C(6)-C(5)-C(8)-C(9)	-173.61(10)
C(4)-C(5)-C(8)-C(9)	64.37(13)
C(7')-O(4')-C(1')-O(2')	-3.73(16)
C(7')-O(4')-C(1')-C(2')	-179.85(9)
C(4')-O(3')-C(2')-O(1')	55.56(11)
C(4')-O(3')-C(2')-C(3')	173.10(9)
C(4')-O(3')-C(2')-C(1')	-67.80(11)
C(6')-O(1')-C(2')-O(3')	-54.86(11)
C(6')-O(1')-C(2')-C(3')	-172.37(9)
C(6')-O(1')-C(2')-C(1')	69.23(11)
O(2')-C(1')-C(2')-O(3')	144.53(10)
O(4')-C(1')-C(2')-O(3')	-39.33(11)
O(2')-C(1')-C(2')-O(1')	19.74(14)
O(4')-C(1')-C(2')-O(1')	-164.12(8)
O(2')-C(1')-C(2')-C(3')	-97.52(12)
O(4')-C(1')-C(2')-C(3')	78.63(11)
C(2')-O(3')-C(4')-C(5')	-57.69(12)
O(3')-C(4')-C(5')-C(8')	-68.71(12)
O(3')-C(4')-C(5')-C(6')	55.73(11)
C(2')-O(1')-C(6')-C(5')	56.13(12)
C(8')-C(5')-C(6')-O(1')	71.65(11)
C(4')-C(5')-C(6')-O(1')	-55.22(11)
C(4')-C(5')-C(8')-C(13')	9.13(15)
C(6')-C(5')-C(8')-C(13')	-112.42(12)
C(4')-C(5')-C(8')-C(9')	-171.28(9)
C(6')-C(5')-C(8')-C(9')	67.17(12)

2-carboxymethyl-2-methyl-5-(4'-nitro)-phenyl-[1,3]-dioxane (33) :

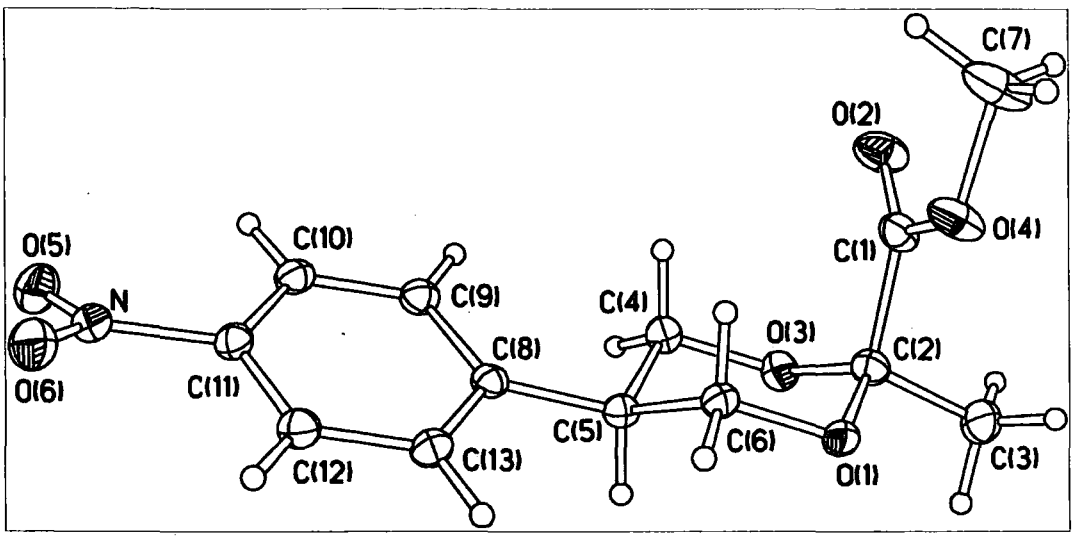


Table 1. Crystal data and structure refinement for 04srv253.

Identification code	NO2 ester acetal major	
Empirical formula	C13 H15 N O6	
Formula weight	281.26	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$ (No. 14)	
Unit cell dimensions	a = 8.3416(13) Å	α= 90°
	b = 7.3432(12) Å	β= 93.83(1)°
	c = 21.059(3) Å	γ = 90°
Volume	1287.1(3) $Å^3$	
Z	4	
Density (calculated)	1.451 g/cm^3	
Absorption coefficient	0.116 mm^{-1}	
F(000)	592	
Crystal size	0.55 × 0.55 × 0.30 mm^3	
θ range for data collection	1.9 to 29.0°.	
Index ranges	$-11 \le h \le 11$, $-9 \le k \le 9$, $-28 \le l \le 28$	
Reflections collected	14582	
Independent reflections	3404 [R(int) = 0.0256]	
Reflections with I>2σ(I)	2977	
Completeness to θ = 29.0°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.914	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3404 / 0 / 241	
Largest final shift/e.s.d. ratio	0.001	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2σ(I)]	R1 = 0.0358, wR2 = 0.0934	
R indices (all data)	R1 = 0.0419, wR2 = 0.0971	
Largest diff. peak and hole	0.380 and -0.194 $e.Å^{-3}$	

Table 2. Atomic coordinates ($\times 10^5$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for 04srv253. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	54335(8)	103137(10)	59419(3)	174(2)
O(2)	74833(10)	92813(12)	74239(4)	288(2)
O(3)	48952(9)	79650(10)	66464(3)	193(2)
O(4)	77404(10)	115907(12)	67406(4)	274(2)
O(5)	93123(11)	5934(12)	42802(4)	308(2)
O(6)	98768(11)	27408(13)	36224(4)	307(2)
N	92875(11)	21959(13)	41070(4)	225(2)
C(1)	70010(13)	101433(14)	69676(5)	201(2)
C(2)	53649(12)	97936(14)	65855(5)	183(2)
C(3)	40900(15)	109473(17)	68701(5)	258(2)
C(4)	58921(12)	67004(14)	63330(5)	174(2)
C(5)	59212(11)	72006(13)	56308(5)	154(2)
C(6)	64845(11)	91767(13)	56004(5)	159(2)
C(7)	92476(18)	120960(20)	70809(7)	372(3)
C(8)	69145(11)	59309(13)	52485(5)	155(2)
C(9)	76083(12)	43511(14)	55127(5)	182(2)
C(10)	84052(12)	31271(14)	51412(5)	183(2)
C(11)	85127(11)	35271(14)	45038(5)	179(2)
C(12)	78839(12)	51047(14)	42233(5)	189(2)
C(13)	70701(12)	62955(14)	46011(5)	180 (2)

Table 3. Bond lengths[Å] and angles [°] for 04srv253.

O(1)-C(2)	1.4129(12)	O(2)-C(1)-O(4)	124.77(10)
O(1)-C(6)	1.4378(12)	O(2)-C(1)-C(2)	124.25(10)
O(2)-C(1)	1.1976(13)	O(4)-C(1)-C(2)	110.87(8)
O(3)-C(2)	1.4071(13)	O(3)-C(2)-O(1)	112.01(8)
O(3)-C(4)	1.4363(12)	O(3)-C(2)-C(3)	106.89(9)
O(4)-C(1)	1.3335(13)	O(1)-C(2)-C(3)	107.64(8)
O(4)-C(7)	1.4531(14)	O(3)-C(2)-C(1)	110.47(8)
O(5)-N	1.2317(13)	O(1)-C(2)-C(1)	111.14(8)
O(6)-N	1.2290(13)	C(3)-C(2)-C(1)	108.50(9)
N-C(11)	1.4641(13)	C(2)-C(3)-H(31)	107.9(9)
C(1)-C(2)	1.5586(14)	C(2)-C(3)-H(32)	109.7(10)
C(2)-C(3)	1.5143(15)	H(31)-C(3)-H(32)	106.2(13)
C(3)-H(31)	0.975(16)	C(2)-C(3)-H(33)	112.8(9)
C(3)-H(32)	0.955(17)	H(31)-C(3)-H(33)	111.5(13)
C(3)-H(33)	0.964(17)	H(32)-C(3)-H(33)	108.5(13)
C(4)-C(5)	1.5255(14)	O(3)-C(4)-C(5)	109.69(8)
C(4)-H(41)	0.987(13)	O(3)-C(4)-H(41)	110.6(8)
C(4)-H(42)	0.977(14)	C(5)-C(4)-H(41)	111.4(7)
C(5)-C(8)	1.5143(13)	O(3)-C(4)-H(42)	105.8(8)
C(5)-C(6)	1.5279(14)	C(5)-C(4)-H(42)	111.2(8)
C(5)-H(5)	0.968(14)	H(41)-C(4)-H(42)	108.1(11)
C(6)-H(61)	0.988(13)	C(8)-C(5)-C(4)	114.32(8)
C(6)-H(62)	0.967(13)	C(8)-C(5)-C(6)	112.44(8)
C(7)-H(71)	0.903(19)	C(4)-C(5)-C(6)	107.11(8)
C(7)-H(72)	0.96(2)	C(8)-C(5)-H(5)	107.8(8)
C(7)-H(73)	1.01(2)	C(4)-C(5)-H(5)	107.3(8)
C(8)-C(9)	1.3955(14)	C(6)-C(5)-H(5)	107.5(8)
C(8)-C(13)	1.4039(13)	O(1)-C(6)-C(5)	109.33(8)
C(9)-C(10)	1.3897(15)	O(1)-C(6)-H(61)	110.2(7)
C(9)-H(9)	0.950(14)	C(5)-C(6)-H(61)	110.8(8)
C(10)-C(11)	1.3828(14)	O(1)-C(6)-H(62)	106.0(8)
C(10)-H(10)	0.950(15)	C(5)-C(6)-H(62)	112.7(8)
C(11)-C(12)	1.3873(14)	H(61)-C(6)-H(62)	107.8(11)
C(12)-C(13)	1.3894(14)	O(4)-C(7)-H(71)	107.0(12)
C(12)-H(12)	0.929(15)	O(4)-C(7)-H(72)	104.5(11)
C(13)-H(13)	0.960(14)	H(71)-C(7)-H(72)	108.2(16)
C(2)-O(1)-C(6)	112.83(7)	O(4)-C(7)-H(73)	110.5(13)
C(2)-O(3)-C(4)	113.69(8)	H(71)-C(7)-H(73)	112.1(16)
C(1)-O(4)-C(7)	115.62(9)	H(72)-C(7)-H(73)	114.1(16)
O(6)-N-O(5)	123.86(10)	C(9)-C(8)-C(13)	118.88(9)
O(6)-N-C(11)	118.22(9)	C(9)-C(8)-C(5)	121.80(9)
O(5)-N-C(11)	117.92(9)	C(13)-C(8)-C(5)	119.23(9)
C(10)-C(9)-H(9)	117.8(9)	C(10)-C(9)-C(8)	120.96(9)
C(8)-C(9)-H(9)	121.2(9)	C(12)-C(11)-N	118.91(9)
C(11)-C(10)-C(9)	118.27(9)	C(11)-C(12)-C(13)	117.85(9)
C(11)-C(10)-H(10)	119.6(8)	C(11)-C(12)-H(12)	121.4(9)
C(9)-C(10)-H(10)	122.1(8)	C(13)-C(12)-H(12)	120.8(9)
C(10)-C(11)-C(12)	122.92(9)	C(12)-C(13)-C(8)	121.09(9)
C(10)-C(11)-N	118.16(9)	C(12)-C(13)-H(13)	119.9(8)
		C(8)-C(13)-H(13)	119.0(8)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for 04srv253. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	202(3)	179(3)	138(3)	-3(3)	-8(3)	41(3)
O(2)	327(4)	294(4)	230(4)	85(3)	-85(3)	-64(3)
O(3)	198(3)	200(4)	183(3)	-11(3)	44(3)	-15(3)
O(4)	325(4)	271(4)	211(4)	59(3)	-95(3)	-118(3)
O(5)	321(4)	214(4)	384(5)	-54(3)	-14(4)	73(3)
O(6)	290(4)	407(5)	229(4)	-38(3)	44(3)	79(4)
N	180(4)	249(5)	242(4)	-53(4)	-24(3)	42(3)
C(1)	237(5)	197(5)	165(4)	-3(4)	-18(4)	-19(4)
C(2)	205(5)	191(5)	150(4)	1(4)	-3(3)	4(4)
C(3)	285(6)	290(6)	201(5)	-38(4)	32(4)	69(5)
C(4)	195(4)	166(5)	162(4)	9(3)	21(4)	-6(4)
C(5)	145(4)	159(4)	155(4)	5(3)	3(3)	-2(3)
C(6)	165(4)	157(4)	154(4)	9(3)	2(3)	14(3)
C(7)	396(7)	408(7)	289(6)	69(6)	-144(5)	-205(6)
C(8)	142(4)	149(4)	171(4)	-2(3)	-7(3)	-14(3)
C(9)	189(4)	171(5)	181(4)	17(4)	-16(4)	-4(4)
C(10)	165(4)	149(4)	228(5)	11(4)	-26(4)	4(3)
C(11)	132(4)	185(5)	219(5)	-32(4)	2(3)	4(3)
C(12)	177(4)	211(5)	179(5)	7(4)	11(3)	0(4)
C(13)	182(4)	174(5)	183(4)	23(4)	4(4)	14(4)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 04srv253.

	x	y	z	U(iso)
H(31)	3071(19)	10710(20)	6630(7)	34(4)
H(32)	3950(20)	10560(20)	7296(8)	42(4)
H(33)	4351(18)	12230(20)	6877(7)	33(4)
H(41)	6986(16)	6676(18)	6543(6)	18(3)
H(42)	5406(16)	5504(19)	6386(6)	20(3)
H(5)	4824(16)	7155(18)	5450(6)	20(3)
H(61)	7603(15)	9298(17)	5782(6)	16(3)
H(62)	6442(15)	9646(18)	5170(6)	17(3)
H(71)	9020(20)	12400(30)	7480(9)	47(5)
H(72)	9580(20)	13180(30)	6871(9)	52(5)
H(73)	10040(30)	11060(30)	7075(10)	68(6)
H(9)	7547(17)	4073(19)	5951(7)	24(3)
H(10)	8852(16)	2020(20)	5310(7)	24(3)
H(12)	7966(17)	5340(20)	3793(7)	26(3)
H(13)	6567(15)	7364(19)	4415(6)	19(3)

Table 6. Torsion angles [°] for 04srv253.

C(7)-O(4)-C(1)-O(2)	0.86(18)
C(7)-O(4)-C(1)-C(2)	177.24(11)
C(4)-O(3)-C(2)-O(1)	55.70(10)
C(4)-O(3)-C(2)-C(3)	173.36(8)
C(4)-O(3)-C(2)-C(1)	-68.78(10)
C(6)-O(1)-C(2)-O(3)	-56.54(10)
C(6)-O(1)-C(2)-C(3)	-173.76(8)
C(6)-O(1)-C(2)-C(1)	67.56(10)
O(2)-C(1)-C(2)-O(3)	-26.38(14)
O(4)-C(1)-C(2)-O(3)	157.22(9)
O(2)-C(1)-C(2)-O(1)	-151.35(11)
O(4)-C(1)-C(2)-O(1)	32.24(12)
O(2)-C(1)-C(2)-C(3)	90.49(13)
O(4)-C(1)-C(2)-C(3)	-85.92(11)
C(2)-O(3)-C(4)-C(5)	-56.47(10)
O(3)-C(4)-C(5)-C(8)	-178.86(8)
O(3)-C(4)-C(5)-C(6)	55.88(10)
C(2)-O(1)-C(6)-C(5)	58.25(10)
C(8)-C(5)-C(6)-O(1)	176.68(7)
C(4)-C(5)-C(6)-O(1)	-56.93(10)
C(4)-C(5)-C(8)-C(9)	5.69(13)
C(6)-C(5)-C(8)-C(9)	128.09(10)
C(4)-C(5)-C(8)-C(13)	-177.91(8)
C(6)-C(5)-C(8)-C(13)	-55.50(11)
O(6)-N-C(11)-C(10)	-155.62(10)
O(5)-N-C(11)-C(10)	24.23(14)
O(6)-N-C(11)-C(12)	26.03(14)
O(5)-N-C(11)-C(12)	-154.11(10)
N-C(11)-C(12)-C(13)	176.22(9)

APPENDIX B: CRYSTAL STRUCTURES OF THE ACID ACETALS (37,38)

2-carboxy-2-methyl-5-phenyl-[1,3]dioxane (37) :

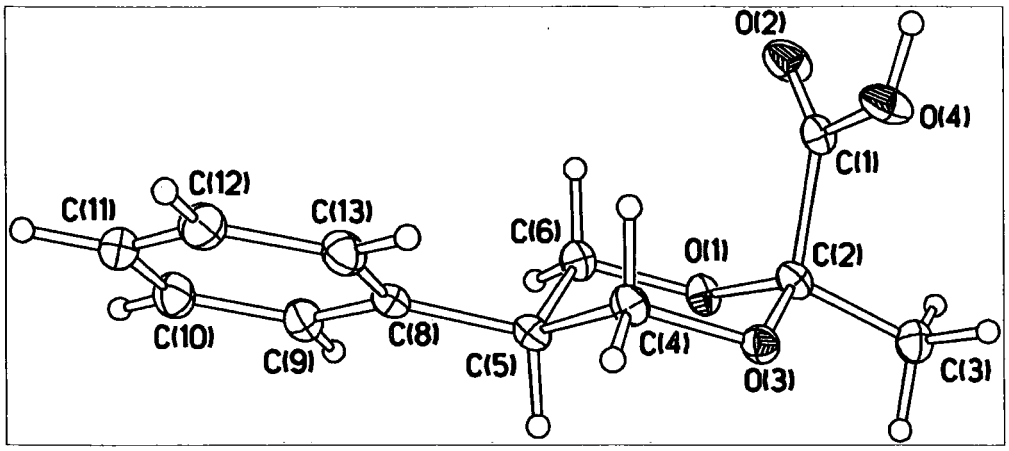


Table 1. Crystal data and structure refinement for 04srv039.

Identification code		
Empirical formula	C12 H14 O4	
Formula weight	222.23	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*Pbca* (No. 61)	
Unit cell dimensions	a = 13.914(2) Å	α= 90°
	b = 9.786(1) Å	β= 90°
	c = 15.605(2) Å	γ = 90°
Volume	2124.8(5) $Å^3$	
Z	8	
Density (calculated)	1.389 g/cm^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	944	
Crystal size	0.64 × 0.53 × 0.06 mm^3	
θ range for data collection	2.6 to 29.0°.	
Index ranges	$-17 \le h \le 18, -13 \le k \le 13, -21 \le l \le 21$	
Reflections collected	22608	
Independent reflections	2846 [R(int) = 0.0364]	
Reflections with I>2σ(I)	2452	
Completeness to θ = 29.0°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2846 / 0 / 201	
Largest final shift/e.s.d. ratio	0.001	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2σ(I)]	R1 = 0.0369, wR2 = 0.0896	
R indices (all data)	R1 = 0.0446, wR2 = 0.0932	
Largest diff. peak and hole	0.380 and -0.239 e.$Å^{-3}$	

Table 2. Atomic coordinates ($\times 10^5$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for 04srv039. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	63499(5)	28645(7)	23930(5)	157(2)
O(2)	77719(6)	10584(9)	27995(6)	260(2)
O(3)	54628(5)	9843(7)	19030(4)	151(2)
O(4)	70363(6)	-6292(8)	20847(5)	214(2)
C(1)	71369(7)	6549(11)	23403(7)	156(2)
C(2)	63690(7)	16037(10)	19327(6)	143(2)
C(3)	66536(8)	19283(11)	10158(7)	191(2)
C(4)	50416(7)	7722(11)	27344(6)	153(2)
C(5)	49338(7)	21364(10)	31910(7)	146(2)

C(6)	59373(8)	27659(10)	32456(7)	159(2)
C(8)	44583(7)	20284(10)	40632(7)	156(2)
C(9)	43256(8)	32096(11)	45556(7)	197(2)
C(10)	38708(9)	31476(13)	53481(7)	238(2)
C(11)	35333(9)	19064(13)	56610(7)	247(3)
C(12)	36516(9)	7322(13)	51770(8)	244(2)
C(13)	41150(8)	7899(11)	43845(7)	203(2)

Table 3. Bond lengths [Å] and angles [°] for 04srv039

		O(2)-C(1)-C(2)	123.57(10)
O(1)-C(2)	1.4280(12)	O(4)-C(1)-C(2)	111.79(8)
O(1)-C(6)	1.4522(12)	O(3)-C(2)-O(1)	111.96(8)
O(2)-C(1)	1.2043(13)	O(3)-C(2)-C(3)	107.12(8)
O(3)-C(2)	1.3998(12)	O(1)-C(2)-C(3)	107.35(8)
O(3)-C(4)	1.4386(12)	O(3)-C(2)-C(1)	112.00(8)
O(4)-C(1)	1.3258(13)	O(1)-C(2)-C(1)	108.88(8)
C(1)-C(2)	1.5518(14)	C(3)-C(2)-C(1)	109.39(8)
C(2)-C(3)	1.5182(14)	O(3)-C(4)-C(5)	109.64(8)
C(4)-C(5)	1.5207(14)	C(8)-C(5)-C(4)	113.72(8)
C(5)-C(8)	1.5169(14)	C(8)-C(5)-C(6)	112.12(8)
C(5)-C(6)	1.5285(14)	C(4)-C(5)-C(6)	106.84(8)
C(8)-C(13)	1.3959(15)	O(1)-C(6)-C(5)	109.69(8)
C(8)-C(9)	1.4003(14)	C(13)-C(8)-C(9)	118.33(10)
C(9)-C(10)	1.3905(16)	C(13)-C(8)-C(5)	122.14(9)
C(10)-C(11)	1.3908(18)	C(9)-C(8)-C(5)	119.50(9)
C(11)-C(12)	1.3848(17)	C(10)-C(9)-C(8)	120.80(11)
C(12)-C(13)	1.3959(16)	C(9)-C(10)-C(11)	120.27(11)
C(2)-O(1)-C(6)	114.26(7)	C(12)-C(11)-C(10)	119.54(10)
C(2)-O(3)-C(4)	113.55(7)	C(11)-C(12)-C(13)	120.31(11)
O(2)-C(1)-O(4)	124.56(10)	C(12)-C(13)-C(8)	120.76(11)

Table 4. Hydrogen bonds for 04srv039 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(4)-H(04)...O(1)#1	0.844(19)	1.89(2)	2.7288(11)	171.8(16)

Symmetry transformations used to generate equivalent atoms: #1 -x+3/2,y-1/2,z

Table 5. Anisotropic displacement parameters ($Å^2 \times 10^4$) for 04srv039. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	176(4)	122(3)	174(3)	-18(3)	39(3)	-13(3)
O(2)	188(4)	272(4)	319(4)	-108(3)	-82(3)	40(3)
O(3)	121(3)	181(3)	150(3)	-20(3)	-3(3)	-10(3)
O(4)	186(4)	149(4)	307(4)	-37(3)	-66(3)	39(3)
C(1)	137(5)	166(5)	167(4)	-15(4)	20(4)	7(4)
C(2)	130(5)	125(4)	173(5)	-21(3)	5(3)	-3(3)
C(3)	213(5)	192(5)	168(5)	-3(4)	32(4)	-2(4)
C(4)	139(5)	148(5)	171(5)	-16(4)	18(4)	-16(4)
C(5)	135(4)	139(4)	163(5)	-2(4)	12(4)	12(3)
C(6)	174(5)	137(5)	167(5)	-19(4)	19(4)	-13(4)
C(8)	123(4)	186(5)	158(4)	6(4)	-3(4)	22(4)
C(9)	190(5)	206(5)	196(5)	-22(4)	10(4)	4(4)
C(10)	234(6)	296(6)	185(5)	-59(4)	5(4)	28(5)
C(11)	207(5)	376(7)	158(5)	36(4)	23(4)	62(5)
C(12)	224(6)	265(6)	242(6)	87(4)	43(4)	30(4)
C(13)	207(5)	182(5)	221(5)	22(4)	30(4)	27(4)

Table 6. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 04srv039.

	x	y	z	U(iso)
H(04)	7527(14)	-1079(18)	2232(10)	39(4)
H(31)	7266(11)	2403(15)	996(9)	27(4)
H(32)	6699(10)	1074(14)	688(9)	23(3)
H(33)	6155(11)	2492(17)	758(9)	30(4)
H(41)	4430(10)	354(13)	2621(8)	16(3)
H(42)	5445(9)	136(14)	3073(8)	15(3)
H(5)	4520(9)	2727(13)	2818(8)	14(3)
H(61)	6376(9)	2205(13)	3609(8)	17(3)
H(62)	5936(10)	3684(15)	3456(9)	21(3)
H(9)	4541(10)	4085(15)	4328(9)	22(3)
H(10)	3785(11)	3979(15)	5686(9)	27(4)
H(11)	3223(11)	1883(15)	6208(10)	30(4)
H(12)	3410(11)	-134(16)	5374(10)	33(4)
H(13)	4184(10)	-39(15)	4060(9)	25(4)

Table 7. Torsion angles [°] for 04srv039.

C(4)-O(3)-C(2)-O(1)	-55.13(10)	O(4)-C(1)-C(2)-C(3)	-78.08(11)
C(4)-O(3)-C(2)-C(3)	-172.56(8)	C(2)-O(3)-C(4)-C(5)	59.28(10)
C(4)-O(3)-C(2)-C(1)	67.50(10)	O(3)-C(4)-C(5)-C(8)	177.74(8)
C(6)-O(1)-C(2)-O(3)	53.06(11)	O(3)-C(4)-C(5)-C(6)	-58.02(10)
C(6)-O(1)-C(2)-C(3)	170.35(8)	C(2)-O(1)-C(6)-C(5)	-54.57(10)
C(6)-O(1)-C(2)-C(1)	-71.33(10)	C(8)-C(5)-C(6)-O(1)	-179.06(8)
O(2)-C(1)-C(2)-O(3)	-142.81(10)	C(4)-C(5)-C(6)-O(1)	55.72(10)
O(4)-C(1)-C(2)-O(3)	40.53(11)	C(4)-C(5)-C(8)-C(13)	-2.97(14)
O(2)-C(1)-C(2)-O(1)	-18.45(13)	C(6)-C(5)-C(8)-C(13)	-124.32(10)
O(4)-C(1)-C(2)-O(1)	164.89(8)	C(4)-C(5)-C(8)-C(9)	179.27(9)
O(2)-C(1)-C(2)-C(3)	98.58(12)	C(6)-C(5)-C(8)-C(9)	57.92(12)

2-carboxy-2-methyl-5-phenyl-[1,3]dioxane (38) :

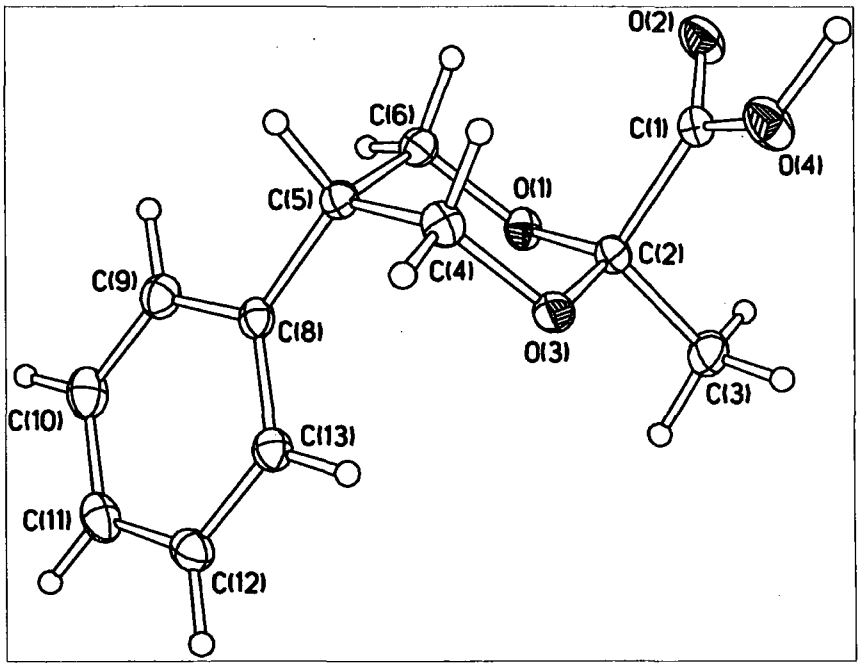


Table 1. Crystal data and structure refinement for 04srv052.

Identification code	minor acid	
Empirical formula	C12 H14 O4	
Formula weight	222.23	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$ (No. 14)	
Unit cell dimensions	a = 8.7994(9) Å	α= 90°
	b = 8.3908(7) Å	β= 101.44(1)°
	c = 15.0052(15) Å	γ = 90°
Volume	1085.88(18) $Å^3$	
Z	4	
Density (calculated)	1.359 g/cm^3	
Absorption coefficient	0.102 mm^{-1}	
F(000)	472	
Crystal size	0.35 × 0.53 × 0.66 mm^3	
θ range for data collection	2.77 to 30.51°.	
Index ranges	$-12 \le h \le 12, -11 \le k \le 11, -21 \le l \le 21$	
Reflections collected	14638	
Independent reflections	3299 [R(int) = 0.0198]	
Reflections with I>2σ(I)	3020	
Completeness to θ = 30.51°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.9120	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3299 / 0 / 201	
Largest final shift/e.s.d. ratio	0.002	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2σ(I)]	R1 = 0.0374, wR2 = 0.1049	
R indices (all data)	R1 = 0.0402, wR2 = 0.1078	
Largest diff. peak and hole	0.447 and -0.253 $e.Å^{-3}$	

Table 2. Atomic coordinates ($\times 10^5$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for 04srv052. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	19438(7)	21696(7)	11414(4)	173(1)
O(2)	35230(9)	46370(7)	5637(5)	249(2)
O(3)	35019(7)	4384(7)	4912(4)	173(1)
O(4)	47602(8)	29767(8)	-2174(5)	238(2)
C(1)	37494(9)	32844(9)	2667(5)	158(2)
C(2)	26762(9)	18751(9)	4055(5)	158(2)
C(3)	14127(11)	17671(13)	-4428(6)	258(2)
C(4)	46527(9)	3618(10)	13184(6)	176(2)
C(5)	39041(9)	5737(9)	21463(5)	158(2)
C(6)	29940(10)	21421(10)	20078(5)	176(2)
C(8)	29247(9)	-8199(9)	23512(5)	155(2)
C(9)	23699(10)	-7986(11)	31669(6)	204(2)
C(10)	14812(11)	-20421(12)	34030(6)	239(2)
C(11)	11357(10)	-33494(11)	28271(6)	230(2)
C(12)	16897(10)	-34013(10)	20222(6)	208(2)
C(13)	25692(9)	-21400(10)	17817(6)	177(2)

Table 3. Bond lengths [Å] and angles [°] for 04srv052.

O(1)-C(2)	1.4064(9)	C(10)-H(10)	0.966(16)
O(1)-C(6)	1.4381(10)	C(11)-C(12)	1.3899(13)
O(2)-C(1)	1.2497(10)	C(11)-H(11)	0.970(15)
O(3)-C(2)	1.4002(10)	C(12)-C(13)	1.4000(11)
O(3)-C(4)	1.4393(10)	C(12)-H(12)	0.979(14)
O(4)-C(1)	1.2813(10)	C(13)-H(13)	0.963(13)
O(4)-H(04)	1.08(3)	C(2)-O(1)-C(6)	113.24(6)
C(1)-C(2)	1.5529(11)	C(2)-O(3)-C(4)	112.40(6)
C(2)-C(3)	1.5176(12)	C(1)-O(4)-H(04)	114.7(14)
C(3)-H(31)	0.991(15)	O(2)-C(1)-O(4)	124.26(7)
C(3)-H(32)	0.960(15)	O(2)-C(1)-C(2)	119.97(7)
C(3)-H(33)	0.997(15)	O(4)-C(1)-C(2)	115.57(7)
C(4)-C(5)	1.5275(11)	O(3)-C(2)-O(1)	112.92(6)
C(4)-H(41)	0.982(13)	O(3)-C(2)-C(3)	107.82(7)
C(4)-H(42)	0.971(13)	O(1)-C(2)-C(3)	107.19(7)
C(5)-C(8)	1.5198(11)	O(3)-C(2)-C(1)	110.46(6)
C(5)-C(6)	1.5331(11)	O(1)-C(2)-C(1)	110.92(6)
C(5)-H(5)	0.994(12)	C(3)-C(2)-C(1)	107.27(6)
C(6)-H(61)	1.011(13)	C(2)-C(3)-H(31)	110.3(9)
C(6)-H(62)	0.993(13)	C(2)-C(3)-H(32)	108.6(9)
C(8)-C(13)	1.3960(11)	H(31)-C(3)-H(32)	108.3(12)
C(8)-C(9)	1.4049(11)	C(2)-C(3)-H(33)	108.5(8)
C(9)-C(10)	1.3913(12)	H(31)-C(3)-H(33)	109.0(12)
C(9)-H(9)	0.996(13)	H(32)-C(3)-H(33)	112.2(12)
C(10)-C(11)	1.3922(14)	O(3)-C(4)-C(5)	110.67(6)

O(3)-C(4)-H(41)	110.7(7)	C(13)-C(8)-C(9)	117.97(7)
C(5)-C(4)-H(41)	109.3(7)	C(13)-C(8)-C(5)	123.63(7)
O(3)-C(4)-H(42)	105.9(8)	C(9)-C(8)-C(5)	118.39(7)
C(5)-C(4)-H(42)	113.2(7)	C(10)-C(9)-C(8)	121.48(8)
H(41)-C(4)-H(42)	107.0(10)	C(10)-C(9)-H(9)	119.7(7)
C(8)-C(5)-C(4)	115.36(7)	C(8)-C(9)-H(9)	118.9(7)
C(8)-C(5)-C(6)	112.70(6)	C(9)-C(10)-C(11)	119.83(8)
C(4)-C(5)-C(6)	106.72(6)	C(9)-C(10)-H(10)	120.2(9)
C(8)-C(5)-H(5)	108.1(7)	C(11)-C(10)-H(10)	119.9(9)
C(4)-C(5)-H(5)	106.6(7)	C(12)-C(11)-C(10)	119.54(8)
C(6)-C(5)-H(5)	106.9(7)	C(12)-C(11)-H(11)	120.0(9)
O(1)-C(6)-C(5)	111.16(6)	C(10)-C(11)-H(11)	120.4(9)
O(1)-C(6)-H(61)	104.4(7)	C(11)-C(12)-C(13)	120.49(8)
C(5)-C(6)-H(61)	111.8(7)	C(11)-C(12)-H(12)	119.7(8)
O(1)-C(6)-H(62)	109.9(7)	C(13)-C(12)-H(12)	119.8(8)
C(5)-C(6)-H(62)	109.4(7)	C(8)-C(13)-C(12)	120.68(8)
H(61)-C(6)-H(62)	110.0(10)	C(8)-C(13)-H(13)	120.2(8)
C(12)-C(13)-H(13)	119.0(8)		

Table 3a. Hydrogen bonds for 04srv052 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(4)-H(04)...O(2)#1	1.08(3)	1.55(3)	2.6216(9)	176(2)

Symmetry transformations used to generate equivalent atoms: #1 -x+1,-y+1,-z

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^4$) for 04srv052. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	150(3)	205(3)	174(3)	24(2)	57(2)	9(2)
O(2)	364(4)	155(3)	270(3)	-15(2)	163(3)	-30(2)
O(3)	215(3)	148(3)	164(3)	-11(2)	56(2)	-12(2)
O(4)	262(3)	212(3)	284(3)	5(2)	161(3)	-19(2)
C(1)	170(3)	157(3)	152(3)	13(2)	41(3)	-11(3)
C(2)	164(3)	162(3)	152(3)	10(2)	41(3)	-22(3)
C(3)	237(4)	323(5)	189(4)	47(3)	-20(3)	-86(4)
C(4)	153(3)	182(4)	202(4)	17(3)	56(3)	6(3)
C(5)	153(3)	168(3)	151(3)	6(3)	22(3)	-14(3)
C(6)	210(4)	169(3)	155(3)	-13(3)	53(3)	-9(3)
C(8)	133(3)	172(3)	157(3)	27(3)	20(2)	9(3)
C(9)	213(4)	230(4)	175(3)	8(3)	54(3)	-5(3)
C(10)	217(4)	298(4)	220(4)	61(3)	86(3)	1(3)
C(11)	161(4)	241(4)	282(4)	93(3)	33(3)	-16(3)
C(12)	184(4)	177(4)	248(4)	28(3)	10(3)	-12(3)
C(13)	171(4)	178(4)	182(3)	15(3)	34(3)	2(3)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 04srv052.

	x	y	z	U(iso)
H(04)	5460(30)	3980(30)	-334(17)	109(9)
H(31)	1874(17)	1580(17)	-985(10)	36(4)
H(32)	865(17)	2762(17)	-522(10)	33(3)
H(33)	720(17)	856(18)	-372(10)	40(4)
H(41)	5446(14)	1187(15)	1325(8)	21(3)
H(42)	5165(15)	-660(15)	1307(9)	24(3)
H(5)	4765(14)	729(15)	2679(8)	22(3)
H(61)	2304(15)	2276(15)	2467(9)	23(3)
H(62)	3730(15)	3049(15)	2051(9)	22(3)
H(9)	2621(15)	132(16)	3582(9)	26(3)
H(10)	1128(18)	-2014(19)	3973(11)	40(4)
H(11)	522(17)	-4225(18)	2987(10)	35(4)
H(12)	1467(16)	-4329(16)	1622(9)	27(3)
H(13)	2894(16)	-2176(16)	1206(9)	25(3)

Table 6. Torsion angles [°] for 04srv052.

C(4)-O(3)-C(2)-O(1)	-56.97(8)	O(4)-C(1)-C(2)-C(3)	-80.63(9)
C(4)-O(3)-C(2)-C(3)	-175.20(6)	C(2)-O(3)-C(4)-C(5)	57.90(8)
C(4)-O(3)-C(2)-C(1)	67.88(8)	O(3)-C(4)-C(5)-C(8)	71.19(8)
C(6)-O(1)-C(2)-O(3)	55.51(8)	O(3)-C(4)-C(5)-C(6)	-54.84(8)
C(6)-O(1)-C(2)-C(3)	174.11(6)	C(2)-O(1)-C(6)-C(5)	-54.69(8)
C(6)-O(1)-C(2)-C(1)	-69.09(8)	C(8)-C(5)-C(6)-O(1)	-74.31(8)
O(2)-C(1)-C(2)-O(3)	-148.37(7)	C(4)-C(5)-C(6)-O(1)	53.30(8)
O(4)-C(1)-C(2)-O(3)	36.63(9)	C(4)-C(5)-C(8)-C(13)	-6.91(11)
O(2)-C(1)-C(2)-O(1)	-22.38(10)	C(6)-C(5)-C(8)-C(13)	116.01(8)
O(4)-C(1)-C(2)-O(1)	162.62(7)	C(4)-C(5)-C(8)-C(9)	171.76(7)
O(2)-C(1)-C(2)-C(3)	94.37(9)		
C(6)-C(5)-C(8)-C(9)	-65.32(9)		

APPENDIX C: CRYSTAL STRUCTURE OF THE C-H INSERTION PRODUCT **(56)**

1-methyl-4-phenyl-2,8-dioxa-bicyclo[3.2.1]octan-7-one (56) :

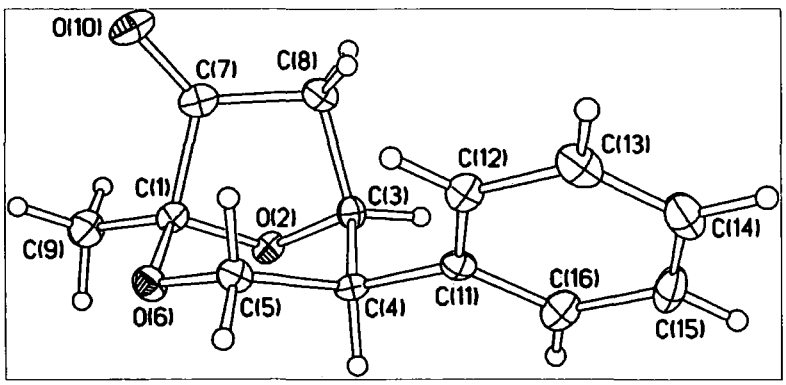


Table 1. Crystal data and structure refinement for 04srv149.

Identification code	AG404	
Empirical formula	C13 H14 O3	
Formula weight	218.24	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*Pbca* (No. 61)	
Unit cell dimensions	a = 18.523(2) Å	α= 90°
	b = 6.448(1) Å	β= 90°
	c = 36.847(4) Å	γ = 90°
Volume	4401(1) $Å^3$	
Z	16	
Density (calculated)	1.318 g/cm^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	1856	
Crystal size	0.35 × 0.27 × 0.04 mm^3	
θ range for data collection	1.56 to 25.00°.	
Index ranges	$-21 \le h \le 22, -7 \le k \le 6, -41 \le l \le 43$	
Reflections collected	20387	
Independent reflections	3871 [R(int) = 0.0774]	
Reflections with I>2σ(I)	2483	
Completeness to θ = 25.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3871 / 0 / 293	
Largest final shift/e.s.d. ratio	0.001	
Goodness-of-fit on F^2	0.989	
Final R indices [I>2σ(I)]	R1 = 0.0465, wR2 = 0.1041	
R indices (all data)	R1 = 0.0869, wR2 = 0.1164	
Largest diff. peak and hole	0.279 and -0.230 $e.Å^{-3}$	

Table 2. Atomic coordinates ($\times 10^5$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for 04srv149. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	36442(12)	67800(30)	49355(7)	145(5)
O(2)	33834(8)	58090(20)	52545(4)	152(4)
C(3)	36474(12)	71110(30)	55457(6)	143(5)
C(4)	32255(11)	91590(30)	55330(6)	139(5)
C(5)	33611(12)	101740(40)	51651(6)	157(6)
O(6)	32701(8)	86750(20)	48748(4)	173(4)
C(7)	44307(12)	72640(30)	50437(7)	156(5)
C(8)	44491(12)	73450(40)	54529(6)	167(6)
O(10)	49279(8)	74760(30)	48333(5)	245(4)
C(9)	35451(13)	53920(40)	46161(7)	222(6)
C(11)	33906(11)	104460(30)	58649(6)	142(5)
C(12)	38800(11)	120870(30)	58723(7)	156(6)
C(13)	40388(13)	130990(40)	61944(7)	216(6)
C(14)	37142(13)	125060(40)	65138(7)	242(6)
C(15)	32218(13)	108820(40)	65126(7)	243(6)
C(16)	30635(13)	98850(40)	61916(7)	202(6)
C(1')	63710(12)	31350(40)	74650(7)	184(6)
O(2')	66036(8)	22410(30)	71346(4)	190(4)
C(3')	62712(12)	35260(40)	68560(7)	174(6)
C(4')	66621(12)	56310(40)	68651(6)	171(6)
C(5')	65904(13)	65690(40)	72451(6)	187(6)
O(6')	67377(8)	50480(20)	75256(4)	196(4)
C(7')	55665(13)	35910(40)	73880(7)	191(6)
C(8')	54844(12)	35670(40)	69820(6)	204(6)
C(9')	65121(14)	17070(40)	77768(7)	256(7)
O(10')	51117(9)	38910(30)	76169(5)	283(5)
C(11')	64216(12)	70840(40)	65648(7)	166(6)
C(12')	57606(13)	81330(40)	65720(7)	220(6)
C(13')	55442(14)	93480(40)	62834(7)	262(6)
C(14')	59836(14)	96000(40)	59840(7)	265(7)
C(15')	66469(14)	86230(40)	59758(7)	265(7)
C(16')	68607(13)	73660(40)	62627(7)	205(6)

Table 3. Bond lengths [Å] and angles [°] for 04srv149.

C(1)-O(2)	1.417(3)	C(5)-C(4)-C(3)	108.20(18)
C(1)-O(6)	1.423(3)	O(6)-C(5)-C(4)	110.48(18)
C(1)-C(9)	1.490(3)	C(1)-O(6)-C(5)	113.54(17)
C(1)-C(7)	1.542(3)	O(10)-C(7)-C(8)	128.2(2)
O(2)-C(3)	1.447(3)	O(10)-C(7)-C(1)	125.1(2)
C(3)-C(8)	1.531(3)	C(8)-C(7)-C(1)	106.64(18)
C(3)-C(4)	1.535(3)	C(7)-C(8)-C(3)	101.41(18)
C(4)-C(11)	1.509(3)	C(12)-C(11)-C(16)	117.5(2)
C(4)-C(5)	1.526(3)	C(12)-C(11)-C(4)	124.4(2)
C(5)-O(6)	1.452(3)	C(16)-C(11)-C(4)	117.9(2)
C(7)-O(10)	1.211(3)	C(13)-C(12)-C(11)	120.8(2)
C(7)-C(8)	1.509(3)	C(14)-C(13)-C(12)	120.6(2)
C(11)-C(12)	1.394(3)	C(13)-C(14)-C(15)	119.6(2)
C(11)-C(16)	1.395(3)	C(16)-C(15)-C(14)	119.6(2)
C(12)-C(13)	1.386(3)	C(15)-C(16)-C(11)	121.8(2)
C(13)-C(14)	1.376(4)	O(2')-C(1')-O(6')	110.01(18)
C(14)-C(15)	1.389(4)	O(2')-C(1')-C(9')	110.92(19)
C(15)-C(16)	1.377(3)	O(6')-C(1')-C(9')	109.2(2)
C(1')-O(2')	1.414(3)	O(2')-C(1')-C(7')	102.32(19)
C(1')-O(6')	1.426(3)	O(6')-C(1')-C(7')	108.86(18)
C(1')-C(9')	1.495(3)	C(9')-C(1')-C(7')	115.3(2)
C(1')-C(7')	1.545(3)	C(1')-O(2')-C(3')	104.24(17)
O(2')-C(3')	1.456(3)	O(2')-C(3')-C(8')	101.47(18)
C(3')-C(8')	1.530(3)	O(2')-C(3')-C(4')	106.73(18)
C(3')-C(4')	1.538(3)	C(8')-C(3')-C(4')	115.3(2)
C(4')-C(11')	1.517(3)	C(11')-C(4')-C(5')	113.41(19)
C(4')-C(5')	1.531(3)	C(11')-C(4')-C(3')	113.01(19)
C(5')-O(6')	1.451(3)	C(5')-C(4')-C(3')	109.12(19)
C(7')-O(10')	1.208(3)	O(6')-C(5')-C(4')	111.60(19)
C(7')-C(8')	1.504(3)	C(1')-O(6')-C(5')	112.58(17)
C(11')-C(16')	1.390(3)	O(10')-C(7')-C(8')	128.7(2)
C(11')-C(12')	1.399(3)	O(10')-C(7')-C(1')	125.1(2)
C(12')-C(13')	1.380(3)	C(8')-C(7')-C(1')	106.2(2)
C(13')-C(14')	1.381(4)	C(7')-C(8')-C(3')	101.87(19)
C(14')-C(15')	1.381(4)	C(16')-C(11')-C(12')	117.6(2)
C(15')-C(16')	1.390(3)	C(16')-C(11')-C(4')	119.5(2)
O(2)-C(1)-O(6)	110.13(17)	C(12')-C(11')-C(4')	122.8(2)
O(2)-C(1)-C(9)	110.35(19)	C(13')-C(12')-C(11')	120.9(2)
O(6)-C(1)-C(9)	109.37(19)	C(12')-C(13')-C(14')	120.8(2)
O(2)-C(1)-C(7)	101.38(18)	C(13')-C(14')-C(15')	119.2(2)
O(6)-C(1)-C(7)	109.08(18)	C(14')-C(15')-C(16')	120.2(2)
C(9)-C(1)-C(7)	116.23(19)	C(15')-C(16')-C(11')	121.2(2)
C(1)-O(2)-C(3)	104.08(16)		
O(2)-C(3)-C(8)	102.68(17)		
O(2)-C(3)-C(4)	107.72(17)		
C(8)-C(3)-C(4)	113.69(19)		
C(11)-C(4)-C(5)	116.77(19)		
C(11)-C(4)-C(3)	110.20(18)		

Table 3a. Torsion angles [°] for 04srv149.

C(5)-C(4)-C(11)-C(12)	-24.6(3)
C(5')-C(4')-C(11')-C(12')	-49.6(3)

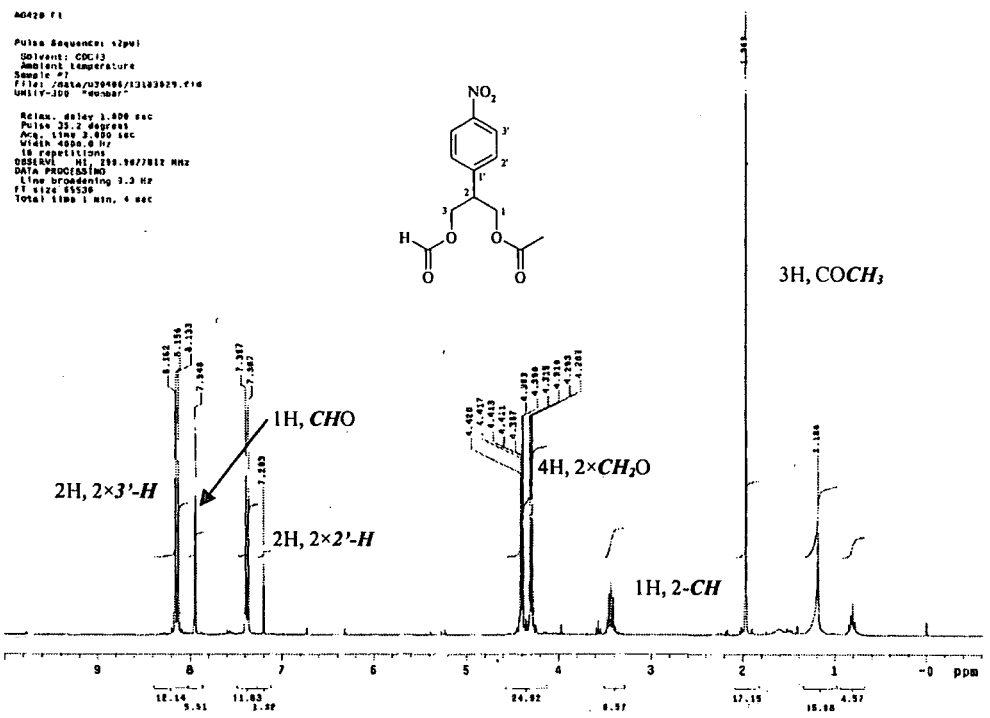
Table 4. Anisotropic displacement parameters ($Å^2 \times 10^4$) for 04srv149. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	156(12)	109(13)	169(14)	1(10)	19(10)	11(10)
O(2)	162(8)	120(9)	173(10)	-12(7)	35(7)	-18(7)
C(3)	175(12)	123(13)	130(14)	-8(10)	-5(10)	-1(10)
C(4)	99(11)	139(13)	178(14)	-1(11)	16(10)	4(10)
C(5)	163(12)	134(13)	172(14)	-19(11)	-11(10)	5(11)
O(6)	192(9)	163(10)	165(10)	-25(7)	-26(7)	27(7)
C(7)	171(12)	43(13)	254(15)	-17(11)	22(11)	18(10)
C(8)	173(12)	133(14)	195(14)	-33(11)	-25(10)	29(11)
O(10)	174(9)	249(11)	313(11)	-31(9)	92(8)	-29(8)
C(9)	234(14)	210(15)	221(16)	-21(12)	8(11)	-17(11)
C(11)	127(12)	123(13)	177(14)	3(10)	-9(10)	45(10)
C(12)	189(13)	97(13)	183(14)	4(11)	14(10)	24(11)
C(13)	230(14)	155(15)	264(16)	-31(12)	-64(11)	24(11)
C(14)	287(14)	210(15)	229(16)	-76(12)	-85(12)	115(13)
C(15)	324(15)	265(16)	139(15)	39(12)	53(12)	138(13)
C(16)	229(13)	148(14)	229(16)	16(12)	43(11)	27(11)
C(1')	210(13)	166(14)	177(15)	20(11)	12(11)	-20(11)
O(2')	215(9)	173(10)	181(10)	3(8)	11(7)	35(8)
C(3')	204(13)	175(14)	144(14)	3(11)	-8(10)	19(11)
C(4')	137(12)	171(14)	204(15)	-14(11)	32(11)	11(11)
C(5')	179(13)	177(14)	206(15)	53(11)	9(11)	-11(11)
O(6')	209(9)	196(10)	184(10)	40(8)	-39(7)	-26(8)
C(7')	203(13)	105(14)	265(16)	6(11)	56(11)	-43(11)
C(8')	194(13)	196(15)	221(15)	-8(12)	-39(11)	-33(11)
C(9')	318(15)	243(16)	206(16)	35(12)	-15(12)	13(12)
O(10')	225(9)	307(11)	317(12)	3(9)	103(9)	-40(9)
C(11')	191(13)	124(13)	184(14)	-21(11)	-6(10)	-14(11)
C(12')	248(14)	211(15)	200(15)	15(11)	23(11)	48(12)
C(13')	304(15)	215(16)	268(17)	-7(13)	-71(13)	29(12)
C(14')	417(17)	177(15)	200(16)	32(12)	-120(13)	-76(13)
C(15')	367(16)	266(16)	163(15)	-9(13)	25(12)	-168(14)
C(16')	239(13)	174(14)	203(15)	-28(12)	18(11)	-45(11)

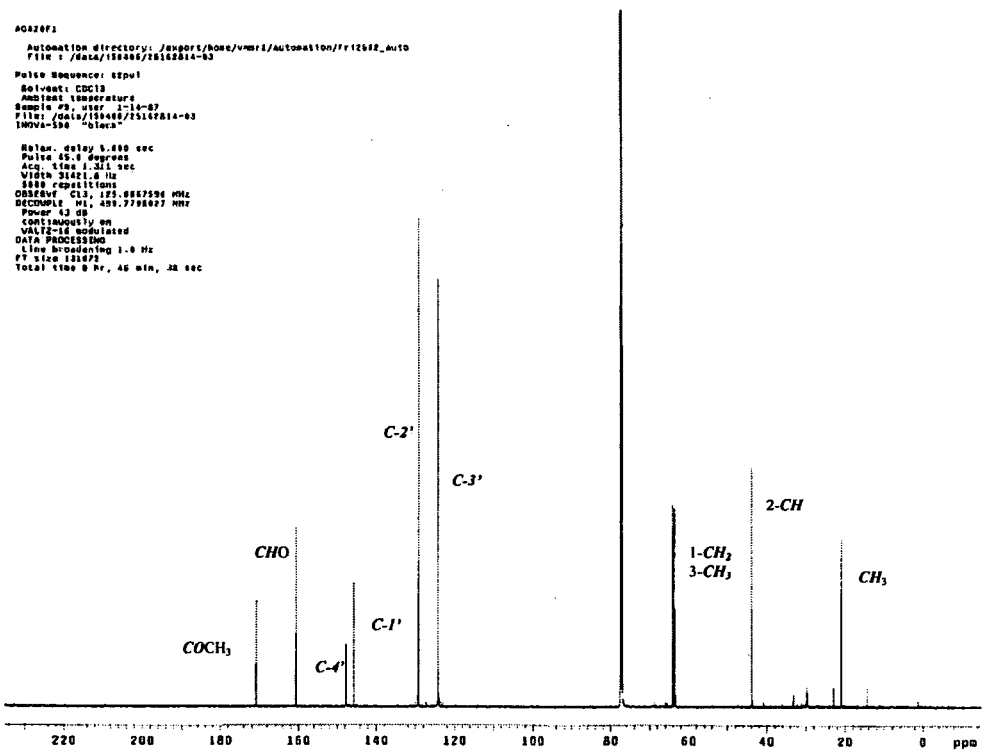
Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 04srv149.

	x	y	z	U(iso)
H(3)	3584	6411	5786	17
H(4)	2701	8800	5543	17
H(51)	3020	11340	5130	19
H(52)	3858	10738	5158	19
H(81)	4644	8683	5541	20
H(82)	4738	6194	5555	20
H(91)	3808	4093	4656	29(4)
H(92)	3732	6077	4398	29(4)
H(93)	3030	5092	4584	29(4)
H(12)	4108	12517	5654	19
H(13)	4374	14214	6195	26
H(14)	3827	13201	6734	29
H(15)	2995	10461	6732	29
H(16)	2722	8787	6193	24
H(3')	6315	2864	6612	21
H(4')	7187	5345	6825	21
H(51')	6095	7118	7277	22
H(52')	6932	7742	7270	22
H(81')	5219	2322	6899	24
H(82')	5233	4825	6894	24
H(91')	7033	1495	7803	35(4)
H(92')	6318	2318	8000	35(4)
H(93')	6277	370	7732	35(4)
H(12')	5456	8007	6778	26
H(13')	5088	10018	6291	31
H(14')	5832	10437	5786	32
H(15')	6958	8810	5773	32
H(16')	7315	6687	6252	25

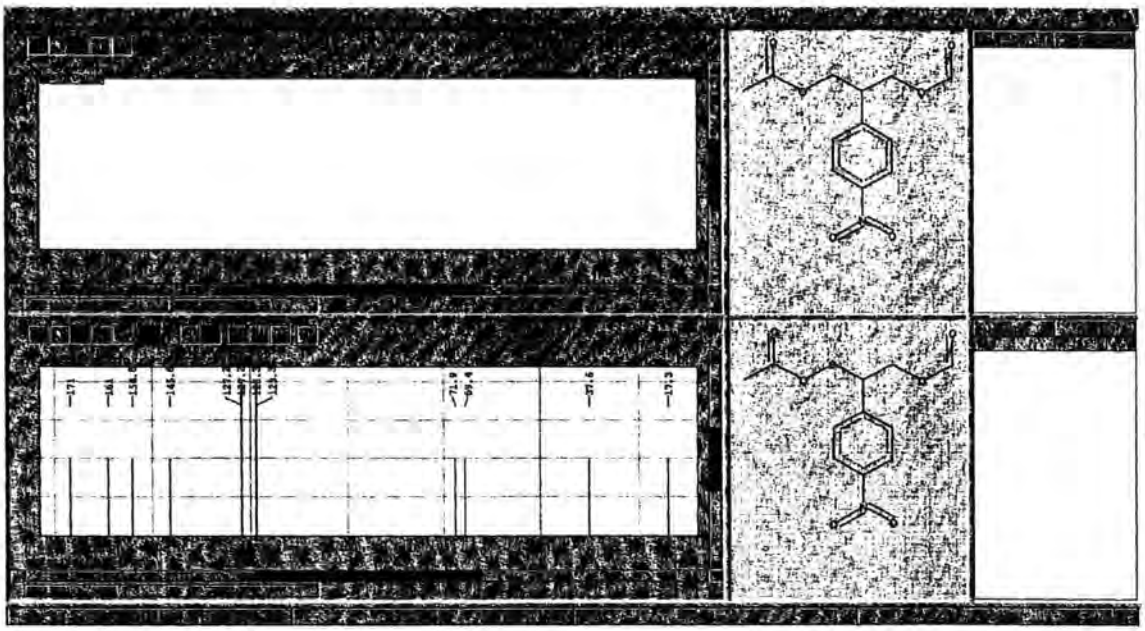
APPENDIX D: ANALYTICAL DATA OF THE BY-PRODUCT **(62)**



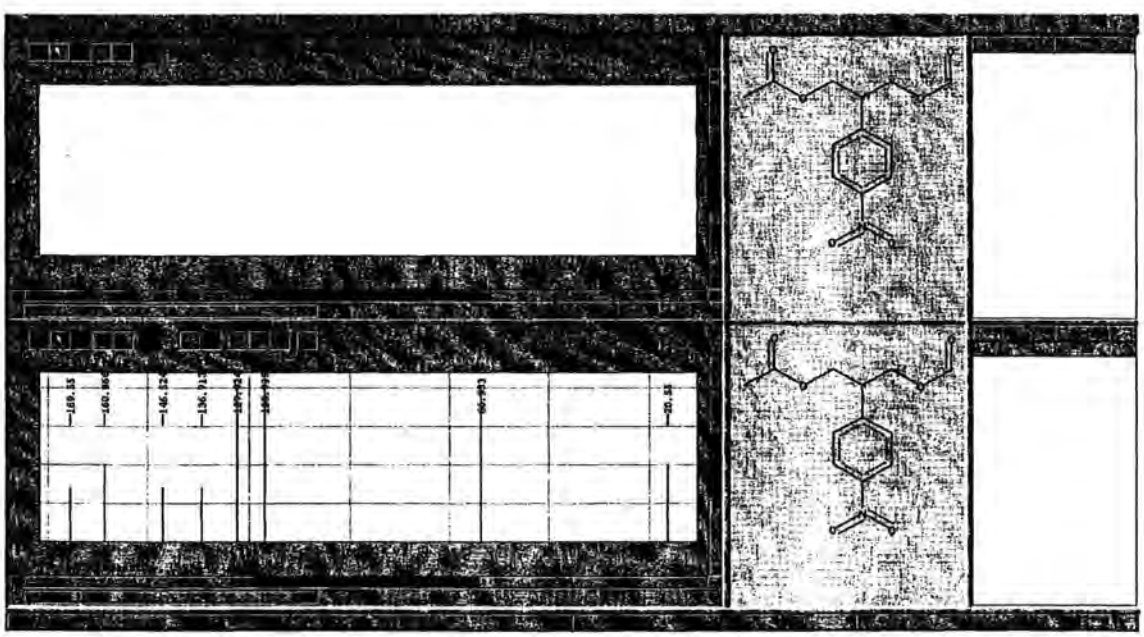
^{1}H NMR spectrum of 3-formyl-2-(4'-nitro)-propyl acetate **(62)**



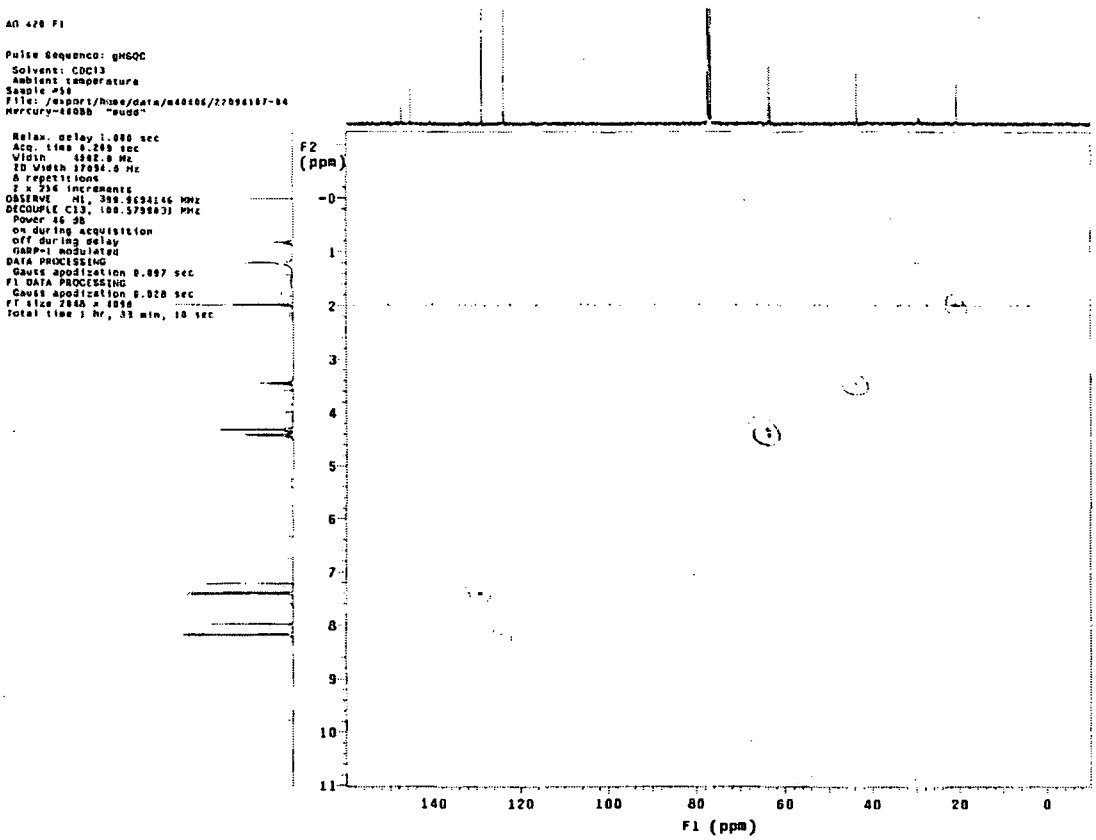
^{13}C NMR spectrum of 3-formyl-2-(4'-nitro)-propyl acetate **(62)**



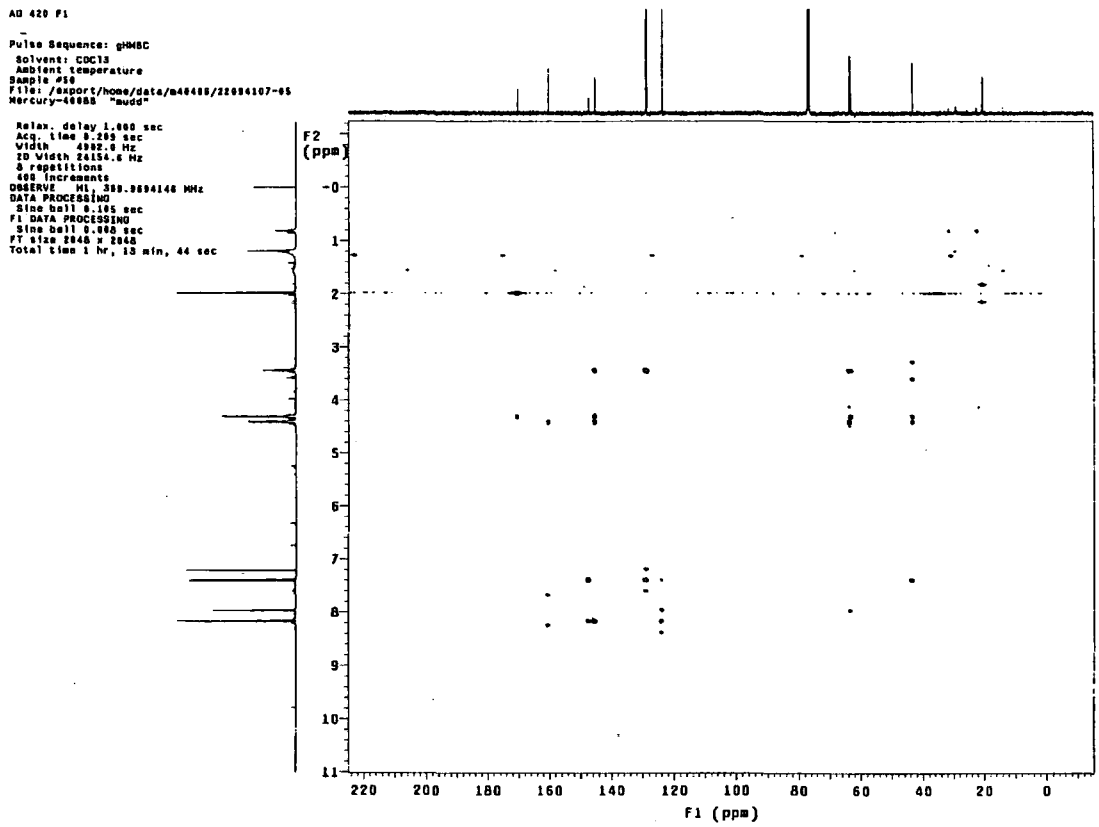
Data-base prediction of the ^{13}C spectrum of 3-formyl-2-(4'-nitro)-propyl acetate **(62).**
(Chemical Concepts SpecSurf, http://cds7.dl.ac.uk:8080)



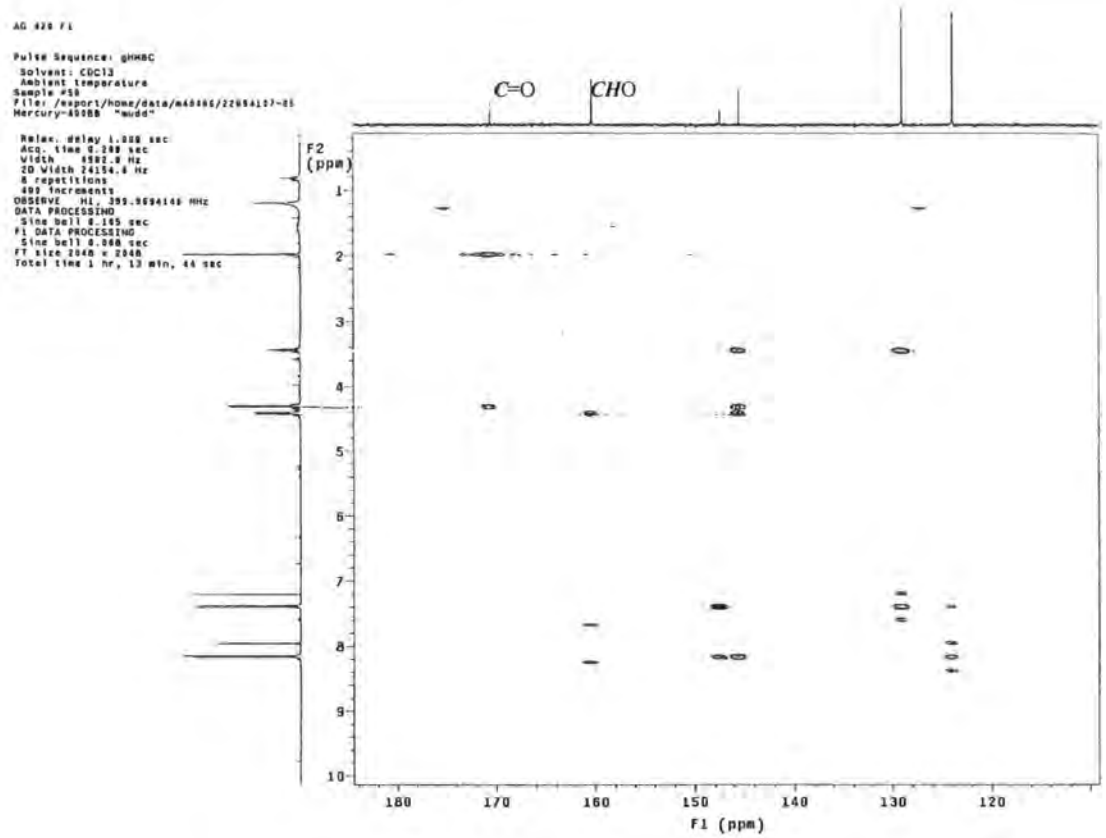
Rule-based prediction of the ^{13}C spectrum of 3-formyl-2-(4'-nitro)-propyl acetate **(62).**
(Chemical Concepts SpecSurf, http://cds7.dl.ac.uk:8080)



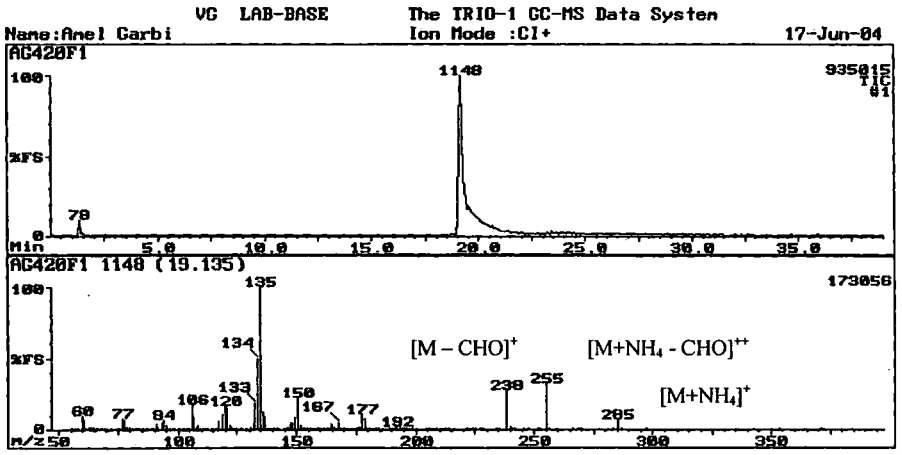
HSQC spectrum of 3-formyl-2-(4'-nitro)-propyl acetate **(62)**



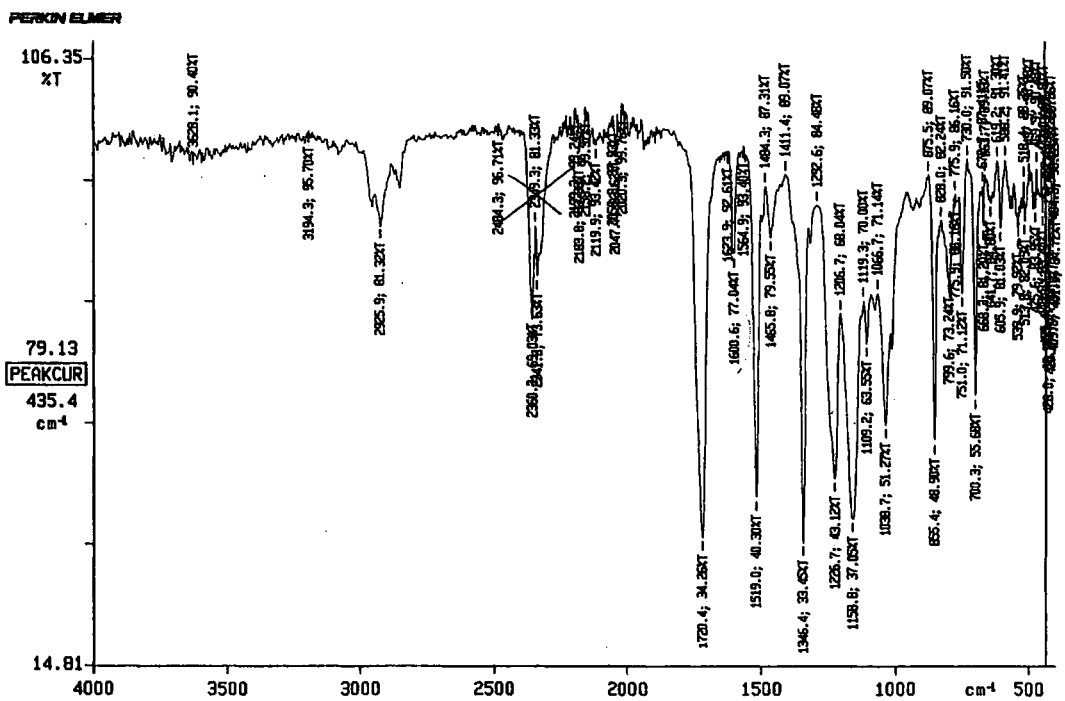
HMBC spectrum of 3-formyl-2-(4'-nitro)-propyl acetate **(62)**



HMBC spectrum of 3-formyl-2-(4'-nitro)-propyl acetate **(62)**

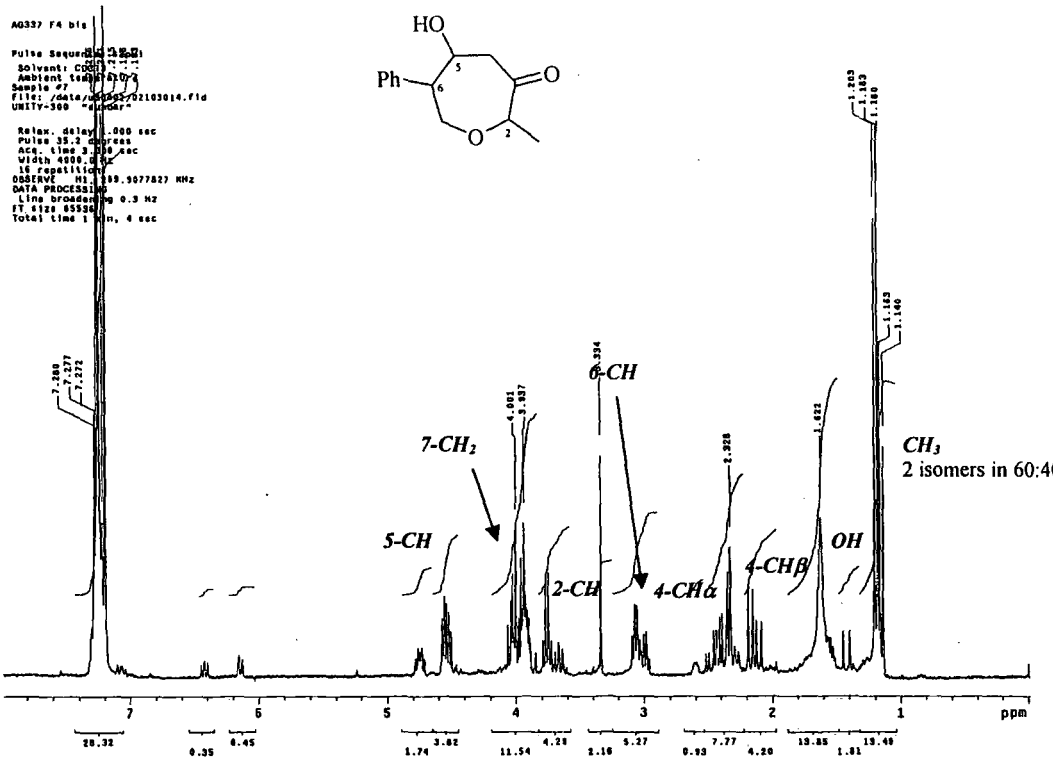


GC/MS spectrum of 3-formyl-2-(4'-nitro)-propyl acetate **(62)**

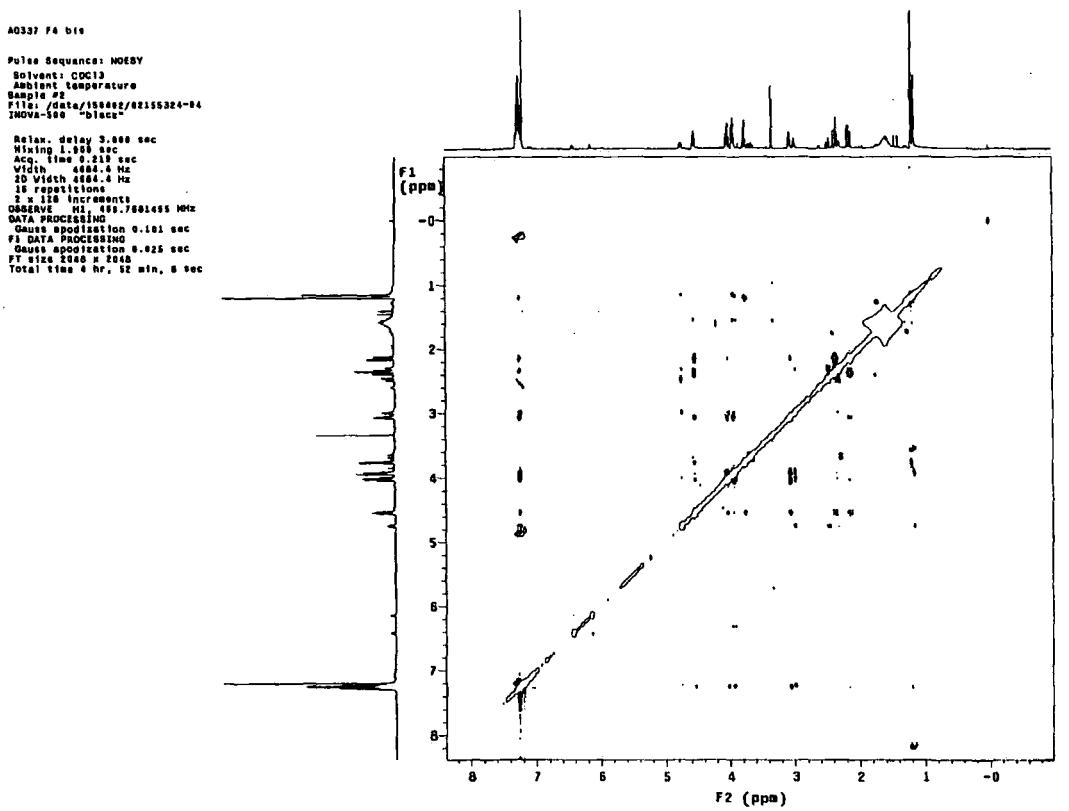


IR spectrum of 3-formyl-2-(4'-nitro)-propyl acetate **(62)**

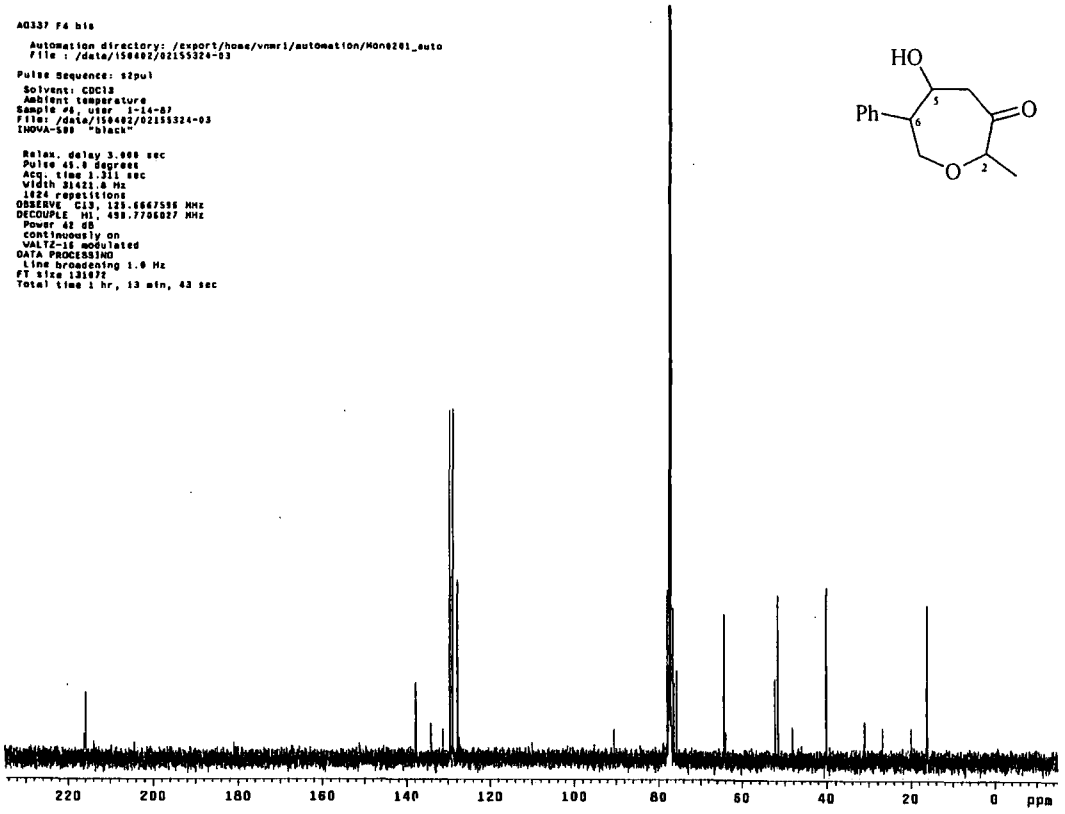
APPENDIX E: ANALYTICAL DATA OF THE PRODUCT OF THE SmI_2 REACTION



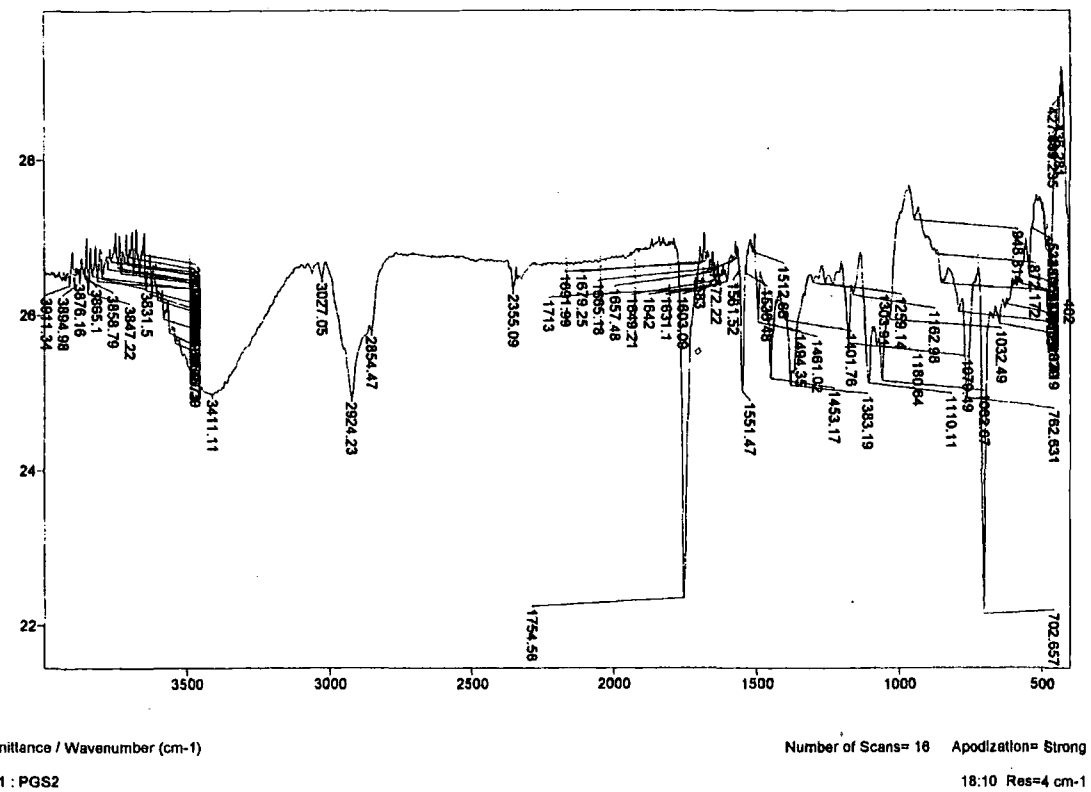
^{1}H NMR spectrum of 5-hydroxy-2-methyl-6-phenyl-oxepan-3-one.
(SmI_2 reaction product)



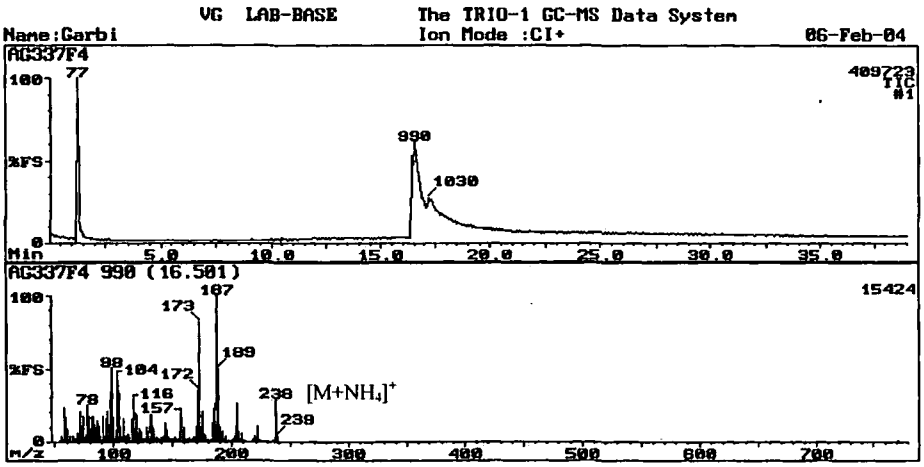
NOESY spectrum of 5-hydroxy-2-methyl-6-phenyl-oxepan-3-one.

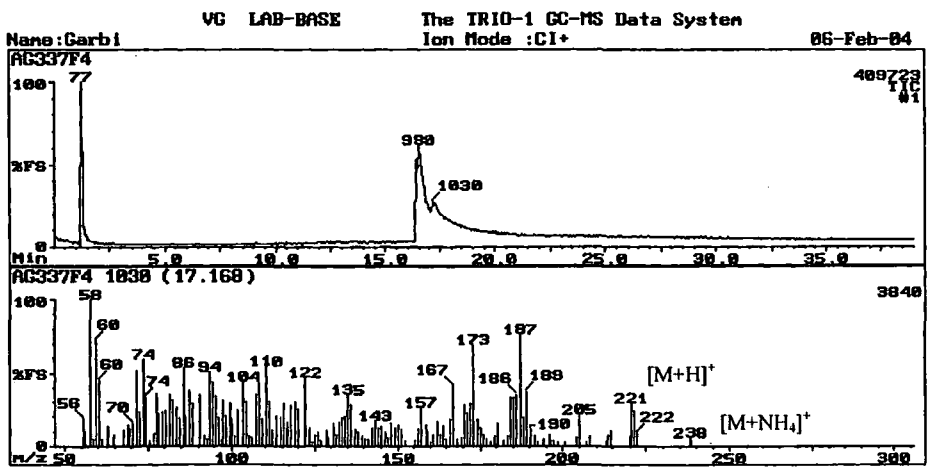


^{13}C NMR spectrum of 5-hydroxy-2-methyl-6-phenyl-oxepan-3-one.

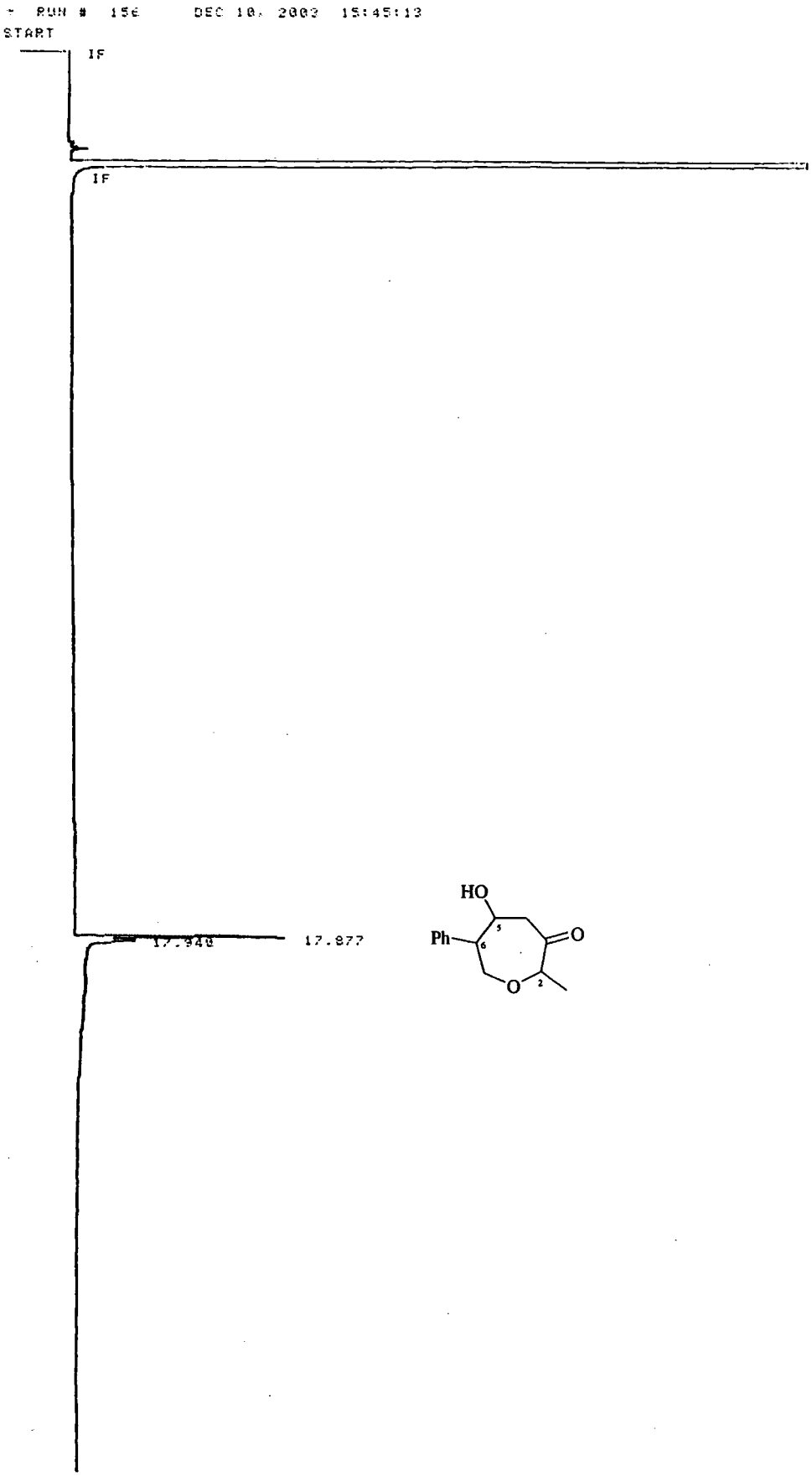


IR spectrum of 5-hydroxy-2-methyl-6-phenyl-oxepan-3-one.

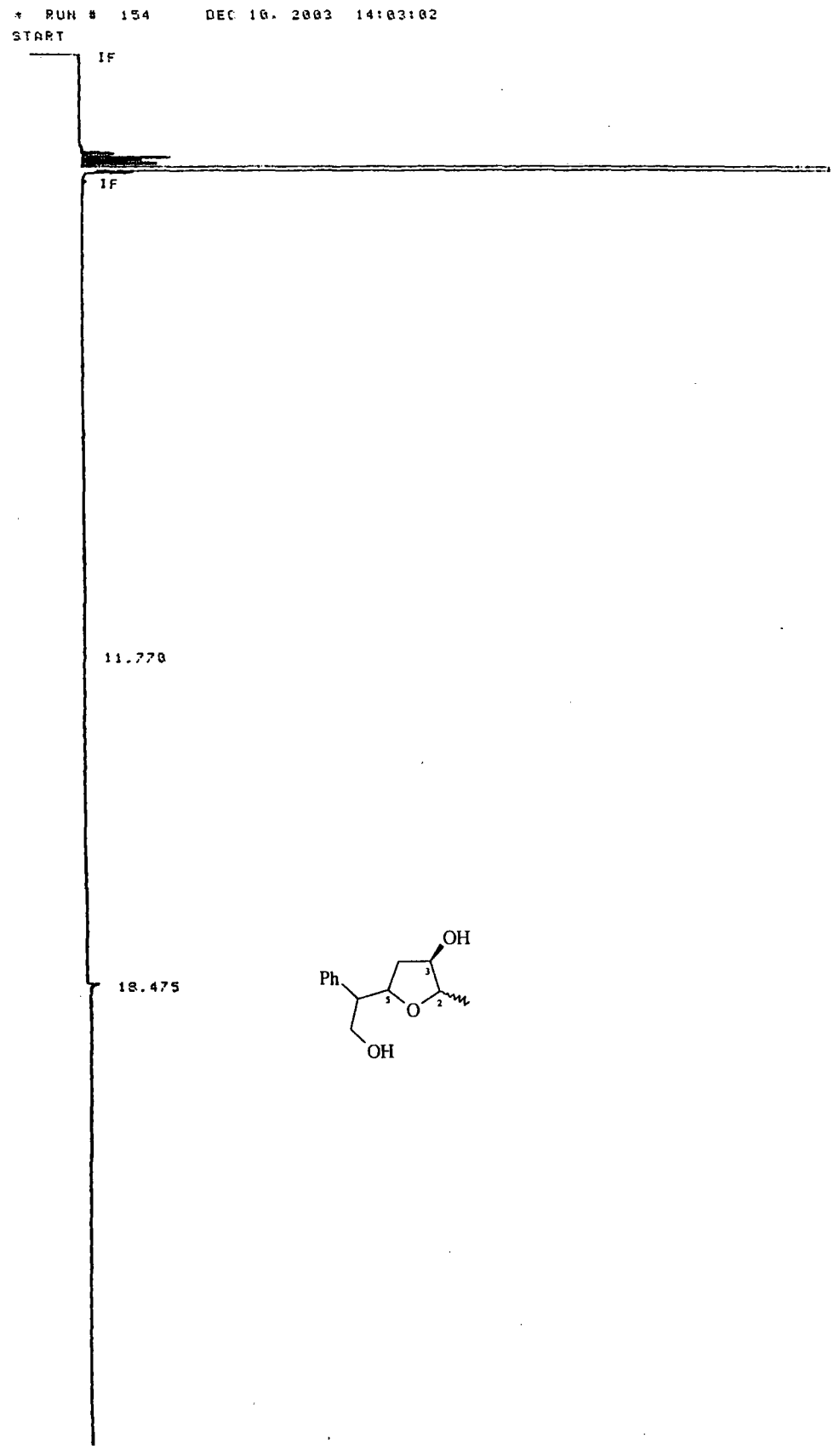




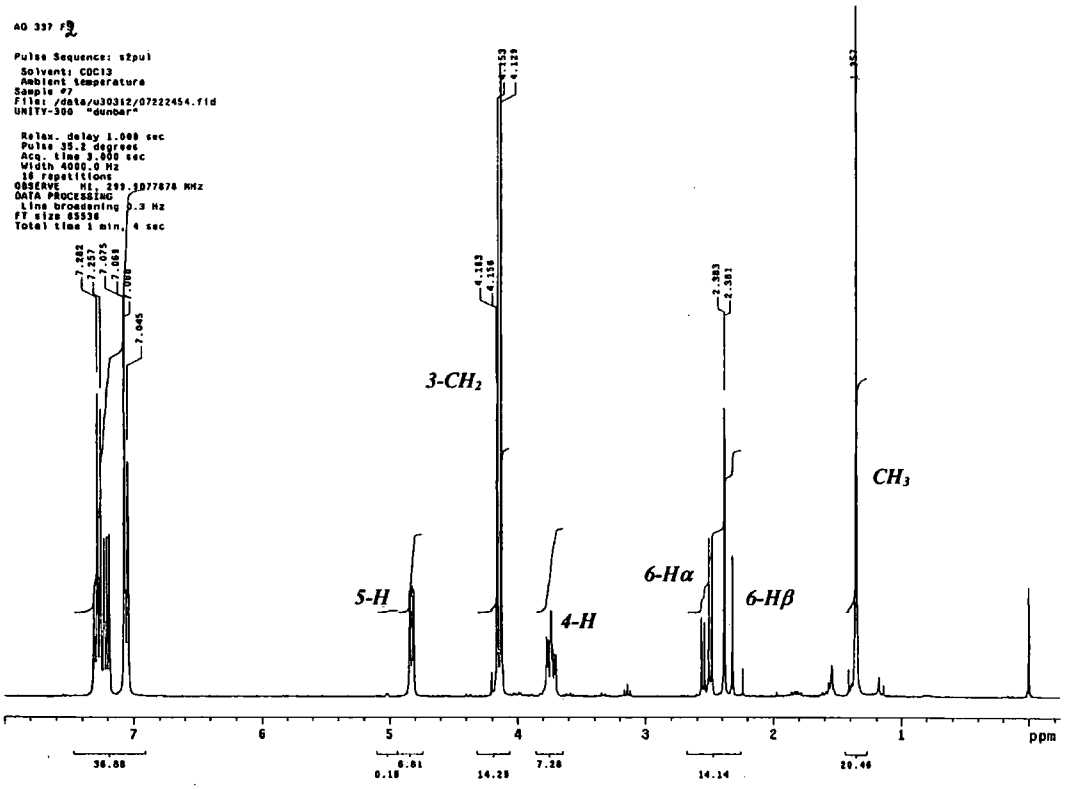
GC/MS spectra of 5-hydroxy-2-methyl-6-phenyl-oxepan-3-one.



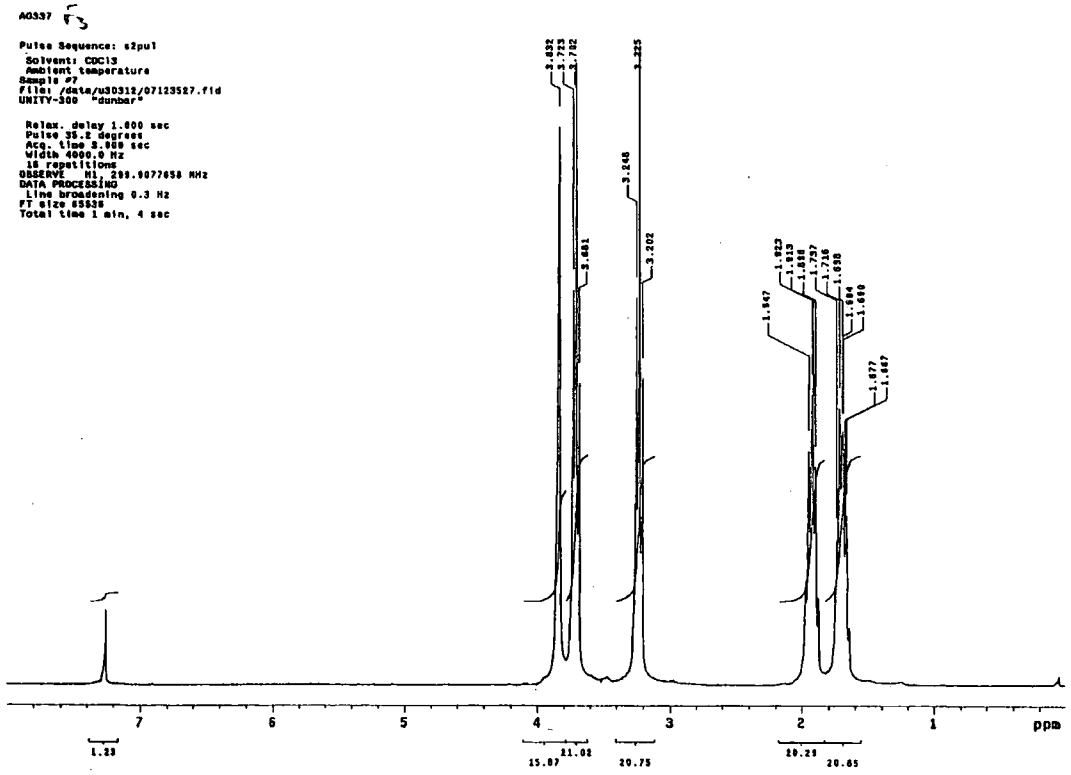
GC spectrum of 5-hydroxy-2-methyl-6-phenyl-oxepan-3-one (2 isomers).



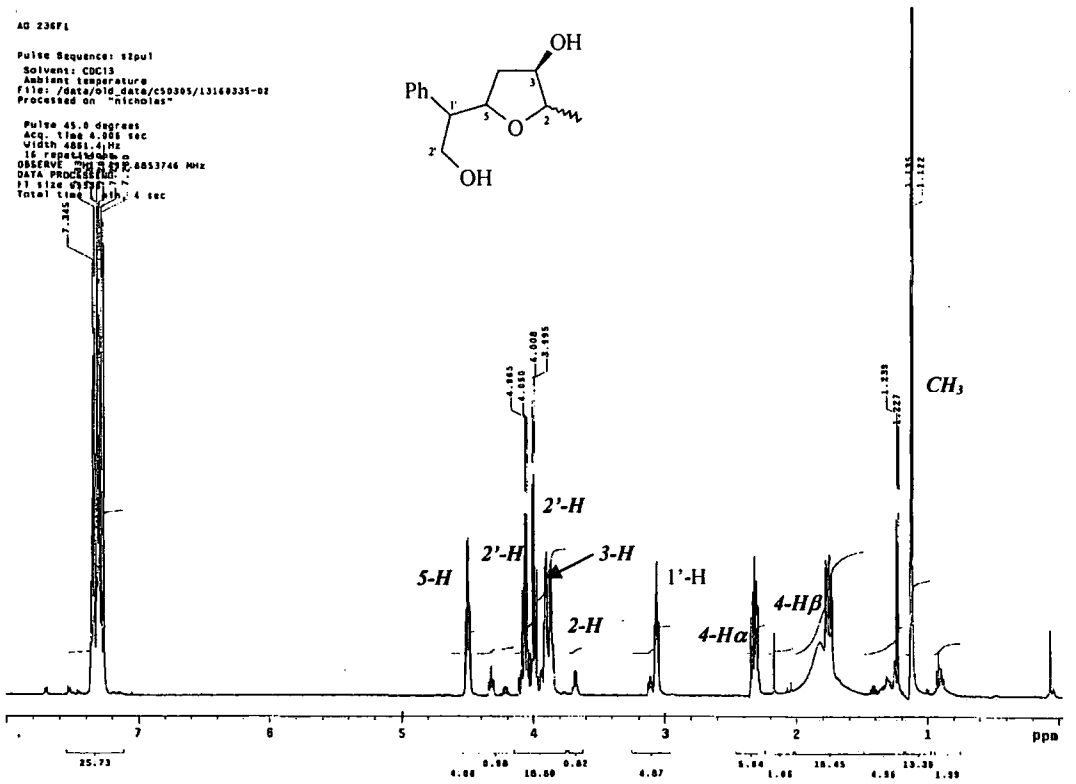
GC of 5-(2'-hydroxy-1'-phenyl-ethyl)-2-methyl-tetrahydrofuran-3-ol **(68)** (major isomer). (for comparison with oxepane product).



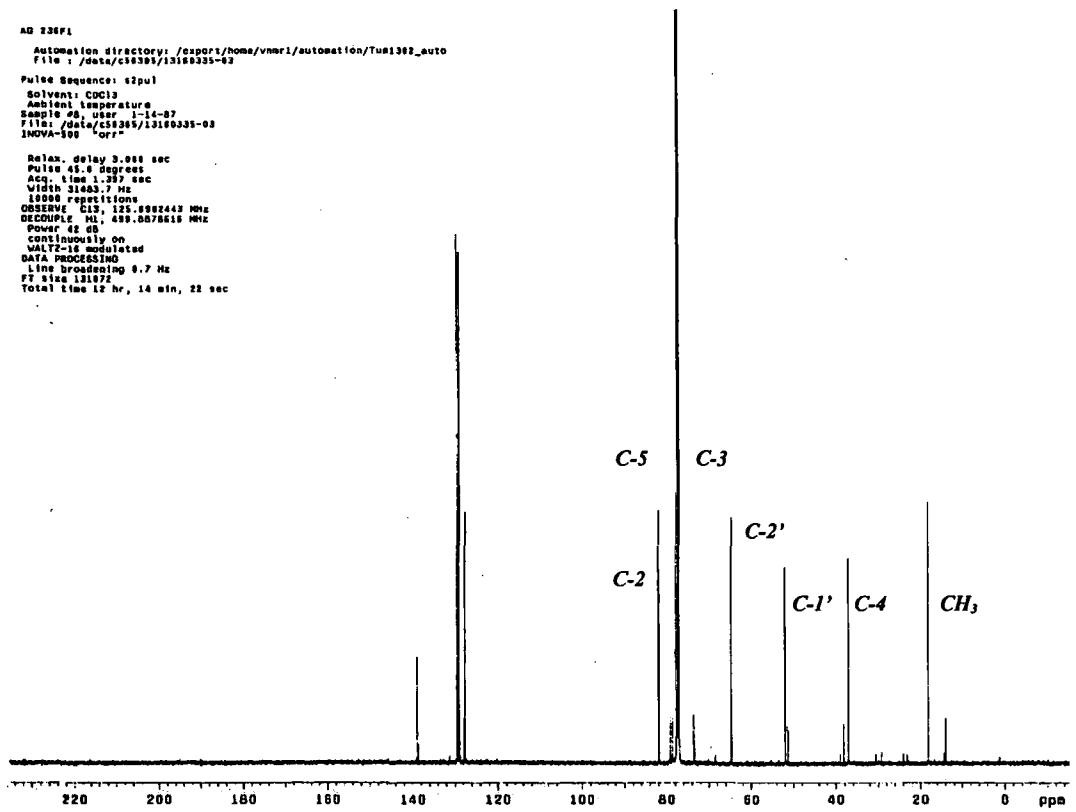
^{1}H NMR spectrum of 1-methyl-4-phenyl-2,8-dioxa-bicyclo[3.2.1]octan-7-one **(56).** (starting material recovered after reaction).



^{1}H spectrum of a by-product of the SmI_2 reaction.



^{1}H NMR spectrum of 5-(2'-hydroxy-1'-phenyl-ethyl)-2-methyl-tetrahydrofuran-3-ol **(68,69).** (for comparison with the oxepane spectrum)



^{13}C NMR spectrum of 5-(2'-hydroxy-1'-phenyl-ethyl)-2-methyl-tetrahydrofuran-3-ol **(68,69).** (for comparison with the oxepane spectrum)

APPENDIX F:
ORAL AND PRESENTATIONS GIVEN BY THE AUTHOR AND RESEARCH CONFERENCES ATTENDED BY THE AUTHOR DURING THE PhD

Oral and Poster Presentations given by the author and Research Conferences attented by the author during the PhD.

- **May (4^{th}-9^{th}) 2004 :** Poster Presentation by the author

International Symposium on Advances in Synthetic, Combinatorial and Medicinal Chemistry. Moscow, Russia.

- **April 2004 :** Poster Presentation by the author

RSC Perkin North East Regional Meeting. Leed University, UK.

- **Mars 2004 :** Poster Presentation by the author

Avecia Poster Competition. Durham University, UK.

- **January (9^{th}) 2004 :** Research Conference attented by the author

Young Chemistst' Panel Review Meeting, SCI fine chemicals. Organic Synthesis, it's not just carbon. University of Strathclyde, Glascow, UK.

- **June 2003 :** Oral Presentation by the author

Durham Postgraduate Symposium. Durham University, UK

- **April (4^{th}) 2003 :** Research Conference attented by the author

Synthesis using Carbenes, Nitrenes and Radicals. Reactivity free of charge. SCI Fine Chemicals. London, UK.

- **January to April 2004 :** Industrial placement of the author

GSK Stevenage. Stevenage, UK.

- **December 2002 :** Research Conference attented by the author

Modern Aspects of Stereochemistry. Sheffield University, UK.

- **June 2002 :** Research Conference attented by the author

GSK-Neurology Case Student two-day seminars. GSK, Harlow. Harlow, UK.

- **April 2002 :** Research Conference attented by the author

RSC Perkin North East Regional Meeting. University of York, UK.

- **December 2001 :** Research Conference attented by the author

Modern Aspects of Stereochemistry. Sheffield University, UK.

Paper in Press :