NOVEL SYNTHETIC METHODOLOGIES FOR THE SYNTHESIS OF HETEROCYCLIC RINGS

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Thesis submitted for the degree of Doctor of Philosophy at
Sussex University

February 2010

Declaration

I hereby declare that this thesis has not been and will not be submitted in whole or in part to another University for the award of any other degree.

Signature:

Date:

This thesis is dedicated to
my parents, James, Natasha
and Séverine

Abstract

Part 1. Synthesis of Stereodefined Heterocyclic Rings.

We wish to report the development of novel methodology for the synthesis of stereodefined heterocyclic rings, which could be used for the synthesis of natural products containing for example tetrahydrofuran motifs, such as members of the pamamycin family. Due to their ambivalent properties, organoaluminium reagents can easily react with acetals by transfering an alkyl group after prior coordination with the substrates. This work has led to the development of a novel cascade reaction. It involves the reaction of acetals with trialkylaluminium reagents, which is followed by a cyclisation reaction, generating consequently tetrahydrofuran or tetrahydropyran rings. In addition, investigation towards the synthesis of pyrrolidines was also carried out.

Part 2. Investigation and Development of a Novel Cascade Reaction.

The Bergman cycloaromatisation reaction is based on the formation of a biradical intermediate species and has been, over the years, a constant source of inspiration for scientists. Continued efforts over the last 40 years permitted, among other things, a better understanding of the mode of action of the enediyne antibiotics, a class of natural compounds with exceptional biological activities. The Parsons group recently developed a novel cyclisation reaction, which also generates a biradical species, and which could, after being trapped with a suitable alkene, lead to the formation of tricyclic molecules containing heterocyclic cores. As a result, we wish to further investigate this novel reaction and develop a tandem reaction, involving this reaction combined with a Diels-Alder reaction in order to generate pentacyclic molecules, in one synthetic operation, and from an acyclic precursor.

Acknowledgements

I would first like to thank Prof. Philip J. Parsons for giving me the opportunity to carry out this Ph.D. and also for his support and guidance over the years.

I would also like to thank Dr Alaa Abdul-Sada (mass spectrometry) and Prof. James Hanson for their continuous encouragements over the course of my Ph.D.

I would like to thank my colleagues in the chemistry department for their friendships and stimulating discussions. Special thanks go to Joe McKenna and Dr Alex Waters for proof reading this thesis.

Most of all, I would like to thank my parents, sister and husband for their endless support and love.

Abbreviations

Ac	Acetyl
aq.	Aqueous
AIBN	*N,N*-Azo*bis*-*iso*-butyronitrile
Boc	Butyloxycarbonyl
Bn	Benzyl
Bu	Butyl
BuLi	Butyllithium
Bz	Carboxybenzyl (Cbz, Z)
18C6	1,4,7,10,13,16-hexaoxacyclooctadecane (18-Crown-6)
CAN	Ceric Ammonium Nitrate
cat.	Catalytic
CDA	Cyclohexane-1,2-diacetals
CPK	Corey-Pauling-Koltun
CSA	Camphorsulfonic Acid
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	Diastereomeric Excess
DEAD	Diethylazocarboxylate
DFT	Density Functional Theory
DIBAL-H	Di*iso*butylaluminium Hydride
Dispoke	Dispiroketal
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DNA	Deoxyribonucleic Acid
e.e.	Enantiomeric Excess
EDTA	2-[2-(Bis(carboxymethyl)amino)ethyl-(carboxymethyl)amino] acetic acid

EGTA	Ethylene Glycol *Bis*(*β*-amino ethyl ether)-*N,N,N',N'*-tretraacetic acid
Et	Ethyl
eq.	Equivalent
Grubbs' catalyst, 2^{nd} generation	1,3-Bis-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene) (dichlorophenylmethylene)(tricyclohexylphosphine) ruthenium
hmim	Hexylmethylimidazolium
HMPA	Hexamethylphosphoramide
h	Hour
Hz	Hertz
imid.	Imidazole
k	Rate Constant
Kbar	Kilobar
LDA	Lithium Di*iso*propylamine
LPDE	Lithium Perchlorate – Diethyl Ether
Me	Methyl
MOM	Methoxymethyl Ether
Ms	Mesyl
MW	Microwave
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
p	Para
P	Power
P_4 *t*-Bu	Phosphazene Base
Ph	Phenyl
Phth	Phthalimide
PMB	*para*-Methoxybenzyl
Pr	Propyl
psi	Pounds per Square Inch
py	Pyridine
R	Universal Gas Constant
RNA	Ribonuleic Acid
RT	Room Temperature

salen	2,2'-Ethylene*bis*(nitrilomethylidene)diphenol,*N*,*N*'-Ethylene*bis*(salicylimine)
SOMO	Singly Occupied Molecular Orbital
TBA	Tetrabutylammonium
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidin-1-oxyl
TES	Triethylsilyl
Tf	Trifluoromethylsulfonyl
Th	Thiophene
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
p-Tol	*para*-Toluyl
Triphos	1,1,1-*Tris*(diphenylphosphinomethyl)ethane
Ts	*p*-Toluenesulfonyl
W	Watt
Xc	Chiral Auxiliary

Contents

Part 2. Investigation and Development of a Novel Cascade Reaction.

Part 1

Synthesis of Stereodefined Heterocyclic Rings

Chapter 1 | INTRODUCTION

Heterocyclic rings, such as tetrahydrofurans and tetrahydropyrans are widely found in natural products. These rings are usually substituted at different positions and scientists are driven to develop novel and if possible enantioselective methodologies in order to synthesise these ring systems. Of particular interest were the members of the pamamycin family. Their isolation and interesting biological activities are described in **Section 1.1.1**. In addition, in order to illustrate different methodologies to synthesise tetrahydrofuran rings, the key steps of their total syntheses and also, the developed methodologies to synthesise these rings are reported in **Section 1.1.2**.

Finally, **Section 1.2** will be dedicated to the functional use of the acetal group in organic chemistry. The novel methodologies to synthesise acetals are reported in **Section 1.2.1** and their possible reactions with nucleophiles when reacted in the presence of Lewis acid is discussed in **Section 1.2.2**. In addition, a short paragraph on organoaluminium reagents has been included in this section.

1.1 TETRAHYDROFURAN : A MOTIF FOUND IN NATURAL PRODUCTS.

1.1.1 PAMAMYCIN FAMILY.

1.1.1.1 Isolation and Structure Determination.

i. History and Isolation of Pamamycin Antibiotics.

Actinobacteria, also known as actinomycetes are a group of Gram positive bacteria, which can produce a range of interesting secondary metabolites.[1] They germinate from spores and expand by forming filamentous vegetative mycelia similar to that of fungi, into and on the agar medium. Their life cycle is governed by two morphological differentiations: firstly, there is the formation of aerial mycelia from the substrate mycelia and secondly, there is the production of spores by the division of the aerial mycelia. It was observed that the formation of aerial mycelia was accompanied by the production of secondary metabolites. McCann and Pogell showed that antibiotics could regulate the formation of mycelia in streptomycetes such as *Steptomyces alboniger*.[1] They showed that a low concentration of the antibiotic lincomycin induced the growth of the aerial mycelia, although a higher concentration of this antibiotic had an inhibitory effect. Consequently, a better understanding of the mechanism of differentiation of the mycelia and of the role of the secondary metabolites produced by the bacteria, could lead to the improvement of the fermentation production. As a result, the isolation of the active substances from *Steptomyces alboniger* ATCC 12461 was achieved and new compounds, named pamamycin, with antibiotic activity and with molecular weights of 621, 635, 649 and 663 were isolated.[1]

The major member of this family, pamamycin 621, was active against Gram positive bacteria, *Mycobacteria* and *Neurospora*. Their structures were not determined, but they found that pamamycin of molecular weight 621 had the following formula: $C_{36}H_{63}NO_3$. The infra-red spectra showed the presence of a carbonyl group and no aromatic, OH or NH and amide groups. The absence of OH or NH functionalities was also confirmed by NMR analysis, which showed no exchangeable protons upon addition of deuteriated water. They concluded that pamamycin was a highly saturated molecule containing a tertiary amine.[1]

Pamamycin 621 was also isolated from mycelium of *Streptomyces aurantiacus* IMET 43917 and its structure was elucidated in 1991 by MS, NMR and chemical degradation experiments.[2]

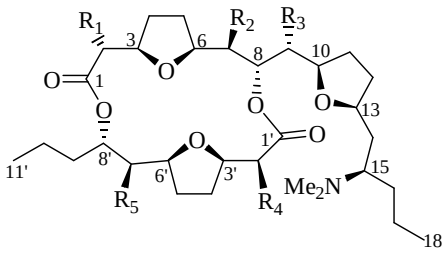
ii. Pamamycin 607 and Homologues: Structures and Biosynthesis.

* Structure.[3,4]

To date, fourteen members of the pamamycin family with molecular weights ranging from 593 to 649 have been isolated from different sources of *Streptomyces* and structurally characterised. Their structures are shown in **Figure 1**.

They all share a similar backbone, which is constituted of three *syn*-disubstituted tetrahydrofuran motifs with two of them contained in a sixteen membered macrocycle ring system linked by two ester functionalities. The different members of the pamamycin family are substituted at the 2, 7, 9, 2' and 5'-positions with methyl or ethyl groups. In addition, one common features among these metabolites is the presence of a dimethyl amino group at the 15-position.

Figure 1. Pamamycin 607 **1** and Homologues **2-14**.



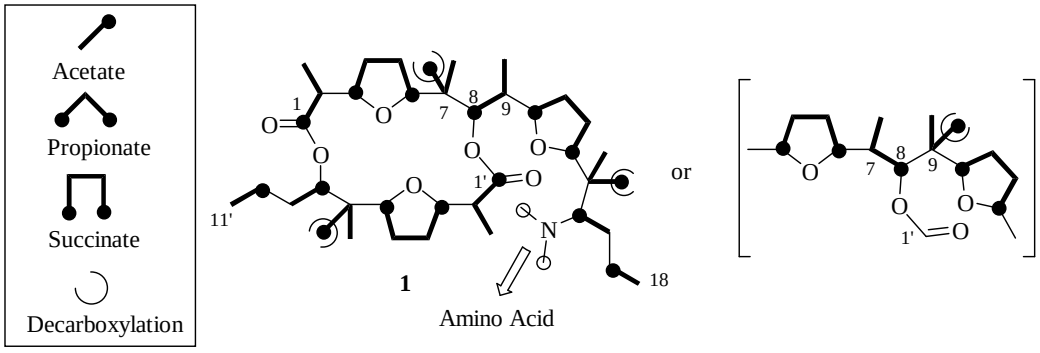
		R_1	R_2	R_3	R_4	R_5
1	Pamamycin 607:	Me	Me	Me	Me	H
2	Pamamycin 593:	Me	H	Me	Me	H
3	Pamamycin 621A:	Me	Me	Me	Me	Me
4	Pamamycin 621B:	Et	H	Me	Me	Me
5	Pamamycin 621C:	Me	Me	Et	Me	H
6	Pamamycin 621D:	Et	Me	Me	Me	H
7	Pamamycin 635A:	Me	Me	Et	Me	Me
8	Pamamycin 635B:	Me	Me	Me	Et	Me
9	Pamamycin 635C:	Et	Me	Me	Me	Me
10	Pamamycin 635D:	Et	Me	Me	Et	H
11	Pamamycin 635E:	Me	Me	Et	Et	H
12	Pamamycin 635F:	Et	Me	Et	Me	H
13	Pamamycin 649A:	Et	Me	Et	Et	H
14	Pamamycin 649B:	Et	Me	Et	Me	Me

* Biosynthesis.[5]

Feeding experiments, using labelled ^{13}C and ^{15}N units in *Streptomyces alboniger* showed that the skeleton of pamamycin 607 **1** was derived from six acetates, four propionates and three succinates. The amino group was derived from glutamic acid or valine and the two methyl groups on the nitrogen from methionine. Addition of cerulenin, an inhibitor of the fatty acid and steroid biosyntheses, reduced the formation

of pamamycin 607 **1**. It was consequently postulated that the biosynthesis of pamamycin 607 **1** occurred *via* the polyketide pathway and by polymerisation of the different subunits. The subunits used to biosynthesise pamamycin 607 **1** are shown in **Figure 2**.

Figure 2. Biosynthesis of Pamamycin 607 **1**.

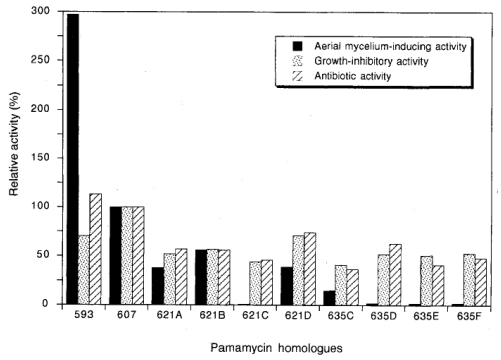


1.1.1.2 Structure-Activity.

i. Effect of the Alkyl Groups.[6,7]

The different members of the pamamycin family possess interesting biological activity. They can induce the formation of aerial mycelia as well as inhibit their growth. They also exhibit antibacterial properties. The effect of the alkyl substituents on the autoregulatory activity in *Streptomyces alboniger* and the antibiotic activity against *Bacillus subtilis* was studied. The activities of the different analogues were determined as pamamycin 607 equivalents and are summarised in the **Figure 3** below.

Figure 3. Relative Activities of Pamamycin Homologues.[7]



Pamamycin 593 **2** was the most active compound towards the production of aerial mycelia and it was observed in general that the activity of the other homologues decreased when their molecular weights increased. Replacement of a methyl group by an ethyl group at the 9 or 2'-position (R_3 or R_4) suppressed any aerial mycelium-

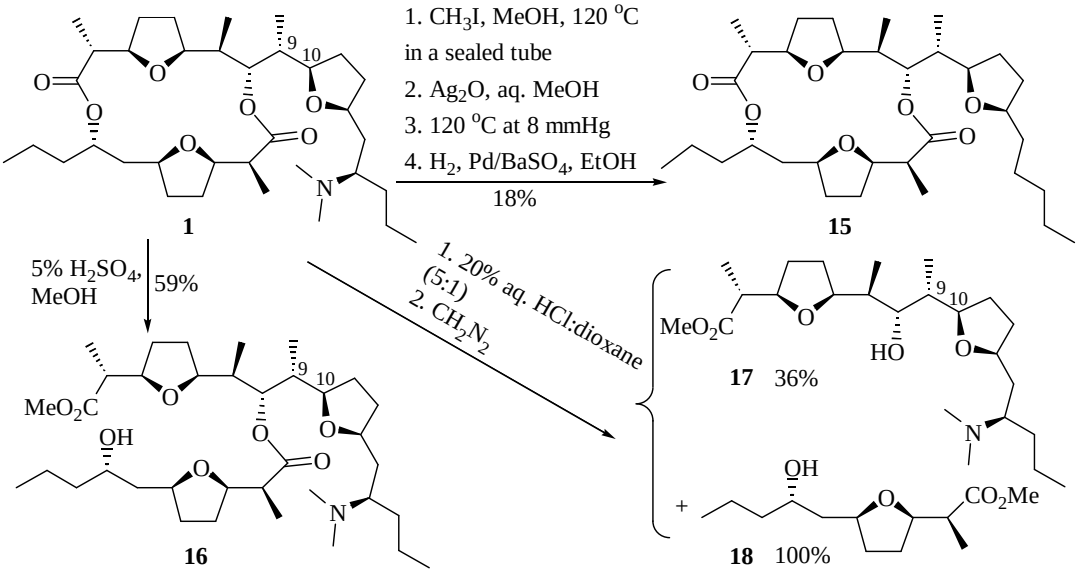
inducing activity (see **Figure 3**). Pamamycin 635A **7** and a mixture of pamamycins 649A **13** and 649B **14** (with R_3 = Et) have also been previously reported to have no activity on the differentiation and production of aerial mycelia.[6] Observation of the pamamycin 635A.CF_3CO_2D using a space filling CPK model showed that R_3 was sticking out the folded molecule.[6] It was speculated that this dramatic effect was due to the introduction of a bulkier group, which prevented the molecule in fitting into the active site and consequently in activating the formation of aerial mycelia.

However, these modifications led to the loss of less than 50% of the growth-inhibitory and antibacterial activities. This suggested that these biological activities were due to a different mechanism of action than the inducing-aerial mycelia properties. Substituting the pamamycin skeleton with different alkyl groups could result in the modification of the hydrophobic properties of the molecules and this consequently explains the different activity observed.[7]

ii. Role of the Dimethyl Amino Group and of the Macrodiolide Ring.[8]

The role of the amino group on the aerial mycelium-inducing activity of *S. alboniger* has also been studied. Compound **15** was obtained by Hoffman degradation and subsequent hydrogenation of the double bond. Treatment of pamamycin 607 **1** with sulfuric acid in methanol led to the cleavage of only one ester linkage to give compound **16**. Fragments **17** and **18** were obtained by hydrolysis of both ester groups of pamamycin 607 **1** with aqueous hydrochloric acid in dioxane and methylation of the carboxylic acids previously formed with diazomethane.

Scheme 1. Amino Group and Ring Effects: Synthesis of the Fragments.



The removal of the amino group in pamamycin 607 **1** resulted in the suppression of the aerial mycelium-inducing activity. Ring-opened pamamycin **16** showed half of the activity of pamamycin 607 **1** and fragment **17** possessed 1/30 of its activity. Finally fragment **18** showed no activity at all. Thus, the presence of the amino group was essential for the molecule to exhibit any activity. NMR studies showed that the coupling constant $J_{9\text{-}10}$ of fragment **17** was different to the one of pamamycin 607 **1** and ring-opened pamamycin **16**. The values obtained for this coupling constant were *J*(pamamycin 607 **1**) = 10.2 Hz, *J*(ring-opened pamamycin 607 **16**) = 10.3 Hz and *J*(fragment **17**) = 8.4 Hz. The value obtained for fragment **17** corresponds to the value of vicinal proton rotating freely.[8] It was consequently suggested that fragment **18** was fixing the conformation of the molecule and that the decrease in activity of fragment **17** was due to the flexibility at the C_9-C_{10} bond within this region of the molecule.[8]

1.1.1.3 Mode of Action.

i. Aerial Mycelium-Inducing Activity.

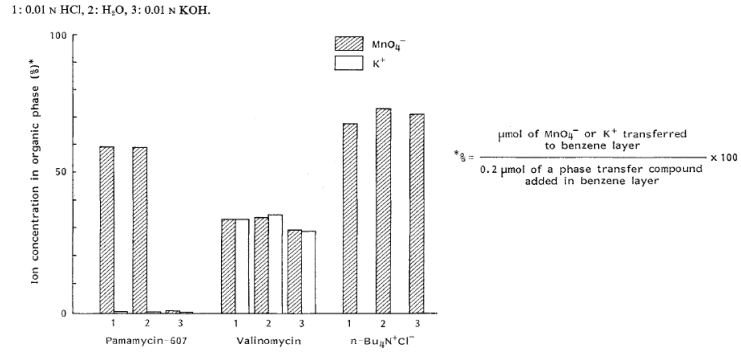
Marumo and co-workers observed that *Streptomyces ambofaciens*, when grown on inorganic salt-starch agar, could produce aerial mycelia although when grown on yeast extract-malt extract agar only substrate mycelia were formed.[9] They isolated the active substance, calcium acetate, and postulated that the Ca^{2+} ions, from the calcium carbonate used in the agar, as neutralisation agent, were inducing the formation of the aerial mycelia. To verify this hypothesis, they added a Ca^{2+} specific chelating agent, EGTA (ethylene glycol bis(*β*-amino ethyl ether)-*N,N,N',N'*-tretraacetic acid) and observed that the aerial formation of mycelia was inhibited. Similar result was obtained with *S. alboniger*.[9]

The formation of the aerial mycelia was also inhibited when Ca^{2+} channel blockers (verapamil hydrochloride, diltiazem hydrochloride, nifedipine) and calmodulin inhibitors (ophiobolin A, prenylamine lactate and chloropromazine) were used. In the presence of EGTA, pamamycin 607 **1** did not induce the production any aerial mycelium.[10]

The pamamycin antibiotics possesses large macrocycles, constructed with oxygen containing functional groups (tetrahydrofurans, lactones) and have a structure similar to those of ionophore antibiotics, such as mononesin, nonactin and etc... As a result, it was expected that the members of the pamamycin family were able to form complexes with cations and would therefore be able to transport them across cell membranes.

Nevertheless, it was shown that pamamycin 607 **1** could not transfer Na^+, K^+ or Ca^{2+} from the aqueous to the organic phase (toluene:BuOH/ 7:3). But, it could transport MnO_4^- anion under neutral and acidic condition, suggesting that this was possible only when the amino group was changed as an ammonium salt (see **Figure 4**).[11]

Figure 4. Transfer Ability of Pamamycin 607 **1**, Valinomycin, TBACl.[11]



Therefore, it was concluded that the aerial mycelium-inducing activity was provoked by a change in the concentration of the Ca^{2+} ions and that this was regulated by the pamamycin metabolites. The antibiotics proved to be ineffective in the transport of cations and as shown in **Section 1.1.2.2** (structure-activity: effect of the substituents), the most plausible mechanism of action was that of binding to an active site, resulting in the activation of the mycelia growth.[11]

ii. Antibacterial Activity.[12,13,14]

Studies on *Staphyloccus aureus*, showed that pamamycin 607 **1** inhibited the intake of nucleosides, adenine, uracil and inorganic phosphate P_i and because of its ability to transport anions, this suggested that the primary mode of action was by inhibition of the oxidative phosphorylation pathway within bacteria. More recently, Content *et al*. showed that pamamycin 607 **1** was active against different strains of mycobacteria, (*Mycobacterium tuberculosis, Mycobacterium bovis BCG and Mycobacterium smegmatis*) and being therefore a potential lead molecule for the development of antituberculous drugs.

1.1.1.4 Conclusion.

Work in order to better understand the mechanism of actions of the different members of the pamamycin family is still ongoing. The lack of material and the difficulty of producing and purifying the metabolites are a drawback and a limitation to the work of

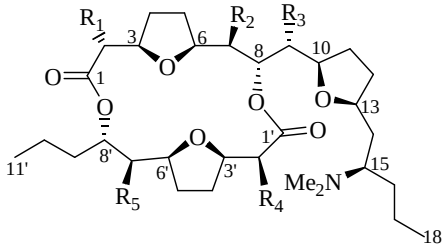
any biologists or/and biochemists. It is then the role of synthetic organic chemists to synthesise when possible the natural products and analogues in order to generate the few necessary milligrams to pursue the research.

1.1.2 PAMAMYCIN: TOTAL SYNTHESES AND METHODOLOGY.

Numerous methodologies have been developed to synthesise stereocontrolled and substituted tetrahydrofuran rings and have been previously reviewed in the literature (Figadère,[15] Boivin,[16] Elliott[17,18]). In order to illustrate the formation of these heterocyclic rings, we wish to highlight the key methodologies used in the synthesis of the natural products from the pamamycin family.

Up to date, six total syntheses of the members of the pamamycin family have been published in the literature. Efforts have been mainly focused toward the synthesis of pamamycin 607 **1**, which resulted in the publication of its total synthesis by three research groups in 2001, Thomas (**Section 1.1.2.2**), Lee (**Section 1.1.2.3**) and Metz (**Section 1.1.2.5**). This was shortly followed by the work of Kang in 2002 (**Section 1.1.2.2**). Finally, Hanquet reported the total syntheses of pamamycins 607 **1**, 593 **2** and 621D **6** in 2007 (**Section 1.1.2.4**). Methodologies to construct the tetrahydrofuran motifs have also been developed by Calter ($C_{1'}$-$C_{10'}$ of pamamycin 621A **3**, **Section 1.1.2.1**), Pelmutter ($C_{1'}$-$C_{11'}$ and C_6-C_{18} synthons of pamamycin 607 **1**, **Section 1.1.2.2**), Bloch ($C_{1'}$-$C_{11'}$ and C_8-C_{18} of pamamycin 607 **1**, **Section 1.1.2.3**) and Walkup (C_1-C_{14} of pamamycins 607 **1** and 635B **8**, **Section 1.1.2.2**).

Figure 5. Pamamycins 607 **1**, 593 **2**, 621A **3**, 621D **6** and 635B **8**.



		R_1	R_2	R_3	R_4	R_5
1	Pamamycin 607:	Me	Me	Me	Me	H
2	Pamamycin 593:	Me	H	Me	Me	H
3	Pamamycin 621A:	Me	Me	Me	Me	Me
6	Pamamycin 621D:	Et	Me	Me	Me	H
8	Pamamycin 635B:	Me	Me	Me	Et	Me

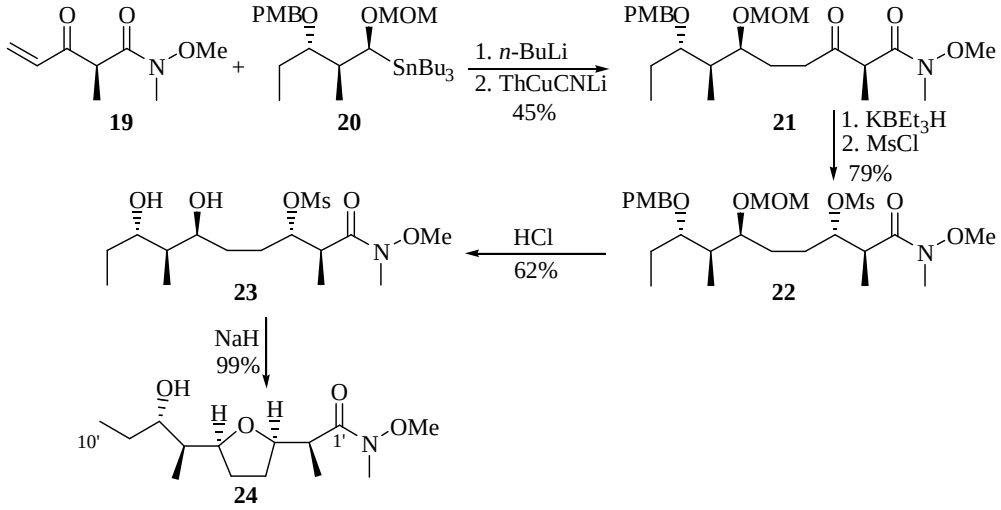
1.1.2.1 Cyclisation of 1,4-Diol.

Displacement of a leaving group, such as a mesylate by an alcohol is a very effective method to generate tetrahydrofuran rings. The stereochemistry of the different centres at the 2 and 5-positions is therefore controlled by the stereochemistry of the alcohols and

methodologies have been designed to obtain the starting materials with high degree of stereocontrol at these centres.

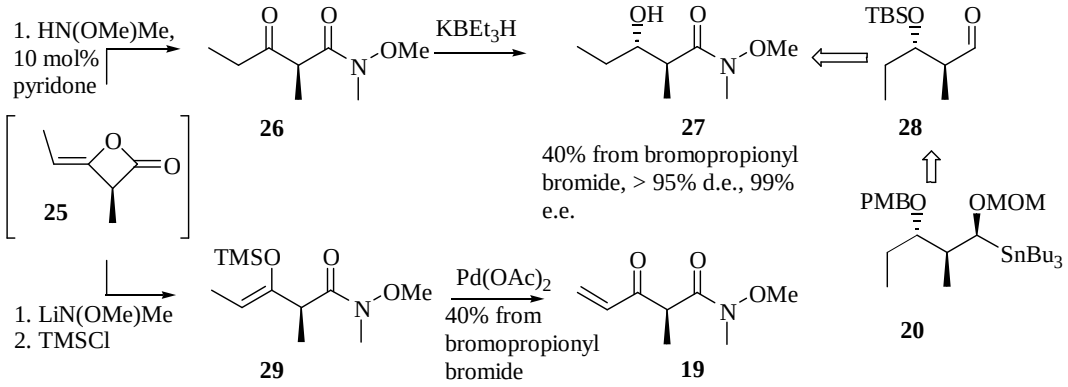
Calter *et al*. synthesised $C_{1'}$-$C_{10'}$ of pamamycin 621A **3** by intramolecular displacement of the mesylate group by the alcohol at the $C_{6'}$-position.[19] The fragment **21** could be synthesised by reaction of *α*,*β*-unsaturated ketone **19** with a higher order cuprate, generated by transmetallation of alkoxystannane **20** with *n*-butyllithium and subsequently reacted with ThCuCNLi. Transmetallation of alkoxystannane **20** occurred with retention of configuration. This was then followed by the reduction of the ketone group using potassium triethylborohydride to give the corresponding *β*-hydroxyamide, which was then reacted with mesylchloride to afford the intermediate **22** in 79% yield. After removal of the MOM and PMB protecting groups with hydrochloric acid and deprotonation using sodium hydride (60% in mineral oil), the corresponding tetrahydrofuran **24** was obtained in 99% yield (**Scheme 2**).

Scheme 2. Formation of Tetrahydrofuran Ring by Displacement of a Mesyl Alcohol.



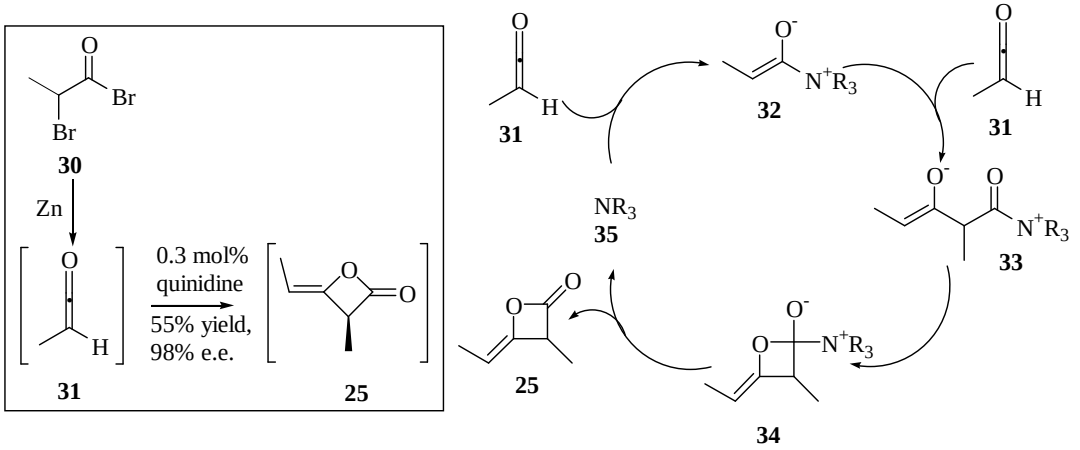
It should also be noted that alkoxystannane **20** was obtained by reaction of the aldehyde **28** (**Scheme 3**) with tributyltin hydride when deprotonated with lithium diisopropideamide. The stereochemistry observed could be explained using the Felkin-Ahn model. Compounds **27** and **19** were both synthesised from *β*-lactone **25**, which was obtained from bromopropionyl bromide. Opening of *β*-lactone **25** with *N*,*O*-dimethylhydroxyamine gave amide **26**, which was then reduced using $KBEt_3H$ to afford hydroxyl-amide **27**. *β*-Lactone **25** could also be opened with lithium amide and the enolate could be trapped with trimethylsilyl chloride. Oxidation of silyl enol ether **29** was achieved using a stoechiometric amount of palladium (II) acetate to give the intermediate **19**.

Scheme 3. Synthesis of Fragments **19** and **27**.



Synthesis of *β*-lactone **25** was achieved by an asymmetric dimerisation of methyl ketene **31**, which was obtained by treatment of bromopropionyl bromide **30** with zinc, in the presence of a catalytic amount of a chiral base. In this case, the enantiopure alkaloid quinidine was used. The mechanism of the reaction is described in **Scheme 4**. The chiral tertiary amine discriminates the faces of ammonium enolate **32**, which when reacted with a second equivalent of methyl ketene **31** leads to the formation of intermediate **33** (Claisen condensation). This intermediate can then undergo an intramolecular cyclisation to give the optically active *β*-lactone **25.**[20]

Scheme 4. Synthesis of *β*-Lactone **25**.[20]



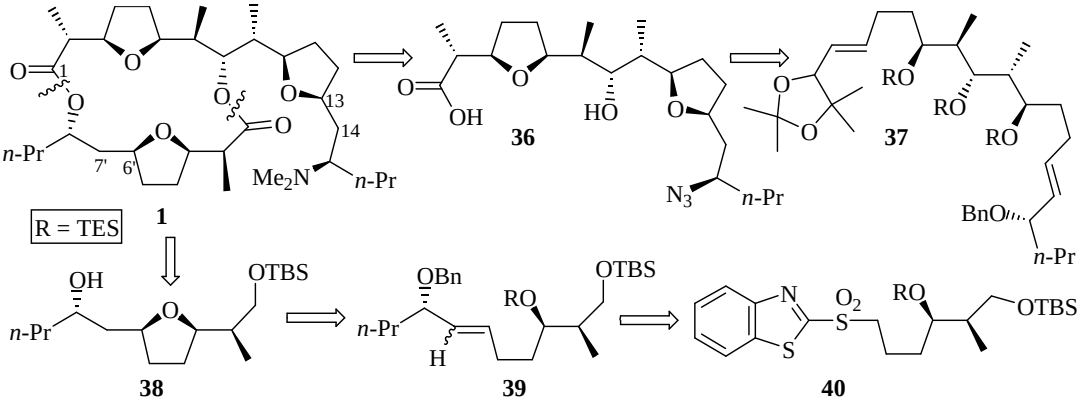
1.1.2.2 Cyclisation of Unsaturated Alcohol.

i. Iodoetherification.

Kang *et al*. reported the total synthesis of (+)-pamamycin-607 **1** in 2002.[21] Kang showed previously that it was possible to obtain *cis*-tetrahydrofurans by

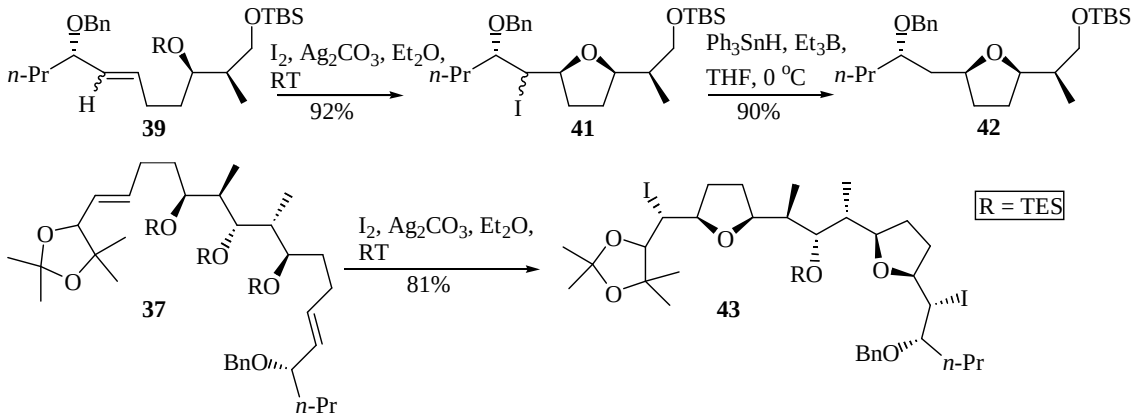
iodoetherification of γ-triethylsilyloxyalkenes when treated with iodine, in the presence of sodium carbonate and in acetonitrile.[22] Consequently, cleavage of the ester linkages gave fragments **36** and **38** (**Scheme 5**). The tetrahydrofuran motifs could be synthesised from alkenes **37** and **39**. The double bonds C_{13}=C_{14} and $C_{6'}$=$C_{7'}$ were introduced using the Julia-Kociensky's sulfone olefination methodology.

Scheme 5. Retrosynthetic Analysis.



Alkene **39** was obtained as a mixture of *cis* and *trans*-isomers, which upon treatment with iodine gave iodo-tetrahydrofuran **41** as a mixture of isomers. Removal of iodine was achieved using triphenyltin hydride to give tetrahydrofuran **42** as a single enantiomer. Similarly, when alkene **37** was treated under similar conditions, both tetrahydrofuran motifs were obtained in a single operation and fragment **43** was obtained as a single enantiomer (**Scheme 6**).

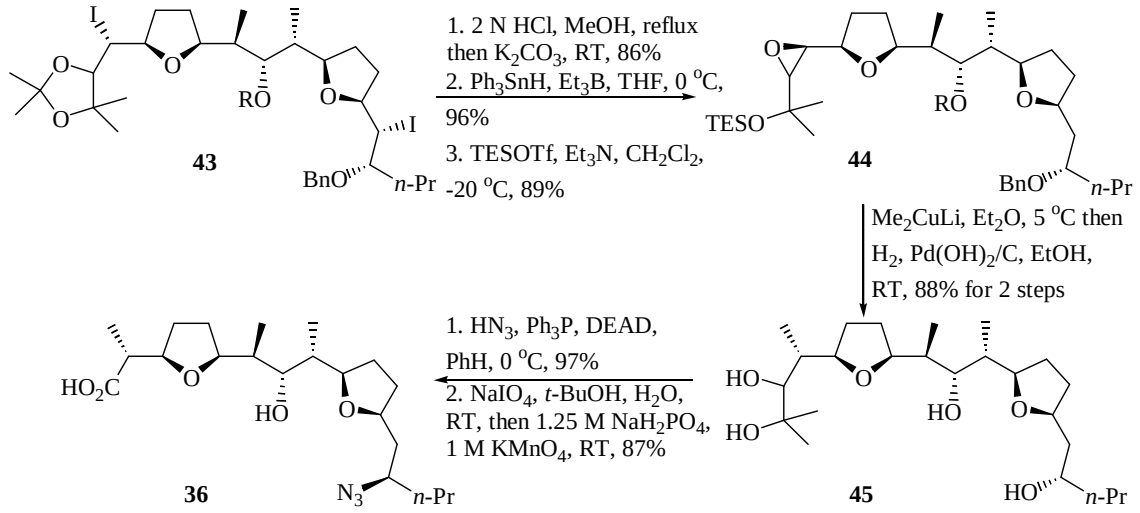
Scheme 6. Iodoetherification.



Cleavage of the acetal group of intermediate **43** using 2 N hydrochloric acid followed by a basic treatment with potassium carbonate generated epoxide **44**, which could, after removal of the iodine group with triphenyltin hydride, be opened using lithium dimethylcuprate in order to introduce a methyl group at the C_2-position. Hydrogenation

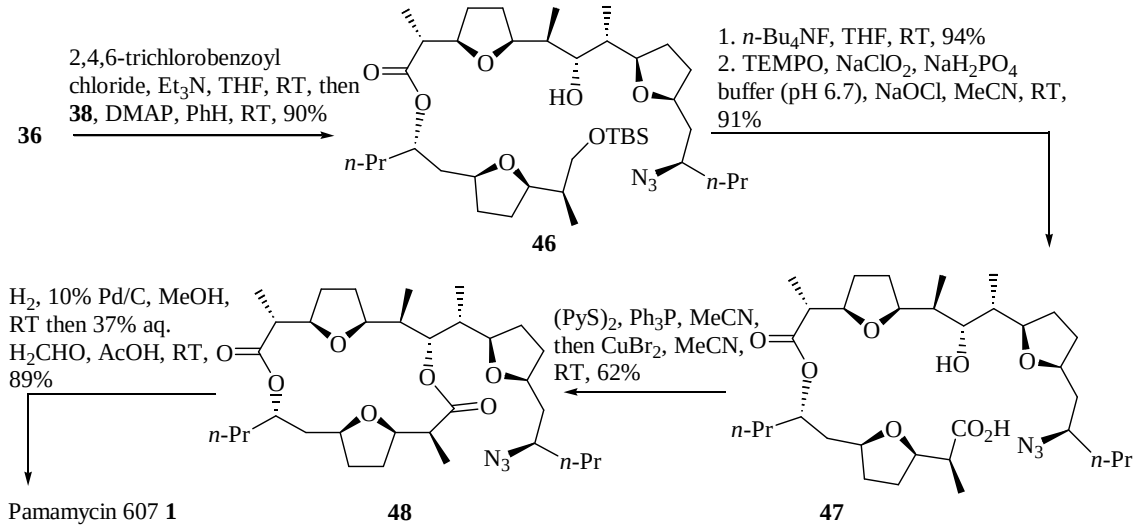
using palladium on carbon cleaved the benzyl and TES protecting groups to give intermediate **45**. Introduction of the azide group was achieved by carrying out a Mitsunobu reaction on the least hindered alcohol. Finally, the diol functionality was then oxidatively cleaved to furnish carboxylic acid **36** (**Scheme 7**).

Scheme 7. Synthesis of Fragment **36**.



Fragments **36** and **38** were coupled using the Yamaguchi conditions. The TBS group was then removed using TBAF in THF and the subsequent primary alcohol oxidised to give carboxylic acid **47**. The second lactonisation was achieved by synthesising the corresponding thiopyridyl ester using 2,2'-dipyridyl disulfide $(PyS)_2$ and triphenylphosphine, followed by coupling with copper bromide. Hydrogenation using 10% palladium on carbon gave the free amine, which was reacted with formaldehyde to afford under the reductive reaction conditions pamamycin 607 **1** (**Scheme 8**).[21]

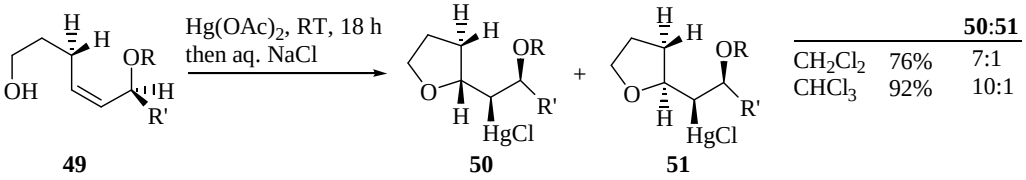
Scheme 8. Esterification and Synthesis of Pamamycin 607 **1**.



ii. Mercuricyclisation.

Intramolecular oxymercuration of alkenes can lead to the stereoselective synthesis of tetrahydrofurans. Perlmutter *et al*. showed that *cis*-alkene bearing a remote allylic protected alcohol, when treated with mercury (II) acetate could give the corresponding tetrahydrofurans in good yield and with good stereoselectivity (**Scheme 9**).[23,24]

Scheme 9. Mercuricyclisation.



		50:51
CH_2Cl_2	76%	7:1
$CHCl_3$	92%	10:1

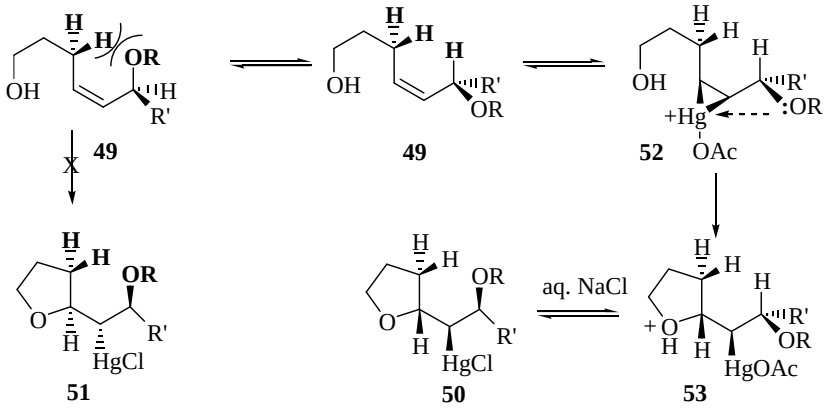
49 **50** **51**

The stereochemistry of the tetrahydrofurans obtained using the *cis*-alkene can be explained by the repulsion of the different substituents at the allylic position with the protons in bold in **Scheme 10**. As a result only one rotamer is favoured. Due to the presence of the protected allylic alcohol, there is also a coordination controlled with the mercury acetate, which leads to the formation of intermediate **52**. Reaction in chloroform increased the stereoselectivity of the reaction. But it was observed that the best result was obtained when acetonitrile was used as solvent.

As expected, the reaction with *trans*-alkene gave a low stereoselectivity. This is due to the possible formation and reaction of the different rotamers.

The proposed mechanism is shown in **Scheme 10**.

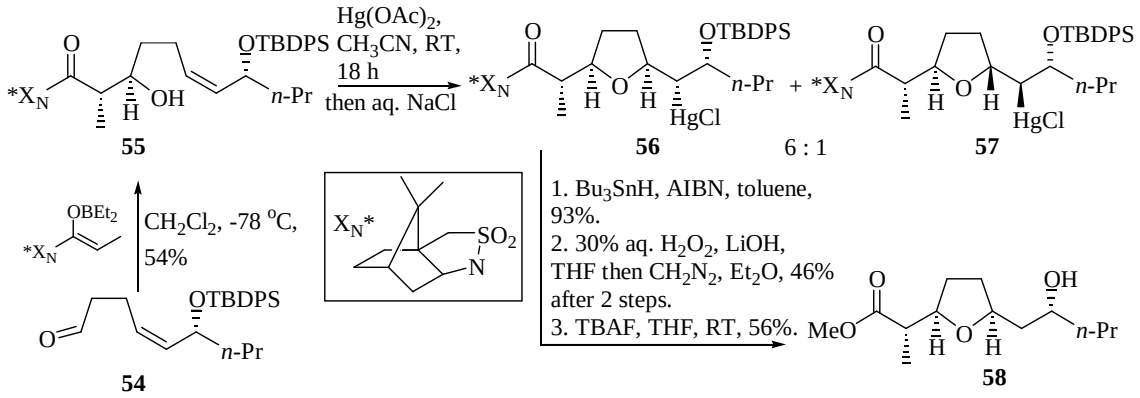
Scheme 10. Proposed Mechanism.



This methodology was then applied for the synthesis of the $C_{1'}$-$C_{11'}$ synthons of pamamycin 607 **1**.[25] The chiral methyl group was obtained using the diethyl boron enolate of Oppolzer's camphor-derived *N*-propionylsultam to give the major *syn*-

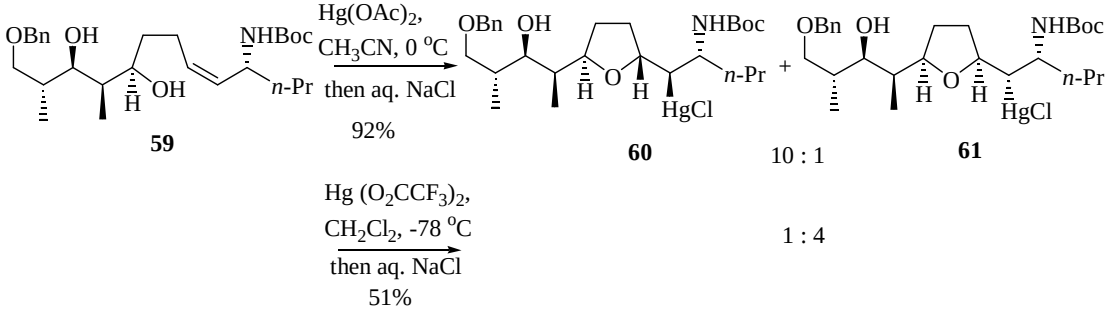
product **55**, upon reaction with aldehyde **54** (**Scheme 11**). When intermediate **55** was reacted with mercury (II) acetate in acetonitrile, followed by sodium chloride, a 6:1 mixture of tetrahydrofurans **56**:**57** was obtained. Finally, demercuration of tetrahydrofuran **56** was achieved using tributyltin hydride and AIBN. This was followed by the cleavage of the chiral auxiliary with hydrogen peroxide and lithium hydroxide in THF to give a carboxylic acid, which was then, subsequently alkylated using diazomethane to afford the corresponding methyl ester. Finally, cleavage of the silyl group was performed using tetrabutylammonium fluoride in THF to give the target intermediate **58**, $C_{8'}$ epimer of the $C_{1'}$-$C_{11'}$ fragment of pamamycin 607 **1**. It is hoped that the inversion of configuration at this centre could be achieved when coupling this fragment with the corresponding C_1-C_{18} fragment or before the macrolactonisation step.

Scheme 11. Synthesis of the $C_{8'}$ Epimer of the $C_{1'}$-$C_{11'}$ Fragment **58**.



A similar strategy was applied for the synthesis of the C_6-C_{18} fragment of pamamycin 607 **1**, which employed an allylic nitrogen precursor instead of an allylic alcohol. It was hoped that a similar stereoselectivity could be observed.[26] Unfortunately, under similar conditions, the undesired *trans*-tetrahydrofuran **60** was the major product obtained. This was overcome by the use of mercuric triflate in acetonitrile and the *cis*:*trans*-isomers were obtained a 4:1 ratio.

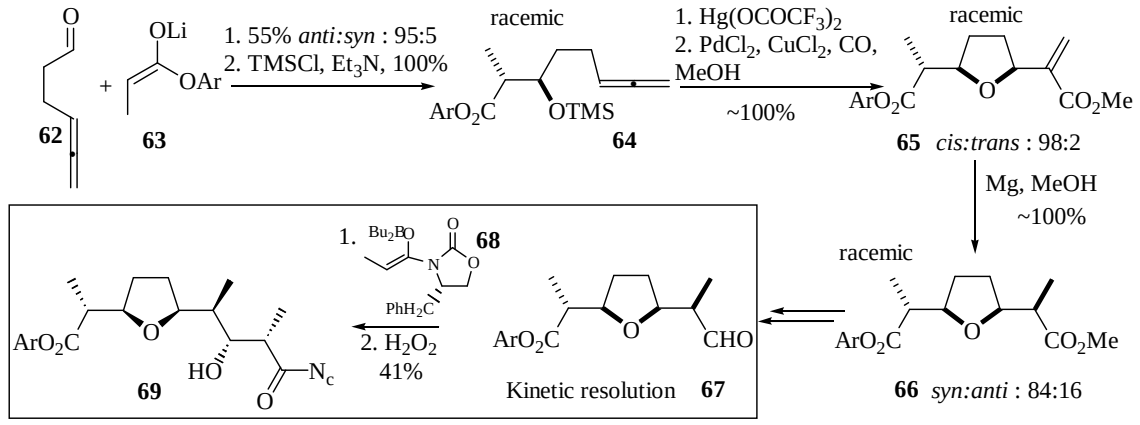
Scheme 12. Synthesis of the C_6-C_{18} Intermediate **61**.



iii. Tandem Mercuration, Transmetallation and Methoxycarbonylation.[27, 28, 29]

Walkup and co-workers developed a one-pot procedure in order to generate *cis*-2,5-disubstituted tetrahydrofurans. This methodology was used to synthesise the C_1-C_{14} subunit of pamamycin 607 **1**, pamamycin 635B **8**. The reaction involved first, the mercuration of *γ*-siloxy allene **64** using mercuric trifluoroacetate, which after an intramolecular attack of the alcohol generated the corresponding vinyl mercuric trifluoroacetate oxacycle. This intermediate was then transmetallated using palladium (II) (*via* oxidation by cupric chloride) and reacted with carbon monoxide and methanol to give the methyl ester **65**. Reduction of the double bond was achieved using magnesium in methanol and tetrahydrofuran **66** was obtained in a *syn:anti*/ 86:14 ratio. This can be explained by the possible coordination of the substrate with Mg (II) and protonation from the least hindered face. After further functional group manipulations, aldehyde **67** was reacted with chiral boron enolate **68** to give the aldol product **69** as a single isomer, suggesting that a kinetic resolution was taking place (**Scheme 13**).

Scheme 13. Synthesis of the C_1-C_{10} Subunit **69**.

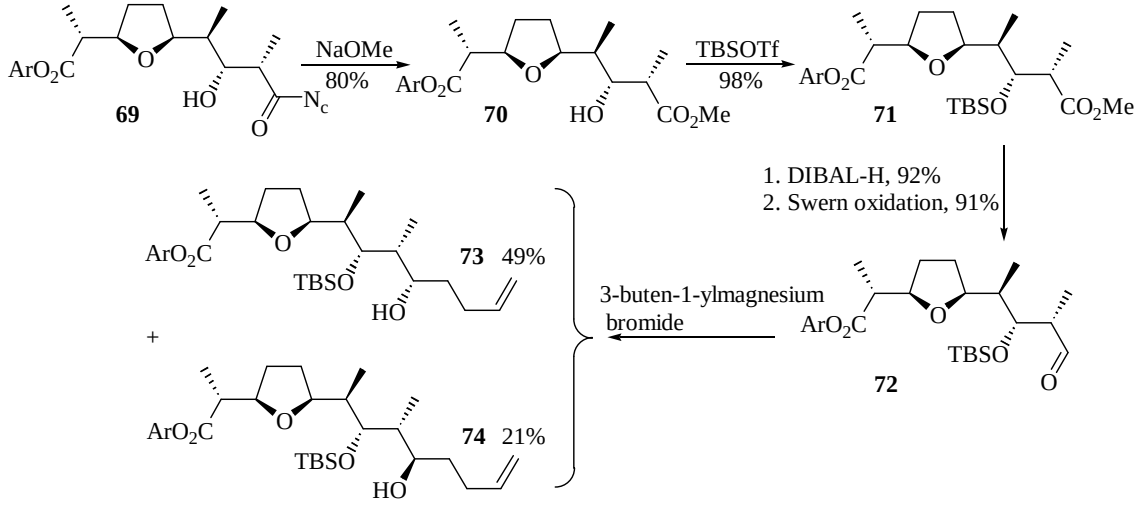


Ar = 2',6'-di-*tert*-butyl-4'-methoxyphenyl

The C_1-C_{14} synthon **74** was finally obtained after cleavage of the chiral auxiliary with sodium methoxide to give the methyl ester **70** in 80% yield, protection of the alcohol group with a TBS group using TBSOTf (98% yield), reduction of the ester groups with DIBAL-H and oxidation using the Swern procedure to give the corresponding aldehyde **72** in 84% after two steps, which was finally reacted with 3-buten-1-ylmagnesium bromide. The major compound **73** and undesired isomer was obtained in accordance with the Felkin Ahn model. Synthesis of the correct isomer **74** could possibly be achieved by changing the silicon protecting group for an alkyl group. This would indeed

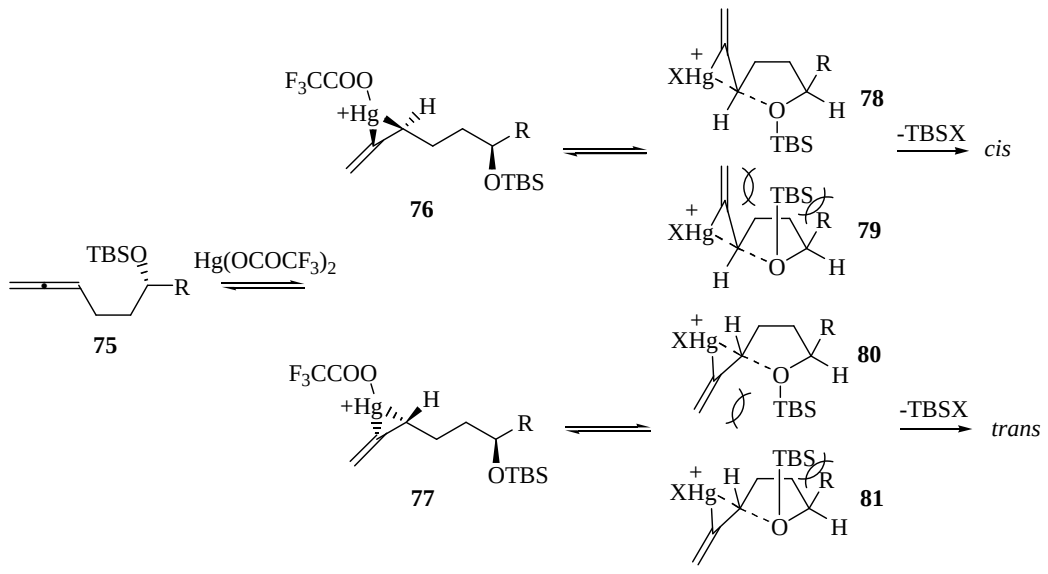
favour the chelation-controlled product when aldehyde **72** was reacted with the Grignard reagent.

Scheme 14. Synthesis of the C_1-C_{14} Subunit of Pamamycins 607 **1** and 635B **8**.



Reaction of allene **75** with mercury (II) trifluoroacetate led to the formation of two intermediates, **76** and **77**. The excellent stereoselectivity observed for this reaction can be explained by the ability of the bulky silicon group to interact with the different substituents of the molecule, and therefore to disfavour the formation of three of the four possible transition states **79**, **80** and **81** (**Scheme 15**). Consequently, after loss of the TBS group, the reaction of intermediate **78** led to the formation of the *cis*-2,5-tetrahydrofuran.[29] This model can also explain the formation of the *cis*-oxacycle in the iodocyclisation previously described in **Section 1.1.2.2-i**.

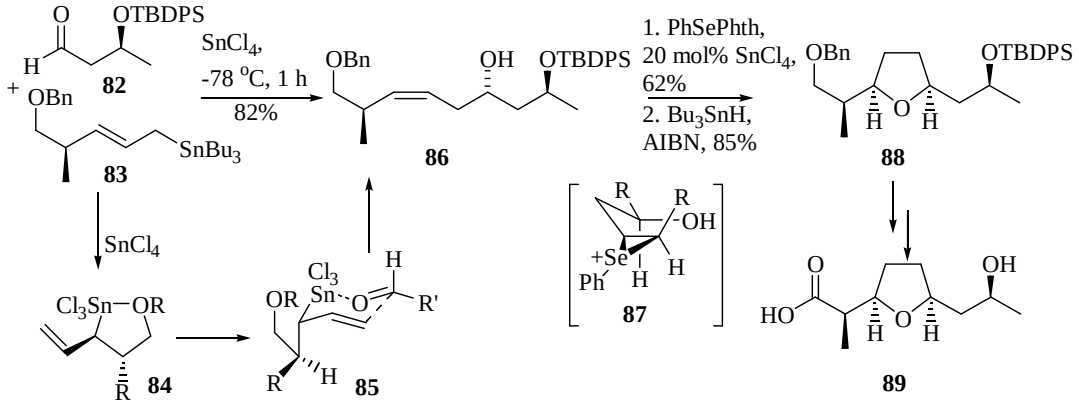
Scheme 15. Proposed Mechanism.[29]



iv. Selenoetherification.

Thomas *et al.* reported the total synthesis of pamamycin 607 **1** in 2001.[30] The three *cis*-tetrahydrofurans were synthesised by selenoetherification using phenylselenyl phthalamide. The methodology was first tested on the synthesis of the methyl ester of nonactic acid **89** and then applied for the construction of the different fragments of the natural product. Reaction of stannane **83** with tin (IV) chloride gave the intermediate **84**, which reacted with aldehyde **82** *via* a 6-membered transition state **85** to give alkene **86** in 82% yield. When alkene **86** was treated with the phenyl selenyl electrophile, tetrahydrofuran **88** was obtained as a single isomer after reduction with tributyltin hydride (**Scheme 16**). This was consistent with the formation of the transition state **87** shown below.

Scheme 16. Selenoetherification.

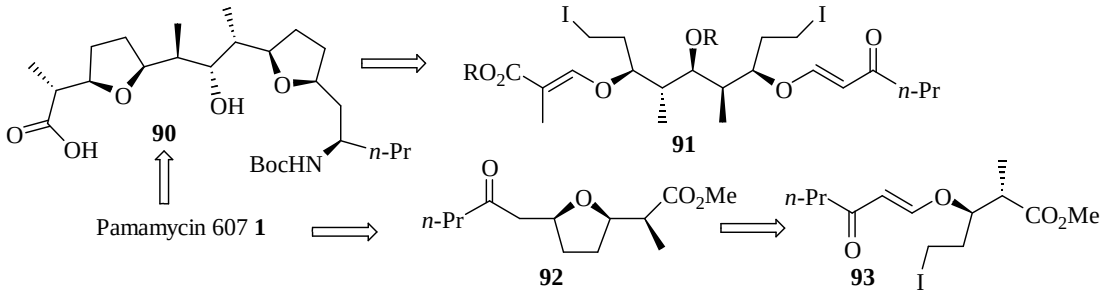


1.1.2.3 1,4-Cyclisation.

i. Radical Cyclisation.

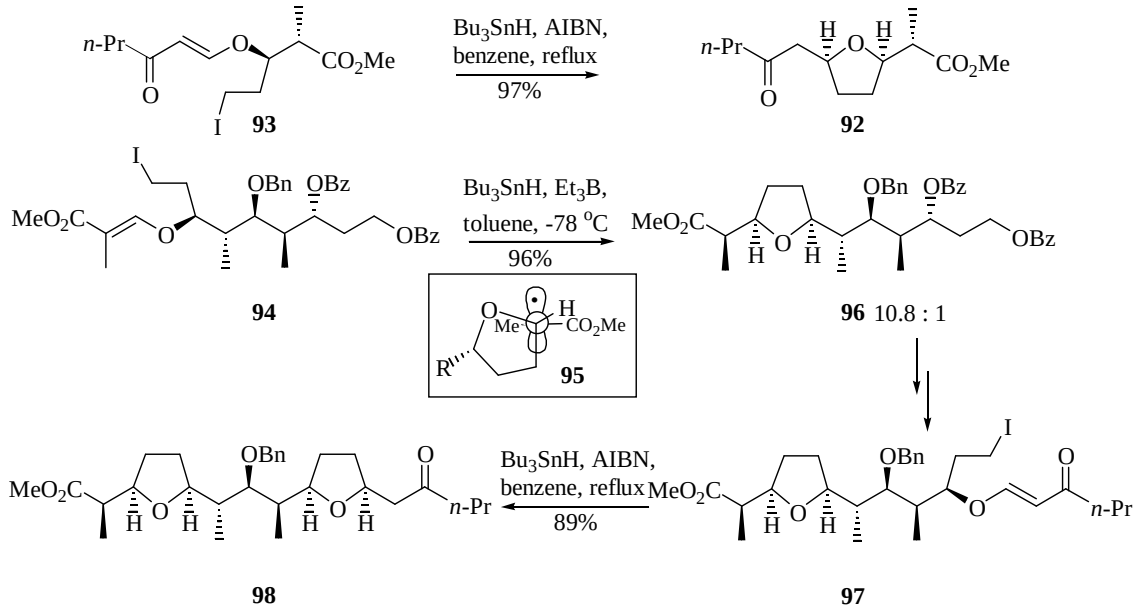
Lee and co-workers were the first to publish the total synthesis of pamamycin 607 **1**.[31,32] Retrosynthetic disconnection of pamamycin 607 **1** using a strategy similar to the one of Kang (**Scheme 5**) gave intermediates **90** and **92**. The key step involved in the synthesis is a radical cyclisation of *β*-alkoxyvinyl ketones **93** and *β*-alkoxyacrylates **91**.

Scheme 17. Retrosynthetic Analysis.



In the case of the *β*-alkoxyvinyl ketones **93** and **97**, when treated with tributyltin hydride in the presence of AIBN and under high dilution conditions, the corresponding tetrahydrofurans **92** and **98** were obtained in excellent yield and as the *cis*-compounds. Similar reaction with *β*-alkoxyacrylate **94** gave also the corresponding tetrahydrofuran **96** and as shown before, the *cis*-compound was obtained. In addition the reaction allowed the control of the stereocentre outside the oxacycle and led preferentially to the formation of the *threo*-compound. The *cis*-relationship observed in both cases, *β*-alkoxyvinyl ketones and *β*-alkoxyacrylate, can be explained by the preference for the "outside alkoxy" conformation, which results in the relief of the allylic strain and the minimisation of the electronic repulsion. Finally, the formation of the *threo*-compound in the case of *β*-alkoxyacrylate **94** is possibly due to the hydrogen abstraction of radical intermediate **95** from the least hindered face.

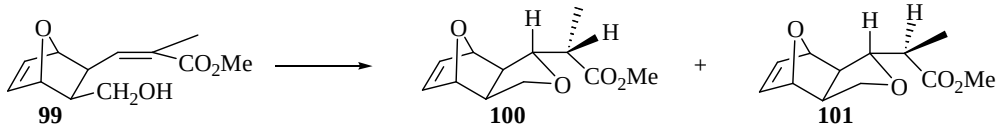
Scheme 18. Radical Cyclisation.



ii. Michael Addition.

Bloch *et al*. reported the synthesis of the $C_{1'}$-$C_{11'}$ synthon of pamamycin 607 **1**.[33] The methodology involved an intramolecular Michael addition onto an *α*,*β*-unsaturated ester in order to generate the corresponding tetrahydrofuran. In order to perform the cyclisation, a wide range of bases were tested on the model system **99** and it was found that TBAF gave the best stereoselectivity in favour of the tetrahydrofuran **100**. The results are summarised in **Table 1**.

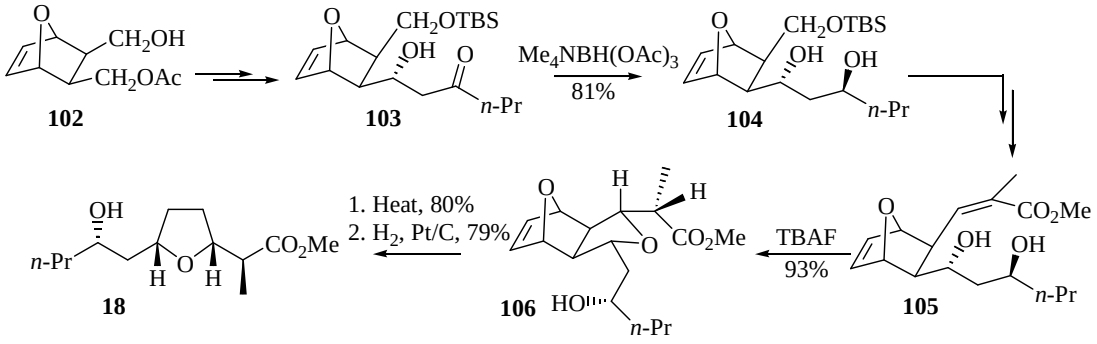
Table 1. Intramolecular Michael Addition.



Entry	Base	Conditions	Ratio
1	$BnMe_3NOMe$	MeOH, 20 °C, 6 h	50 : 50
2	MeONa	MeOH, 20 °C, 6 h	50 : 50
3	P_4-*t*-Bu	THF, 20 °C, 5 min	60 : 40
4	*n*-Bu_4NF	THF, 20 °C, 1 h	80 : 20
5	KF, 18C6	CH_3CN, reflux, 6 h	80 : 20

Synthesis of the $C_{1'}$-$C_{11'}$ fragment started with compound **102**, which was first obtained by enzymatic transesterification of the corresponding diol. After further protecting group manipulations, oxidation of the primary alcohol to an aldehyde and reaction with the kinetic lithium enolate of 2-pentanone, hydroxy-ketone **103** was obtained. Reduction of the ketone group to the *anti*-diastereoisomer **104** was achieved using the Evans procedure using tetramethylammonium triacetoxyborohydride and compound **105** was obtained in five steps from **104**. The intramolecular Michael addition was then performed using TBAF as base and the correct diastereoisomer **106** was majoritary obtained. The stereoselectivity proved to be higher in the case of the real system. Compound **106** was then subjected to a flash thermolysis (400 °C, 10-13 torr) to give the retro-Diels-Alder cyclisation product, which was finally hydrogenated using platinum on carbon to give the $C_{1'}$-$C_{11'}$ fragment **18** of pamamycin 607 **1** (**Scheme 19**).

Scheme 19. Synthesis of the $C_{1'}$-$C_{11'}$ Fragment of Pamamycin 607 **1**.



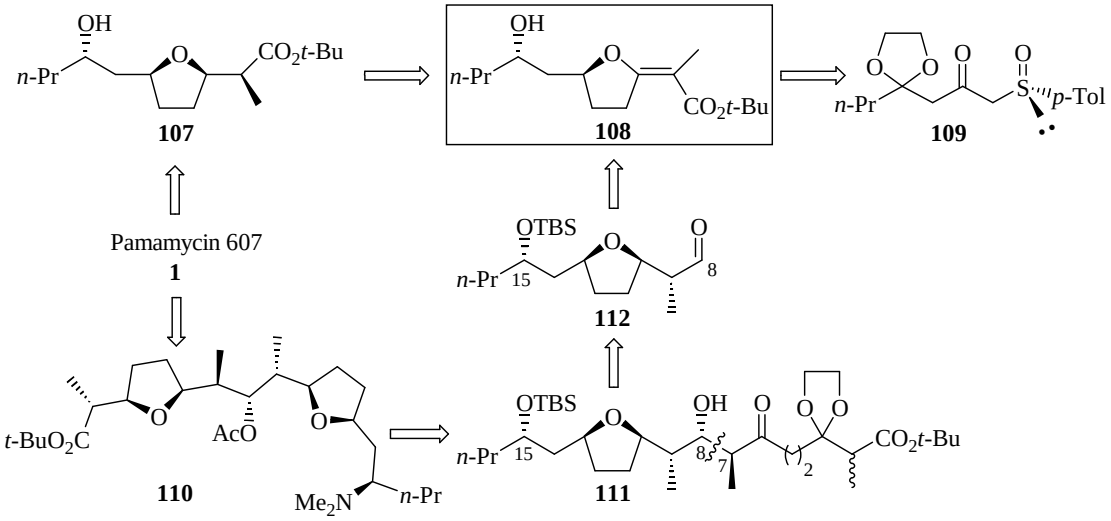
A similar strategy was used for the synthesis of the C_8-C_{18} fragment of pamamycin 607 **1** from the common intermediate **103**.[34]

1.1.2.4 From a Chiral Lactone.

Recently, Hanquet and co-workers reported the total synthesis of pamamycin 607 **1** from (*S*)-methyl *p*-tolyl sulfoxide **109** (**Scheme 20**).[35] Cleavage of the two lactones

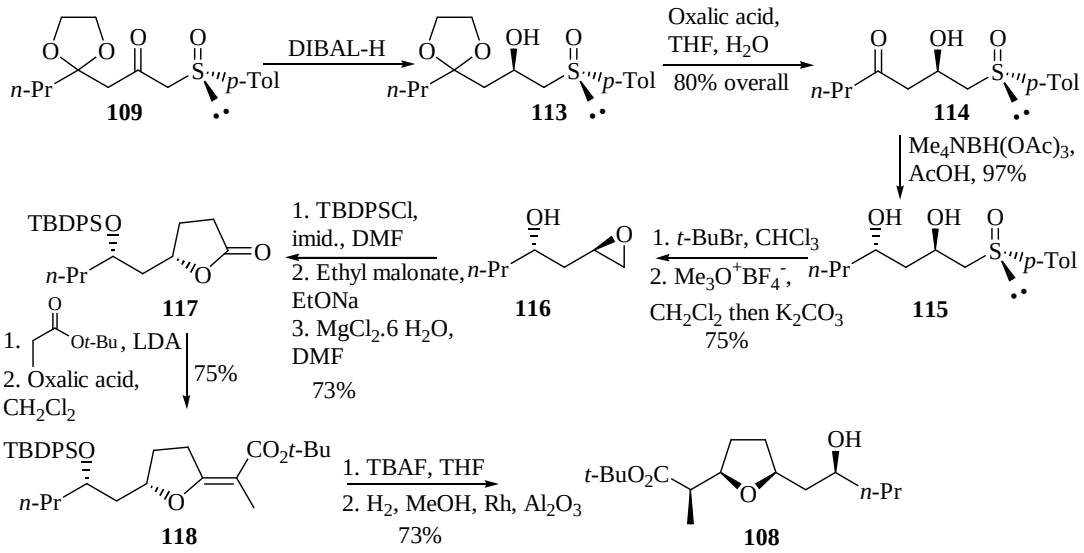
moieties gave as before fragments **107** and **110**. Disconnection of the C_7-C_8 bond gave intermediate **111**, which could be obtained by employing an aldol reaction with aldehyde **112**. Finally, fragments **107** and **112** could be synthesised from the common intermediate **108** (**Scheme 20**).

Scheme 20. Retrosynthesis Analysis.



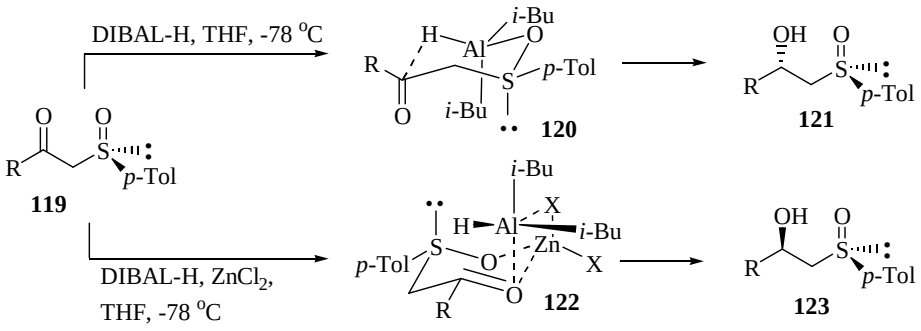
The methodology used can be outlined by the synthesis of the precursor of fragment C_8-C_{18}.[36,37] The synthesis started with *β,γ*-diketosulfoxide **109**, which could be obtained from ethyl butyryl acetate and (*S*)-methyl *p*-tolyl sulfoxide anion. Reduction of the ketone group using DIBAL-H gave hydroxy-sulfoxide **113** as a single diastereoisomer. The opposite diastereoisomer could be obtained by reaction of compound **109** with zinc chloride and DIBAL-H. The acetal group was then removed using oxalic acid to give hydroxyl-ketone **114**, which was subsequently subjected to a chiral reduction using the Evans procedure. Reduction of the sulfoxide group of intermediate **115** to the corresponding sulfide followed by its methyl alkylation and displacement gave hydroxy-epoxide **116**. The alcohol group was then protected as a silyl ether, the epoxide opened with the ethyl malonate anion and after decarboxylation using magnesium chloride hexahydrate, lactone **117** was obtained. Reaction of lactone **117** with *tert*-butyl propionate anion and dehydration under acidic condition gave compound **118** with the most stable geometry as the *trans*-alkene. Finally, after removal of the silicon group with TBAF and hydrogenation over rhodium on alumina, the C_8-C_{18} fragment **108** was obtained (**Scheme 21**).

Scheme 21. Synthesis of Subunit C_8-C_{18} **108**.



The key step of the synthesis was the chiral reduction of the carbonyl of *β*-ketosulfoxide **119** with DIBAL-H or with zinc chloride and DIBAL-H in order to obtain hydroxy-sulfoxide **121** or its opposite diastereoisomer **123**. The different 6-membered transition states **120** and **122** are outlined in the scheme below.[38]

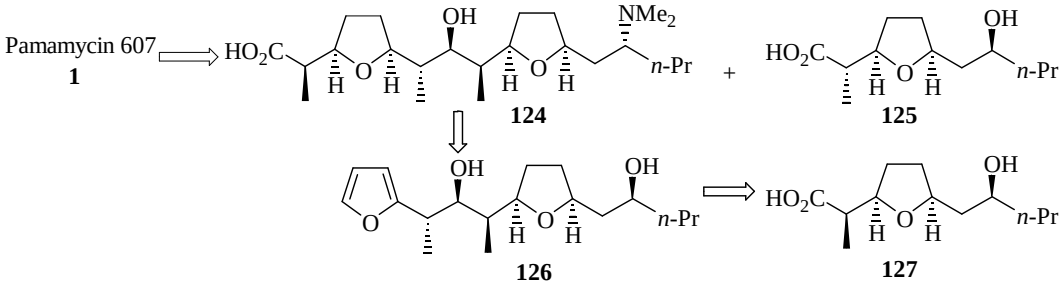
Scheme 22. Reduction of the Ketone Group.



1.1.2.5 Sultone Methodology.

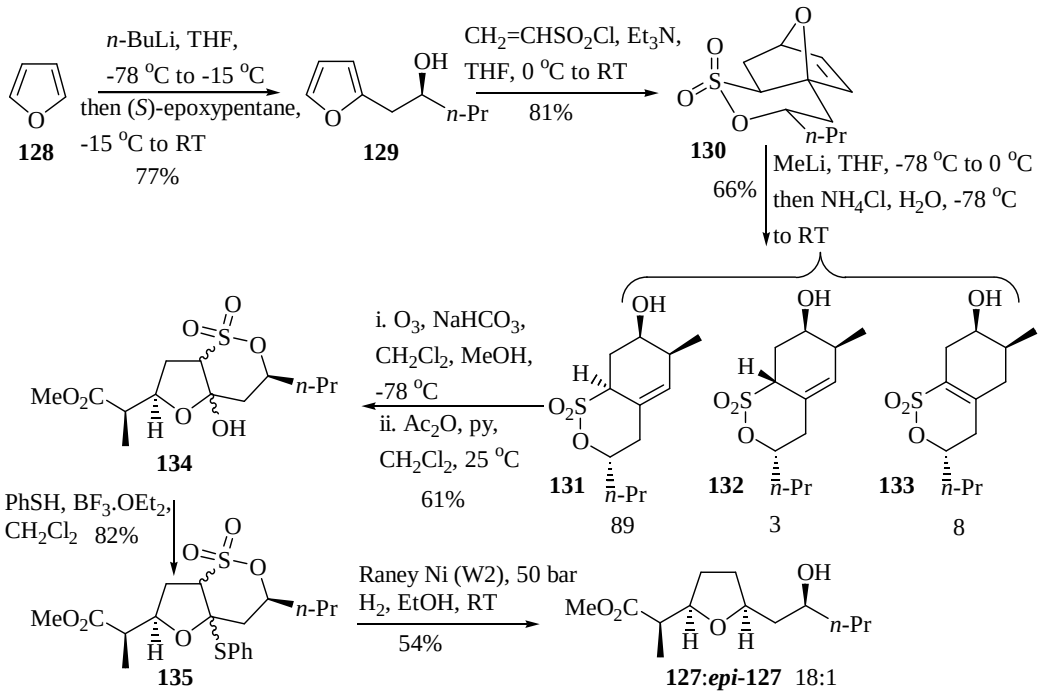
The total synthesis of pamamycin 607 **1** was also achieved by Metz and co-workers in 2001.[39,40] As before, dismantlement of the ester linkage gave fragments **124** and **125**. Further simplifications of fragment **124** gave tetrahydrofuran **126** (**Scheme 23**). The key fragments **125** and **127** were synthesised by using a sultone template, which was easily formed *via* a Diels-Alder reaction (**Scheme 24**).

Scheme 23. Retrosynthetic Analysis.



The key step of this total synthesis can be illustrated by the synthesis of tetrahydrofuran **127**. The synthesis started with alcohol **129**, which was synthesised from furan **128** and (*S*)-epoxypentane. This was followed by a tandem alkylation and cycloaddition with vinylsulfonyl chloride to give sultone **130**, as a single enantiomere. Treatment of sultone **130** with methyl lithium generated a 89:3:8 mixture of compounds **131**:**132**:**133**. The addition of the nucleophilic methyl to the double bond was directed by the bridging oxygen ring, with subsequent ring opening. The mixture of the three isomers was reacted with ozone. It was observed that only compounds **131** and **132** could undergo the ozonolysis and it was possible to remove **133** by flash column chromatography from the product **134**. Finally, after hydrogenation over Raney nickel, the corresponding tetrahydrofuran **127** was obtained as a 18:1 mixture with the *epi*-isomer (**Scheme 24**).

Scheme 24. Synthesis of Fragment **127**.



1.1.2.6 Conclusion.

The structural complexity and the interesting biological properties (autoregulatory, anionophoric, antifungal activities as well as antibacterial activities against Gram-positive bacteria and especially against antibiotic resistant strains of *Mycobacterium turberculosis*) of the members of the pamamycin family represent an exciting synthetic challenge and currently, five total syntheses of pamamycin 607 **1** and other homologues have been reported. But the most striking feature has been the intense development of novel and highly selective methodologies for the synthesis of the tetrahydrofuran fragments.

1.2 ACETALS IN ORGANIC CHEMISTRY.

Cyclic acetals, such as 1,3-dioxanes (6-membered ring) and 1,3-dioxolanes (5-membered ring) are useful intermediates in organic synthesis. Acetal groups are stable to strong reducing agents such as sodium in liquid ammonia and lithium aluminium hydride in boiling THF as well as catalytic hydrogenation. They are also resistant to strong oxidants such as chromium trioxide-pyridine complex. But they can be easily removed using mild acidic conditions and are consequently excellent protecting groups for diols, aldehydes and ketones.[41] On another side, acetal rings in the presence of Lewis acids can open to form oxonium ions. This gives access to whole new dimension of possible reactions as the oxonium ion can react with a wide range of nucleophiles such as hydrides, organometallics and silane reagents.

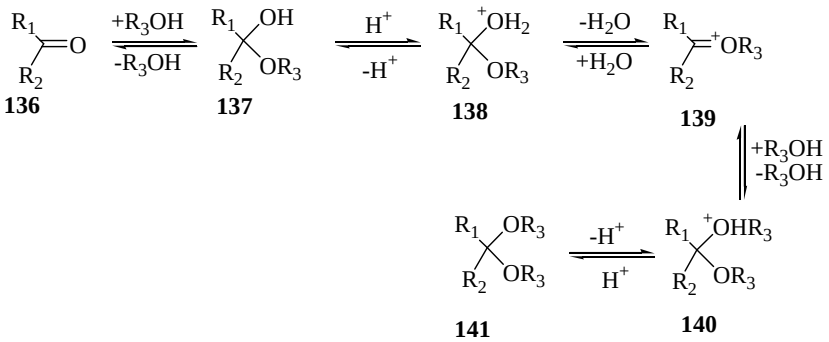
1.2.1 ACETALS AS PROTECTING GROUP.

1.2.1.1 Protection of Aldehydes/Ketones Using Alcohols or Diols.

i. Acid Catalysed Acetal Formation.

Aldehydes and ketones can react with alcohols in the presence of a catalytic amount of acid to give acetals or ketals. Cyclic acetals can be obtained by using 1,2-diols or 1,3-diols. The mechanism of the reaction is described in the **Scheme 25**. All the steps are reversible and a large excess of alcohol has to be used for the reaction to complete. Alternatively, displacement of the equilibrium can be achieved by removal of water. This can be performed by addition of mild dehydrating agents such as orthoformates or by azeotropic distillation when the reaction is heated under reflux in toluene.[41] Finally, it should be noted that the mechanism for the deprotection is the reverse of the protection mechanism (**Scheme 25**).

Scheme 25. Acetal Formation: Mechanism.



136 **137** **138** **139** **140** **141**

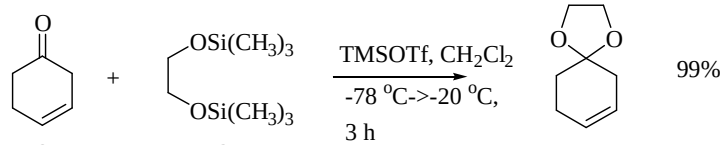
Acetal formation can be catalysed by *p*-toluenesulfonic acid,[42] triflic acid or pyridinium salt. Sheu and co-workers reported the acetalisation of *α,β*-unsaturated aldehydes and ketones using *p*-toluenesulfonic acid or oxalic acid with ethylene glycol in refluxing toluene and with the presence of anhydrous magnesium sulfate.[43] Under these conditions no double bond migration was observed.

Brønsted acid ionic liquids such as [hmim][BF_4] can promote the formation acetals.[44] In this particular case, the removal of water was unnecessary as water was soluble in the ionic liquid while the starting materials and product were immiscible in [hmim][BF_4]. The products were then separated by decantation from the ionic liquid, which could be recovered and reused up to eight times without significant loss of activity.

ii. The Noyori Procedure.

In 1980, Noyori *et al*. reported the acetalisation of ketones under mild aprotic conditions.[45] By treatment of ketones with alkoxytrimethylsilanes in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (1 mol%) (TMSOTf) in CH_2Cl_2 at -78 ^oC, the corresponding acetals were obtained in excellent yields. For instance, under these conditions, ketone **142** when reacted with alkoxysilane **143** afforded the corresponding acetal **144** in 99% yield and no product involving the migration of the double bond was obtained (**Scheme 26**). It should be noted that the formation of a stable intermediate hexamethylsiloxane made the reaction become irreversible and the equilibrium was consequently shifted toward the formation of the desired acetals.

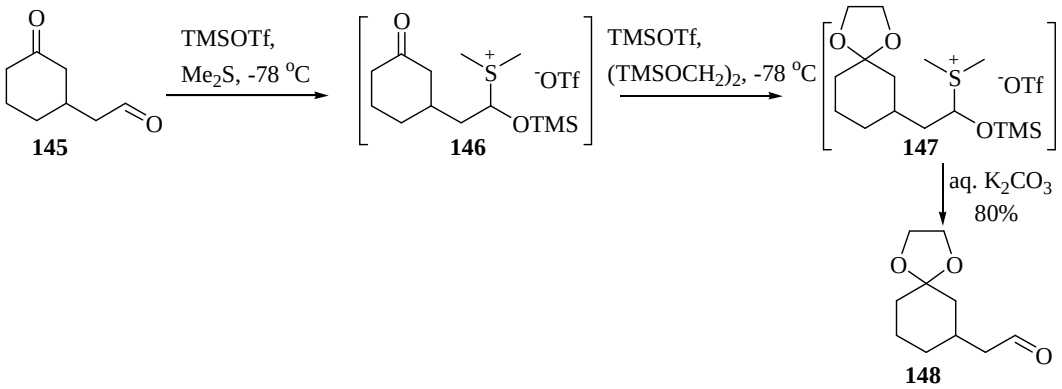
Scheme 26. The Noyori Procedure.



142 **143** **144**

Kim and co-workers modified the Noyori procedure and were able to acetalise ketones in favour of aldehydes.[46] Thus, treatment of ketoaldehyde **145** with TMSOTf and dimethyl sulfide allowed a first protection of the aldehyde by formation of 1-silyloxysulfonium salt **146**. The ketone could then be protected as the acetal by further reaction with TMSOTf and 1,2-*bis*[(trimethylsilyl)oxy]ethane to give acetal **147**. Finally, the corresponding aldehyde **148** could be isolated in excellent yield upon an aqueous work-up.

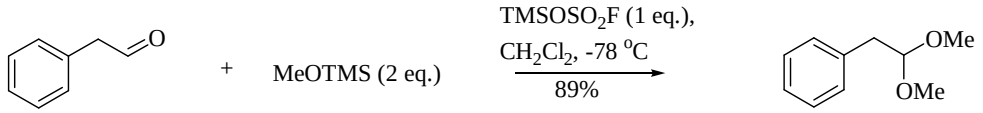
Scheme 27. Chemoselective Dioxolanisation.



145 **146** **147** **148**

Although TMSOTf is commercially available, it is a rather expensive material and efforts have been made to develop inexpensive reagents, source of TMS^+. Lipshutz *et al*. reported the use trimethylsilyl sulfonate ($TMSOSO_2F$) as an alternative to TMSOTf.[47] Trimethylsilyl sulfonate can be easily formed *in situ* by reaction of fluorosulfonic acid (FSO_3H) and allyltrimethylsilane in CH_2Cl_2 at -78 °C. Thus, reaction of aldehyde **149** under the Noyori conditions with $TMSOSO_2F$ and MeOTMS **150** gave the corresponding dimethyl acetal **151** in 89% yield (**Scheme 28**).

Scheme 28. Acetalisation using $TMSOSO_2F$.



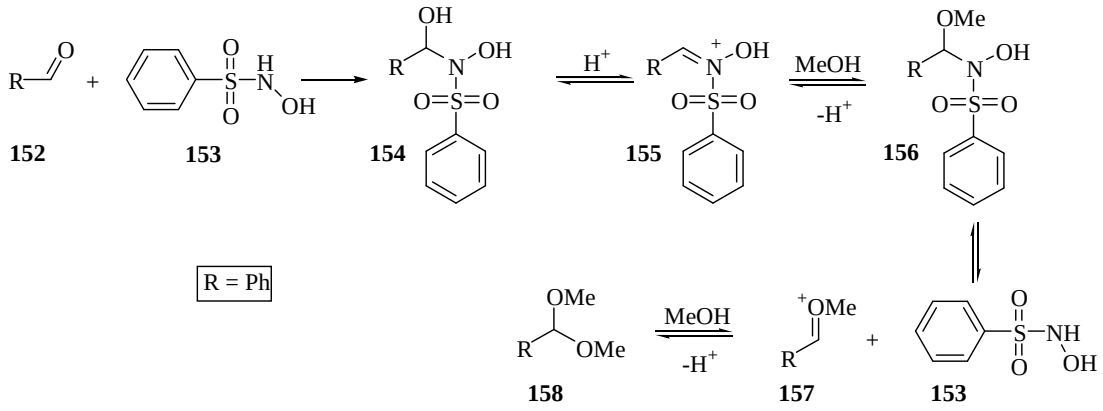
149 **150** **151**

<u>iii. Acetal Formation Catalysed by Nucleophiles</u>.[48]

The Angeli-Rimini reaction is a qualitative test to determine the presence of aldehydes. The treatment of aldehydes with *N*-hydroxybenzene sulphonamide **153** in the presence of base can give hydroxamic acids, which can then be complexed with ferric ions to give a characteristic purple colouration.

Alternatively, without the presence of base, *N*-hydroxybenzene sulfonamide in methanol reacts with aldehydes to give the corresponding dimethyl acetals. For instance, benzaldehyde **152** in methanol and with *N*-hydroxybenzene sulfonamide **153** was converted into the corresponding dimethyl acetal **158** in 87% yield, and within 15 minutes only. The mechanism of the reaction is described in **Scheme 29**. Only a catalytic amount of *N*-hydroxybenzene sulfonamide **153** is required as it is regenerated during the reaction.

Scheme 29. Acetal Formation Catalysed by *N*-Hydroxybenzene Sulfonamide.



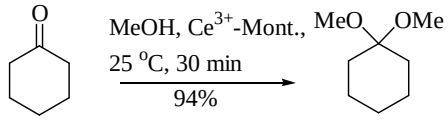
152 **153** **154** **155** **156** **158** **157** **153**

iv. Acetalisation Using Heterogeneous Catalysts.

The use of heterogeneous catalysts such as clays, resins, zeolites or metals for the reaction of acetalisation has been widely studied. The main advantage is that reactions under these conditions can benefit from easy work-ups, generally a high purity of the products and the possibility of reusing the catalysts.

Clays are inexpensive, easy to handle, non corrosive, their acidity can be easily modify by cations exchange and they can be regenerated.[49, 50] They can catalyse reactions of acetalisation effectively and under very mild conditions. For example cation exchange clays such as Ce^{3+}-Montmorillonite (Ce^{3+}-Mont.) can promote the formation of dimethyl acetal **160** in excellent yield when reacted with cyclohexanone **159** in methanol (**Scheme 30**).[51]

Scheme 30. Use of Ce^{3+}-Mont.



159 **160**

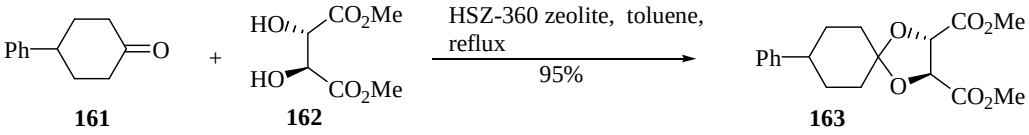
Similarly, in 2004, Wakharkar reported the acetal protection of 1,2-diols and *N*-(Boc)amino alcohols using 2,2-dimethoxypropane with Montmorillonite K10 clay.[52]

Dry silica gel or alumina can be used to acetalise selectively aldehydes into the corresponding 1,3-dioxolanes.[53] Zinc chloride on alumina proved to be also a useful method for the tetrahydropyranilation of alcohols.[54] Mesoporous silica (aluminosilicates)[55] as well as sulfonic acid-functionalised silica[56] can form dimethyl acetals by reaction of aldehydes with methanol or THP protect alcohols. Sulfonic acid-

functionalised silica represents also a novel alternative to sulfonic resins for acetalisation of aldehydes and ketones as resins possess several drawbacks such as low surface area and thermal stability.[57]

HSZ-360 zeolite can catalyse acetalisation of ketones when heated under reflux in toluene with diols and for instance acetal **163** was obtained from ketone **161** in 95% yield when treated with (*R*, *R*)-dimethyltartrate **162** in the presence of the catalyst (**Scheme 31**). It should be noted that HSZ-360 is commercially available and can be reused after being dried.[58]

Scheme 31. Acetalisation over HSZ-360 Zeolite.



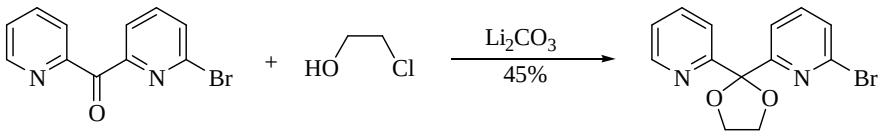
161 **162** **163**

Finally, mild Lewis acids such as cobalt (II) chloride[59] and ruthenium (III) chloride[60] have been reported to chemoselectively promote the acetalisation of aldehydes.

v. Acetalisation Under Basic Media.

sym-Dichlorotetrafluoroacetone[61] and ketone **164** [62] can react with 2-chloroethanol **165** in the presence of potassium or lithium carbonate to give the corresponding dioxolane **166** in 45% yield (**Scheme 32**).

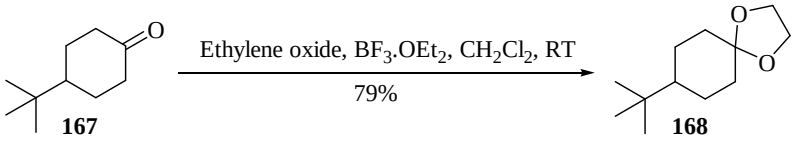
Scheme 32. Reaction with 2-Chloroethanol.



164 **165** **166**

This can be related to the formation of acetals by reaction of ketones (for example ketone **167**) with ethylene oxide in the presence of boron trifluoride (**Scheme 33**). The corresponding acetal **168** was obtained in 79% yield.[63]

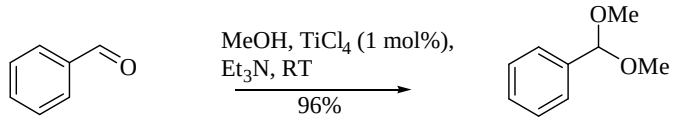
Scheme 33. Reaction of *tert*-Butylcyclohexanone with Ethylene Oxide and $BF_3.OEt_2$.



167 **168**

Porta and co-workers reported the acetal protection of aldehydes using a Lewis acid and under basic conditions.[64] A typical experiment involved the treatment of the substrates with triethylamine in methanol and in the presence of titanium chloride (**Scheme 34**).

Scheme 34. Reaction with a Lewis Acid under Basic Conditions.

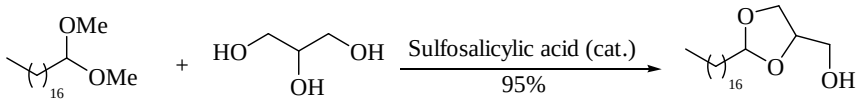


152 **158**

1.2.1.2 Transacetalisation and Acetal Exchange.[41]

Transacetalisation is a useful process permitting to synthesise cyclic acetals. McElvain and Curry showed that halogenated acetals could react with glycol in the presence of sulfuric acid.[65] Similarly, Piantadozi *et al*. reported the formation of acetal **171** by reacting the dimethyl acetal **169** with glycerine **170** using a catalytic amount of sulfosalicylic acid (**Scheme 35**).[66]

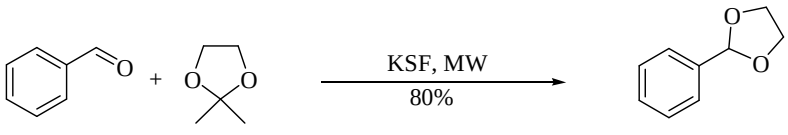
Scheme 35. Transacetalisation.



169 **170** **171**

Under acidic conditions (for instance *p*-toluenesulfonic acid), acetal exchange can occur between a ketone and and acetal.[67, 68] 2,2-Dimethyl-1,3-dioxolane **172** has been widely used to perform this type of reaction. An example using microwave technology using a clay catalyst is described in **Scheme 36**.[69]

Scheme 36. Acetal Exchange under Microwave Irradiation.



152 **172** **173**

1.2.1.3 Deprotection of the Acetal Groups.

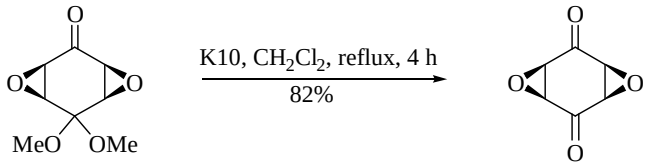
Cleavage of the acetal group is performed under acidic conditions and the mechanism is the reverse of the one of protection (see **Section 2.1.1.1**). Numerous acids, including hydrochloric acid, *p*-toluenesulfonic acid,[70] acetic acid[71] have been employed to perform the reactions of deprotection. However, acid sensitive substrates can lead to

decomposition or formation of by-products when reacted under these conditions. That is why novel methodologies using neutral and/or aprotic conditions have been developed.

i. Using Less Acidic Conditions.

Clay catalysts are well known to promote acetal formation (see **Section 2.1.1.1**) and Montmorillonite K10 has been widely used to carry out these reactions. Taylor and co-workers reported the cleavage of acetals under mild conditions using clay K10 as acid catalyst and when heated under refluxing conditions in CH_2Cl_2.[72] Thus, *bis*-epoxide **174** was cleaved using this procedure and diketone **175** was obtained in good yield (**Scheme 37**). It should be noted that only poor yields were obtained when aqueous acid was used. This was due in this case to the water solubility of the compound.

Scheme 37. Cleavage Using Montmorillonite K10.



174 **175**

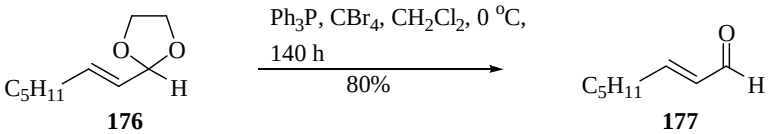
DDQ is a neutral molecule which can in acetonitrile and water (9:1) also deprotect a wide range of acetals. The mechanism of this reaction has not been reported.[73]

ii. Using Phosphorus Compounds.

Phosphorus *tri*-iodide and diphosphorus *tetra*-iodide in CH_2Cl_2 at RT have been reported to deprotect acetals.[74]

More recently, Kerr *et al*. showed that triphenylphosphine and carbon tetrabromine under anhydrous conditions could deprotect acetals in good yield. Deprotection of acetal **176** under these conditions gave aldehyde **177** in 80% yield (**Scheme 38**).[75]

Scheme 38. Cleavage Using Triphenylphosphine and Carbon Tetrabromide.



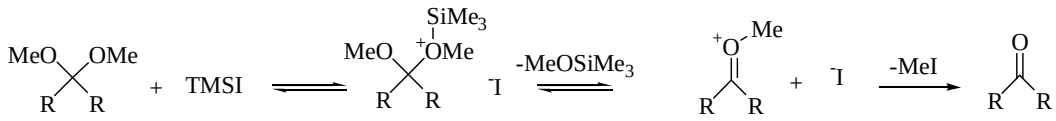
176 **177**

iii. Using Halosilanes.

Trimethylsilyl iodide **179** as well as trichloromethylsilane and sodium iodide can cleave acetal groups. The mechanism of this reaction is described in the scheme below. Dimethyl acetal **178** can react with trimethylsilyl iodide **179** to generate intermediate

180 and after loss of MeOTMS and formation of an oxonium species **181**, the iodide can attack the methyl group to generate the corresponding ketone **182**. [76, 77]

Scheme 39. Cleavage with TMSI-Mechanism.

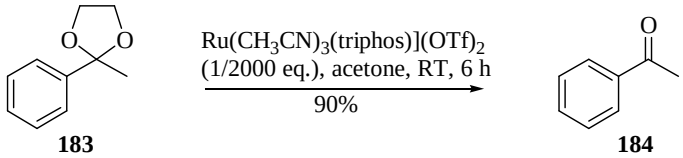


178 **179** **180** **181** **182**

iv. Using Transition Metals and Lewis Acids.

Acetal exchanges can be carried out over ruthenium[78] and palladium[79] catalysts. The reactions are carried out in acetone in order to transfer the acetal goup from the substrates to the solvent. For example, acetal **183** was deprotected under these conditions to afford ketone **184** in 90% yield (**Scheme 40**).

Scheme 40. Deprotection by Acetal Exchange with Acetone.



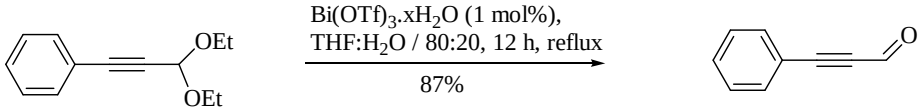
183 **184**

Ferric chloride adsorbed on silica gel[80] and ferric chloride hexahydrate[81] can deprotect acetals. It has been observed that ferric chloride on silica was milder than ferric chloride hexahydrate and that under these conditions TBS and trityl ethers reacted slowly. Reaction with ferric chloride hexahydrate was carried out in CH_2Cl_2 although $FeCl_3$ was poorly soluble in this solvent. It is still unclear if the results obtained were due to the Lewis acidity of $FeCl_3 \cdot 6H_2O$ or to the acid catalysis promoted by an acidic sub-species present in anhydrous ferric chloride.

Bismuth nitrate pentahydrate[82] and bismuth triflate[83] have been reported to catalyse the cleavage of acetal groups. Bismuth compounds benefit from several advantages. They are relatively non-toxic, inexpensive, non-corrosive, air/moisture stable and consequently easy to handle and have Lewis acid properties. In addition bismuth nitrate is commercially available and the synthesis of bismuth triflate has been well documented in the literature. Only acyclic acetals were cleaved with bismuth nitrate (25 mol%) in CH_2Cl_2 although the cleavage of cyclic and acyclic acetals was observed in the case of bismute triflate (1 mol%) in THF/H_2O. For example diethyl acetal **185**

gave the corresponding aldehyde **186** in 87% yield when reacted with bismuth triflate **(Scheme 41**). It should be noted that in both cases, under the reaction conditions, TBS ethers were stable. It was postulated that a catalytic amount of nitric acid and triflic acid formed during the reaction and was consequently responsible for the cleavage of the acetal moieties.[83]

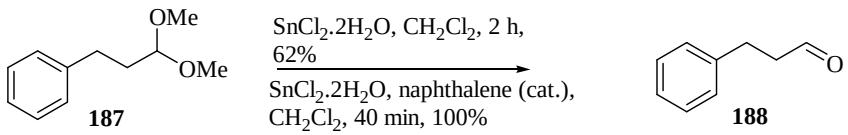
Scheme 41. Cleavage using Bismuth Triflate.



185 **186**

Tin (II) dichloride dihydrate in dichloromethane can catalyse the cleavage of a wide range of acetals.[84] It was observed that leaving the reaction mixture over an extended period of time led to the reprotection of the carbonyl group. This was overcome by the addition of sodium bicarbonate in order to trap any traces of acidity possibly produced by the tin species. Roskamp and Ford described thus the first acetal cleavage under mild basic conditions. This procedure was then optimised and it was found that the addition of naphthalene to the reaction mixture dramatically improved the yields and reduced significantly the time of the reactions; the deprotection of dimethyl acetal **187** to aldehyde **188** occurred in quantitative yield when reacted with the presence of naphthalene *versus* 62% yield without it (**Scheme 42)**.[85] A possible explanation is the formation of an arene complex between tin dichloride and the aromatic compound, which acts as a phase transfer catalyst.[85]

Scheme 42. Cleavage Using Tin Chloride Dihydrate.

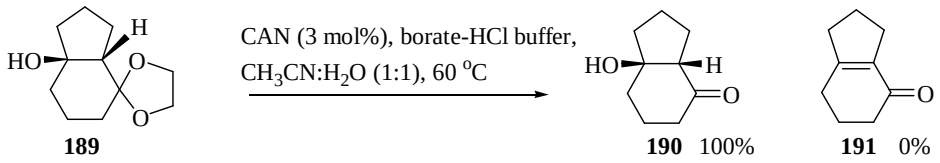


187 **188**

Marcó and co-workers reported the cleavage of acetals by a catalytic amount of cerium ammonium nitrate (CAN) under midly basic conditions.[86] Reaction in a borate-HCl buffer (pH 8) in the presence of CAN led to the deprotection of acid sensitive molecules and for example acetal **189** was cleaved to afford hydroxy ketone **190** in 90% yield (**Scheme 43**) but the formation of *α,β*-unsaturated ketone **191** was not observed under these conditions. Unprotected secondary and tertiary alcohols, ketones and enones were also stable under these conditions, as well as aldehydes, which were not oxidised into

carboxylic acids. Finally, no epimerisation of the chiral centres was observed. This reaction was studied by cyclic voltammetry and only the (IV) species was detected. This suggested that CAN was not acting as oxidant but as a Lewis acid.[86]

Scheme 43. Cleavage using CAN.

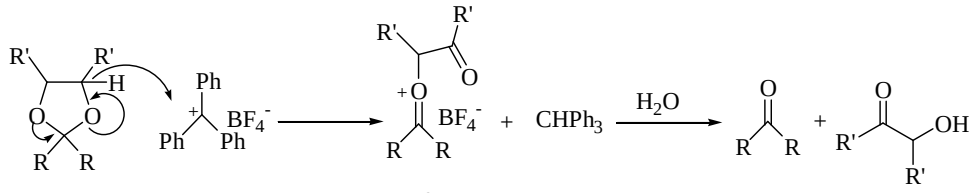


189 **190** 100% **191** 0%

v. Using Oxidation Techniques.

Trityl fluoroborate **193** is a very effective hydride acceptor and has been reported to cleave acetal groups.[87, 88] The proposed mechanism of the reaction is described in **Scheme 44**. Hydrogen transfer of acetal **192** to trityl fluoroborate **193** generates triphenyl methane **195** and the intermediate **194**, which upon hydrolysis furnishes the corresponding ketone **196** and hydroxyl-ketone **197**.

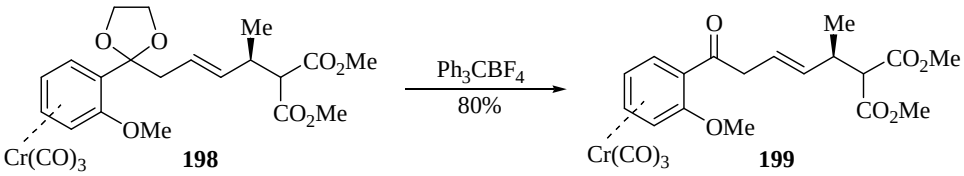
Scheme 44. Cleavage Using Trityl Fluoroborate-Mechanism.



192 **193** **194** **195** **196** **197**

Using this methodology, acetal **198** was deprotected and ketone **199** was obtained in 80% yield and without isomerisation of the double bond (**Scheme 45**).[89]

Scheme 45. Cleavage Using Trityl Fluoroborate.

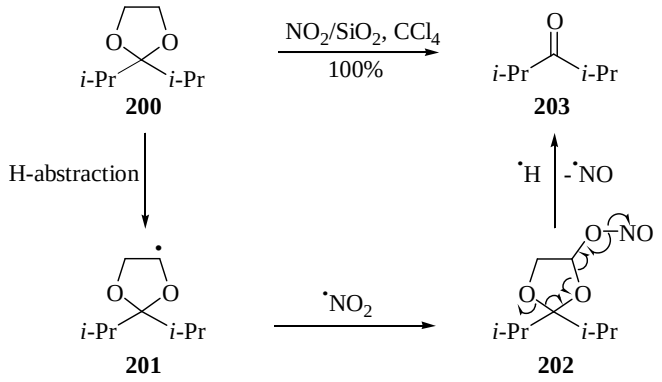


198 **199**

Nitrogen dioxide is known to oxidise benzylic alcohols into benzaldehydes. When adsorbed on silica gel, it can promote acetal deprotection and for instance using this methodology, acetal **200** was quantitalively cleaved into ketone **203**.[90] A possible mechanism involves a first hydrogen abstraction on the dioxolane ring to give radical

201, followed by reaction with $^{\cdot}NO_2$ to give the intermediate **202**, which after fragmentation generates the desired ketone **203**.

Scheme 46. Acetal Cleavage Using Nitrogen Dioxide on Silica Gel.[90]



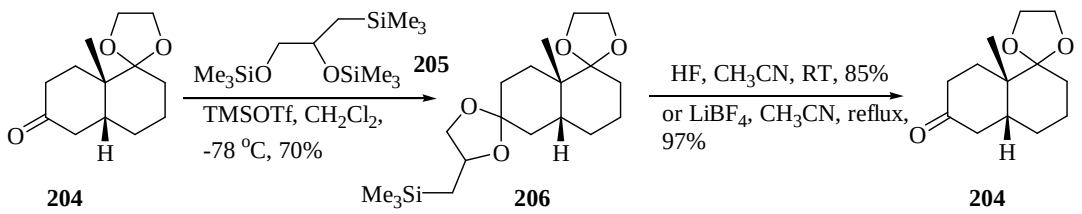
Magtrieve™, a magnetically removable chromium oxidant known for its oxidation properties of alcohols into aldehydes and ketones, has also been reported to cleave also acetals into their corresponding ketones/ aldehydes.[91]

1.2.1.4 New Protecting Groups.

Protecting groups are essential for the synthesis of natural products. The discovery of new molecules with original and unique structures drives the research towards the creation of novel protecting groups, which can be installed and removed under very mild conditions, but also adapted to specific functional groups or structural motifs.

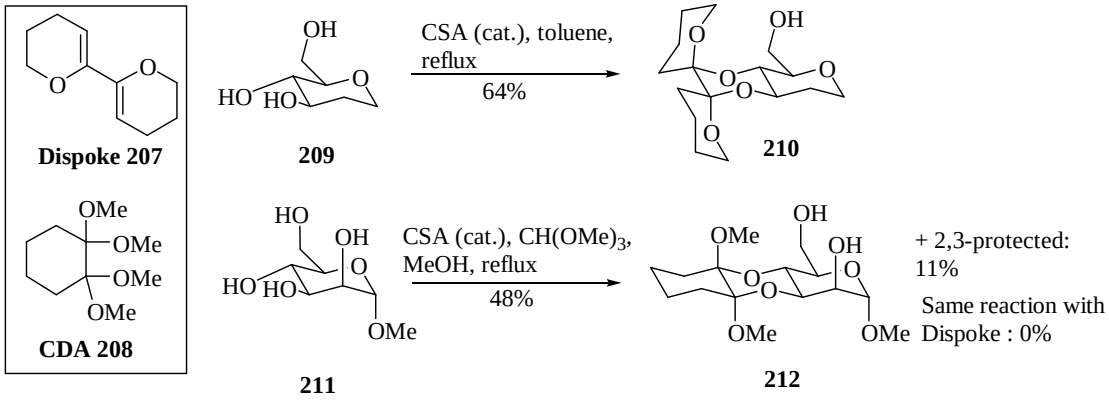
Several modified 1,3-dioxanes and 1,3-dioxolanes have been reported in the literature. For example, Avery *et al*. reported 4-trimethylsilyl methyl-1,3-dioxolane **205** to be a useful protecting group for carbonyls.[92] It can be easily introduced using the Noyori procedure (see **Section 1.2.1.1**) and removed using lithium borofluoride or hydrogen fluoride in acetonitrile (**206→204**, **Scheme 47**). The protecting group is resistant to TBAF, consequently permitting the orthogonal protection of alcohols with silyl ethers.

Scheme 47. Modified 1,3-Dioxolane as New Protecting Group.



New protecting groups (Dispoke **207** [93] and cyclohexane-1,2-diacetal **208** [94]), which permit the protection of *trans*-diequatorial vicinal diols have been reported. They are very useful for the protection of diols in carbohydrate chemistry such as compounds **209** and **211** (**Scheme 48**). The corresponding acetals **210** and **212** were obtained in 64% and 48% respectively.

Scheme 48. Dispoke and CDA Protecting Groups.



1.2.2 CHEMISTRY OF THE ACETAL GROUP.

1.2.2.1 Catalytic Hydrogenation.

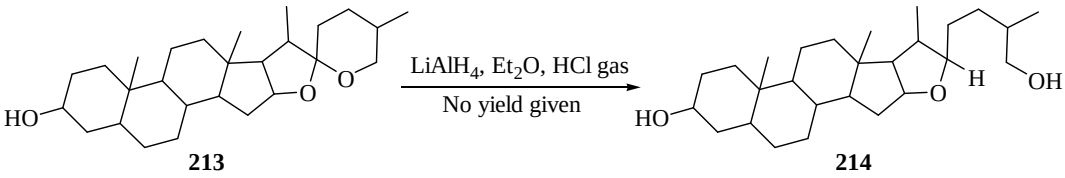
Acetal and ketal groups are stable under hydrogenation conditions and required in general very harsh conditions (high temperature and pressure) to be reduced to the corresponding ethers. Work by Howards and Browns in 1961 showed that ketals could be mildly reduced using metal catalysts in the presence of acid and at RT when secondary alcohols where used or at 50 ^{o}C<T<80 ^{o}C with primary alcohols.[95] The best results were obtained with a rhodium (5%) catalyst on alumina and with a drop of concentrated hydrochloric acid. Palladium catalysts showed some activity while platinum and ruthenium catalysts proved to be inactive.

1.2.2.2 Reduction Using Hydride Sources.

i. Lithium Aluminium Hydride.

In 1951, Doukas and Fontaine showed that the acetal group of spirostane **213** could be reduced when lithium aluminium hydride was added to a saturated solution of **213** in anhydrous hydrochloric acid to give compound **214**.[96]

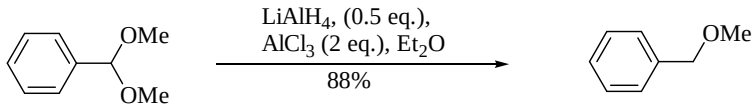
Scheme 49. Reduction of Spirostane with $LiAlH_4$ and Anhydrous HCl.



213 **214**

In 1962, Eliel *et al.* postulated that a lithium aluminium hydride could react with hydrochloric acid in order to form aluminium chloride, which would then be the active species in the reduction of compound **213**.[97] Consequently, the reductive cleavage of acetals in the presence of lithium aluminium hydride and aluminium chloride was investigated. Eliel *et al*. found that when a 4:1 ratio of $AlCl_3$:$LiAlH_4$ was used, the corresponding ethers were obtained in good yield and for example dimethyl acetal **159** afforded methyl ether **215** in 88% yield (**Scheme 50**).

Scheme 50. Reductive Cleavage of Acetals with $AlCl_3$:$LiAlH_4$.



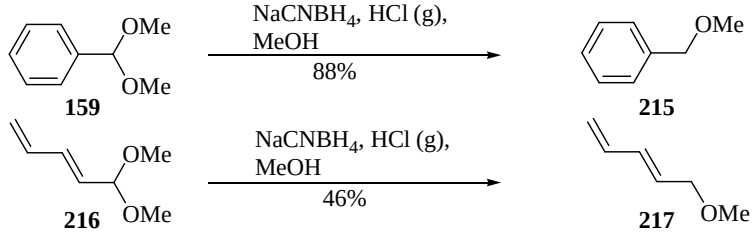
159 **215**

Finally, Abdum-Nur and Issidorides showed that similar reductions could be obtained when a mixture of $BF_3.OEt_2$ and $LiAlH_4$ was used and that higher yields were obtained.[98] Another advantage is the easier handle of $BF_3.OEt_3$ in comparison to $AlCl_3$.

ii. Sodium Cyanoborohydride.

Horne and Jordan reported in 1978, the use of sodium cyanoborohydride in MeOH with hydrogen chloride gas in order to reduce acetals and ketals to their corresponding methyl ethers.[99] For instance, reduction of dimethoxymethyl benzene **159** occurred cleanly (ether **215** was obtained in 88% yield) and the formation of toluene was not observed. In addition, 1,1-dimethoxy-2,4-pentadiadiene **216** gave the corresponding ether **217**, without the isolation of rearranged products or products with addition of hydrogen chloride (**Scheme 51**).

Scheme 51. Reduction with Sodium Cyanoborohydride and HCl gas.



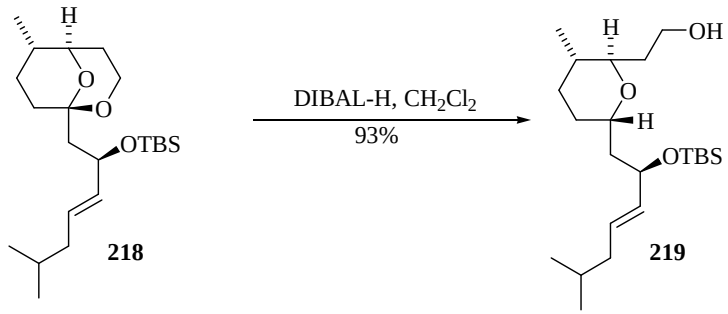
159 **215**

216 **217**

iii. DIBAL-H.

Bicyclic acetals can be reduced with DIBAL-H to give heterocyclic systems, such as tetrahydrofurans and tetrahydropyrans.[100] This methodology has been recently applied by Crimmins *et al*. to the enantioselective total synthesis of (+)-leucascandrolide A macrolactone, which possesses antifungal activities and cyctotoxicity against KB and P388 cells. The key step of the synthesis, the reductive cleavage of acetal **218** with DIBAL-H, is described in **Scheme 52**. Tetrahydropyran **219** was obtained in 93% yield.[100]

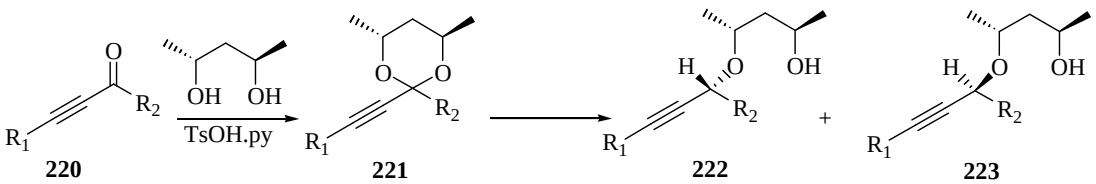
Scheme 52. Reductive Cleavage Using DIBAL-H.



Enantioselective reduction of propargylic ketones have been of wide interest. The optically pure propargylic alcohols are valuable synthetic intermediates and can be used for example for the synthesis of insect pheromones or prostaglandins.[101]

Cleavage of acetals such as compounds **221** formed by reaction of a ketone **220** with (2*R*, 2*S*)-2,4-pentandiol is an effective method to obtain chiral alcohols after removal of the template. DIBAL-H or dibromoaluminium hydride can be used as hydride source. The yields obtained for ethers **222** and **223** were excellent, as well as the enantioselectivity (**Table 2**). In order to generate the chiral alcohols, the compounds could be treated by pyridinium chlorochromate followed by potassium carbonate.

Table 2. Chiral Reduction of Propargylic Ketones.

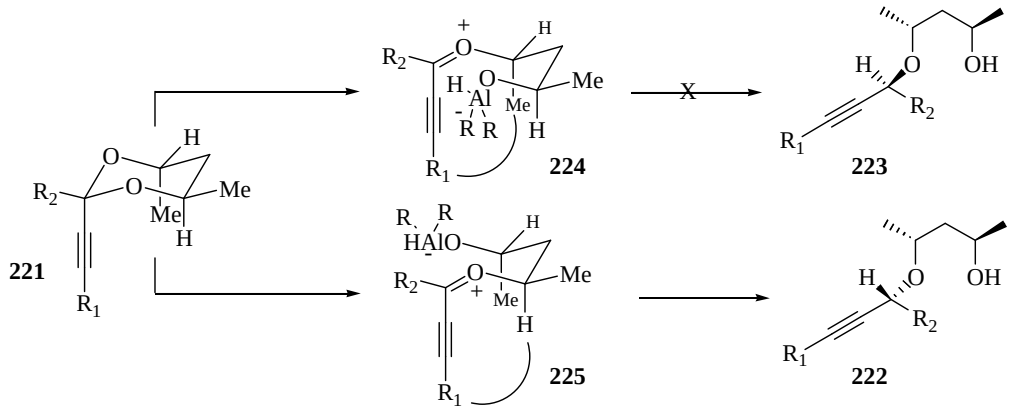


220 **221** **222** **223**

	Conditions		**Ratio**		**Yield**
R_1 = Bu R_2 = Me	DIBAL-H (6 eq., 0 °C, 1 h)	96	:	4	90%
	Br_2AlH (6 eq. -20 °C, 1 h)	93	:	7	100%
R_1 = Ph R_2 = Me	DIBAL-H (6 eq., 0 °C, 2 h)	90	:	10	86%
	Br_2AlH (6 eq. -20 °C, 2 h)	90	:	10	92%

The stereochemistry observed can be explained as follows.[102, 103] The acetylinic group, which is the smallest group is positioned in the axial position. In the presence of the aluminium reducing agent, cleavage of the acetal ring occurred to give intermediates **224** and **225** (**Scheme 53**). The formation of intermediate **224** is disfavoured due to the axial interaction between the methyl group and the acetylinic group and consequently only alcohol **222** is formed.[101]

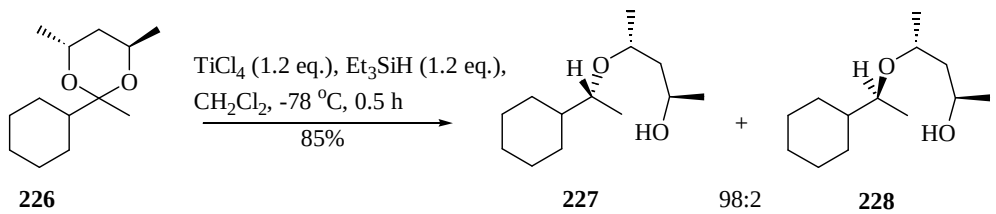
Scheme 53. Proposed Mechanism.



iv. Trialkylsilane Reagents in the Presence of a Lewis Acid.

Homochiral acetals formed for instance by reaction of a ketone with (2*R*, 4*R*)-2,4-pentandiol can also be reduced using hydride sources such as trialkylsilane and a Lewis acid.[104] As previously shown, after removal of the chiral template, optically active alcohols can be obtained. Acetal of 1-cyclohexyl-ethanone **226** could give alcohol **227** as the major product by reaction with titanium chloride and triethylsilane at -78 ^{o}C (**Scheme 54**).

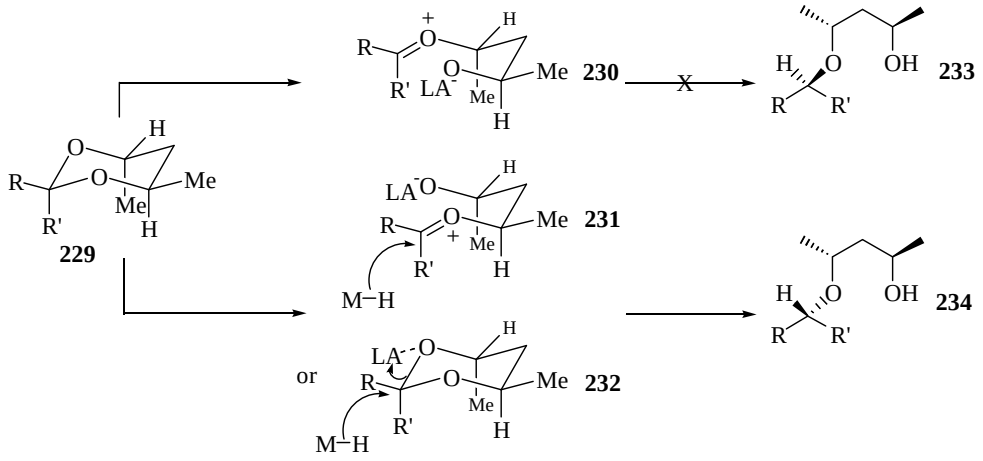
Scheme 54. Reduction of Homochiral Acetals with Triethylsilane and Titanium Chloride.



The proposed mechanism of this reaction is described in **Scheme 55**.[104] As previously shown, the formation of intermediate **230** is disfavoured due the axial repulsion between the methyl and R' groups and intermediates **231** and **232** formed preferably. An S_N2-like mechanism is also plausible and the Lewis acid is coordinated to the less hindered

oxygen atom (intermediate **232**). Finally, nucleophilic attack of the hydride source gives alcohol **234**. This methodology complements the one described in the previous part when DIBAL-H or dibromoaluminium hydride was used. Thus by the choice of the reducing reagent and with the use of only one ligand, it is possible to obtained both optically pure alcohols.

Scheme 55. Proposed Mechanism.

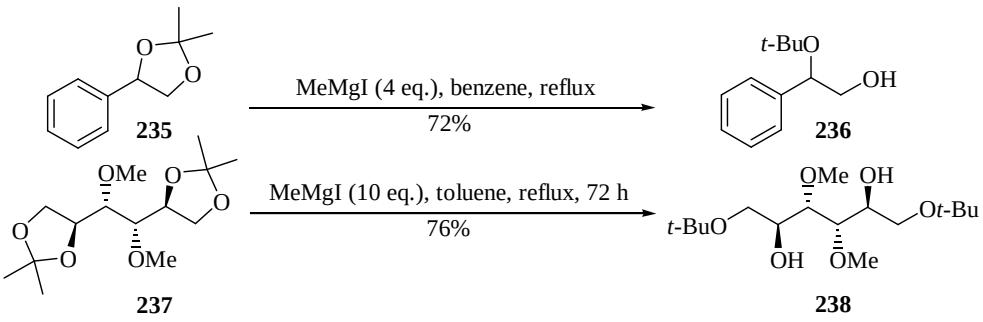


1.2.2.3 Reaction with Organometallic Reagents.

i. Reaction with Grignard Reagents.

Luh *et al*. reported the regioselective acetal opening of acetonides and *bis*-acetonides with methylmagnesium iodide in refluxing benzene or toluene.[105, 106] Coordination of the magnesium to the oxygen atomes in the case of the *bis*-acetonides **237** gave preferentially diols with the less hindered alcohol protected by a *tert*-butyl group **238**. Conversely, opening of the acetal ring in acetonides gave the corresponding hydroxy-alkyl ethers with the most hindered alcohols protected by a *tert*-butyl group **236** (**Scheme 56**). A similar regioselectivity was observed by Takano and Barton when ketals were reacted with trimethylaluminium in the following section.

Scheme 56. Reaction with Methylmagnesium Iodide.

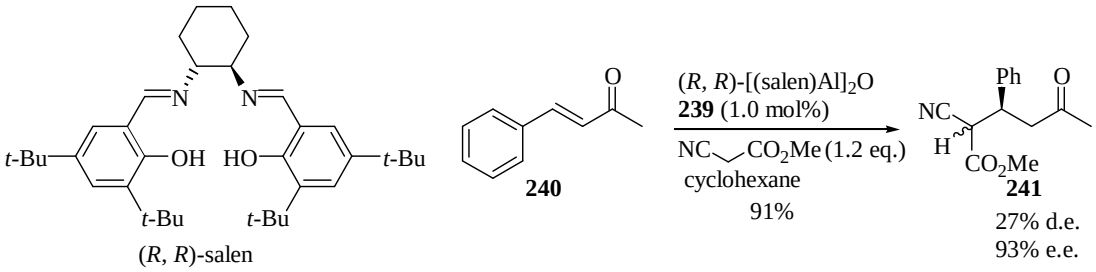


ii. Reaction with Organoaluminium Reagents.

* Organoaluminium Reagents: Properties and Possible Reactions.

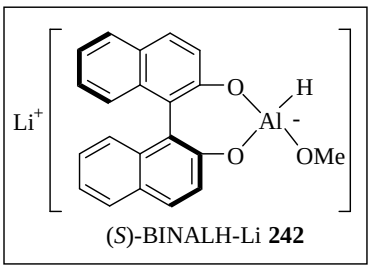
Organoaluminium reagents are strong Lewis acids and can coordinate strongly to oxygen and halogen atoms. They are useful chiral catalysts and have been recently used for instance by Jacobsen to perform conjugate addition of nucleophiles such as nitriles, nitroalkanes and hydrozoic acid to acyclic *α,β*-unsaturated ketones.[107] The catalyst $[(salen)Al]_2O$ **239** did not required inert atmosphere and was easily synthesised from the salen ligand and a solution of trimethylaluminium. In the example shown below in **Scheme 57**, methyl cyanoacetate attacked the *Re* face of the ketone **240** to give the product **241** in excellent yield and as a 1.7:1 mixture of diastereoisomers.

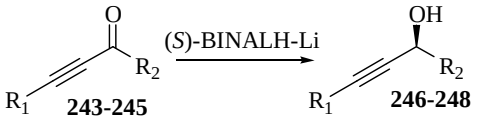
Scheme 57. Michael Addition Using an Aluminium Catalyst.



Modified lithium aluminium hydride reagents, such as BINALH-Li **242**, are very useful reagent and can perform efficiently chiral reduction of acetylenic ketones and *α,β*-unsaturated ketones to give the corresponding propargylic and allylic alcohols in good yield and with high enantioselectivity. The reduction of acetylenic ketones **243**-**245** and their corresponding products **246**-**248** are shown in **Table 3**[108]

Table 3. Reduction Using BINALH-Li.





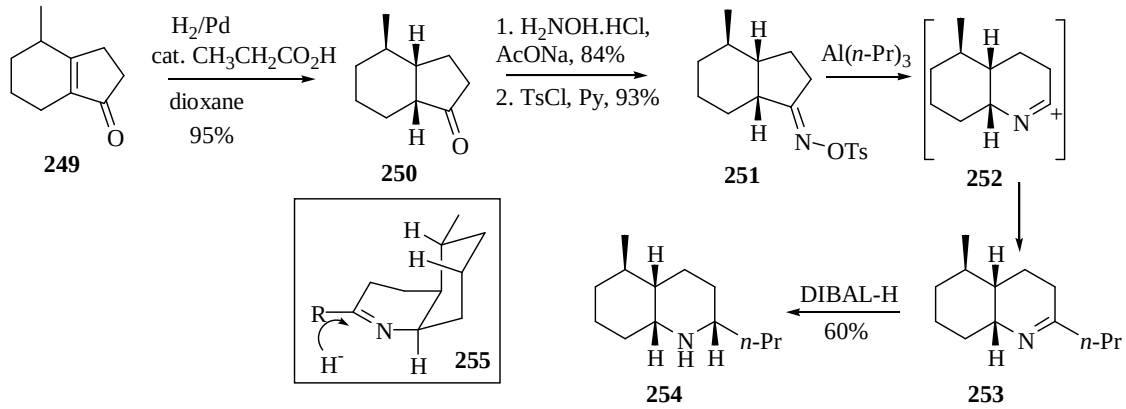
	R_1	R_2	e.e.	Yield
243	H	*n*-C_5H_{11}	84%	87%
244	H	*n*-C_8H_{17}	96%	80%
245	*n*-C_4H_9	*n*-C_5H_{11}	90%	85%

Organoaluminium reagents and especially trivalent aluminium reagents possess an ambivalent character. Due to their oxophilocity, they are excellent Lewis acid and can consequently very easily coordinate to substrates, which contain oxygen atoms. This

results in the formation of an ate complex and of a nucleophilic aluminium species, which can then react with the substrate. For instance, trialkylaluminium have been used as alkylating agents for ketones, epoxides and acetals.[109]

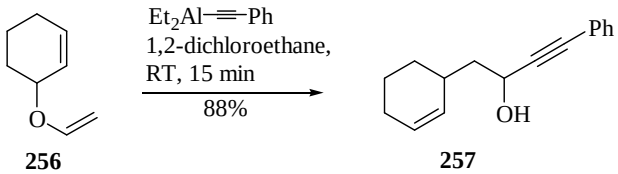
Because of their dual action, Lewis acidity and nucleophilicity, aluminium reagents have also been used to promote Beckmann rearrangement of oxime sulfonates. [110, 111] Yamamoto and co-workers reported the synthesis of racemic pumiliotoxin C, an alkaloid found in the skin of neotropical frogs, which belong to the family of Dendrobatidrae. The synthesis started with the hydrogenation of enone **249** using palladium black as catalyst and in the presence of propionic acid to give ketone **250** in 95% yield. The key step involved a Beckmann rearrangement of oxime sulfonate **251**, obtained in two steps from ketone **250**, using tripropylaluminium followed by reduction of the imine **253** with DIBAL-H. The attack of the hydride source occurred *via* the *exo* face (see **255**, **Scheme 58**).[110]

Scheme 58. Beckmann Rearrangement.



Claisen rearrangements followed by a nucleophilic attack to the carbonyl group formed *in situ* can be performed under mild condition when aluminium reagents are used.[110] As before, this shows the dual properties of aluminium species. It is possible to introduce methyl or ethyl substituents when using trimethyl or triethylaluminium as well as other alkenyl or alkynyl groups (**Scheme 59**).[112] For instance the aluminium species shown in **Scheme 59** can be synthesised from diethylaluminium chloride and lithium phenyl acetylene.

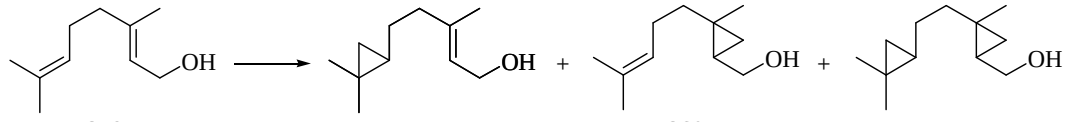
Scheme 59. Claisen Rearrangement.



More recently, Maruoka *et al*. developed methodology to perform chiral Claisen reaction using a chiral *bis*(organoalumium) Lewis acid.[113]

Aluminium reagents and especially tri*iso*butyl aluminium in the presence of iodomethane can undergo cyclopropanation of alkenes. The reaction proved to be regioselective and gave opposite results (cyclopropane **259**) than under the Simmons-Smith conditions (cyclopropane **260**) (**Scheme 60**). It should be noted that di*iso*butyl iodide was isolated. This suggested the formation of di*iso*butyl(iodomethyl)aluminium during the reaction.[114]

Scheme 60. Cyclopropanation.



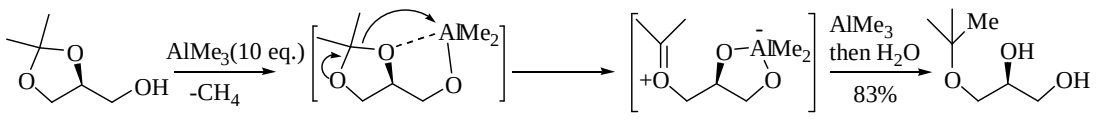
258 **259** **260** **261**

i-Bu_3Al/CH_2I_2	76	:	1	:	4
$ZnEt_2/CH_2I_2$	2	:	74	:	3

* Reaction with Acetals.

Reaction of acetals with trialkylaluminium is again another example, which illustrates the ambivalent property of aluminium reagents. Takano and co-workers showed that acetals with an adjacent oxygen atom could undergo a regioselective nucleophilic cleavage by trimethylaluminium.[115] Trimethylaluminium reacts first with the free alcohol **262** to give alkoxide **263** shown in **Scheme 61**. The aluminium metal can then coordinate to the internal oxygen atom of the acetal due to its close proximity. This leads to the regioselective cleavage of the ring and the generation of an oxonium species **264**. Finally after delivery of a nucleophilic methyl, diol **265** could be obtained.

Scheme 61. Reaction with Trimethylaluminium.

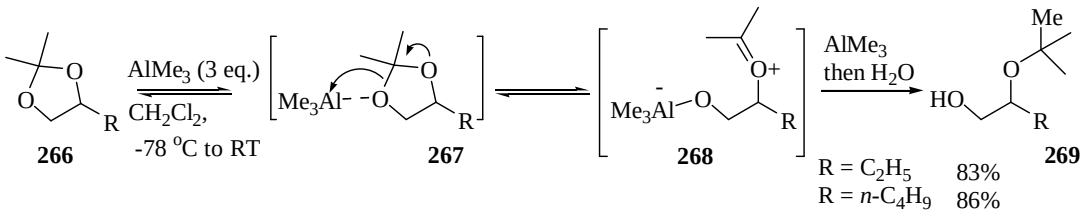


262 **263** **264** **265**

On the other hand, if there is no internal coordination such as in starting material **266** (**Scheme 62**), then trimethylaluminium coordinates to the less hindered oxygen atom of the acetal as in intermediate **267**. This leads to the cleavage of the acetal by the internal

oxygen atom (intermediate **268**) and as before after nucleophilic attack of the aluminium species the more substituted ether **269** is obtained.[116] Therefore, the regiochemistry of the reaction of an acetal with aluminium reagent is similar to the reaction of acetals with Grignard reagents (see **Section 1.2.2.3**).

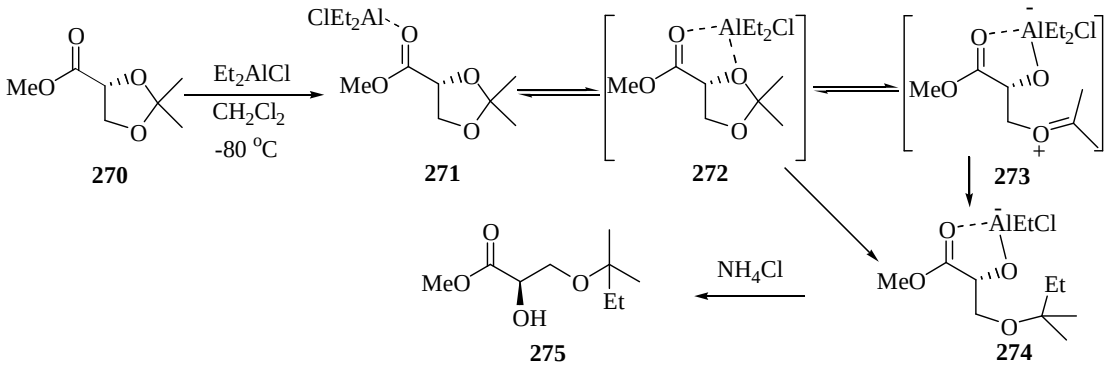
Scheme 62. Reaction with Trimethylaluminium.



266 **267** **268** **269**

Other organoaluminium reagents can be used to perform this reaction. For example, Castellino and co-workers reported the use of diethylaluminium chloride.[117] As before, the chelation controlled reaction furnished the least hindered ether **275**. In addition, NMR studies of this reaction showed the formation of the five-membered chelate **272** as well as the oxonium ion **273**. Nevertheless, it was not possible to determine if the reaction mechanism occurred *via* a four-membered transition state from **272** (S_N2 like mechanism) or *via* a seven-membered transition state involving the oxonium species **273** (S_N1 mechanism).

Scheme 63. Proposed Mechanism.



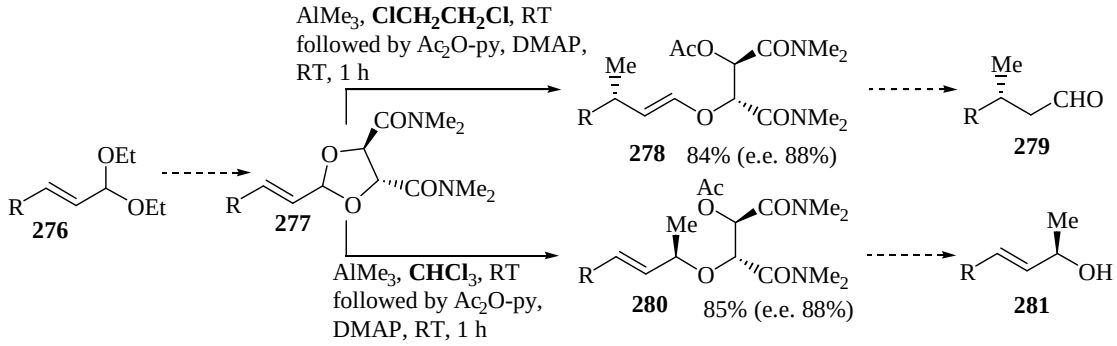
270 **271** **272** **273** **274** **275**

* *α,β*-Unsaturated Acetals.

α,β-Unsaturated acetals are interesting substrates, which can, depending on the reaction conditions, react with organoaluminium reagents at the *α* or *γ*-position.[118, 119] The reaction is consequently regioselective but also stereoselective if chiral acetals are employed. Chiral acetal **277** could be obtained by transacetalisation of *α,β*-unsaturated

diethyl acetal **276** with (*R*,*R*)-*N*,*N*,*N'*,*N'*-tetramethyltartaric acid diamide. Reaction with trimethylaluminium proved to be highly dependant of the solvent and temperature. When the reaction was performed in 1,2-dichloroethane at room temperature with trimethylaluminium (5 equivalents), and after acetylation with acetic anhydride and pyridine compound **278** was isolated in 84% yield and with an enantiomeric excess of 88%. The 1,2-adduct was obtained in 13% yield. However, when the reaction was carried out in chloroform and under similar conditions, only the 1,2-adduct **280** was obtained in 85% yield and with an enantiomeric excess of 88% (**Scheme 64**). After removal of the chiral template, this could lead to the formation of β-substitued chiral aldehyde **279** and chiral allylic alcohol **281**.

Scheme 64. Reaction of *α*,*β*-Unsaturated Acetal with Trimethylaluminium.

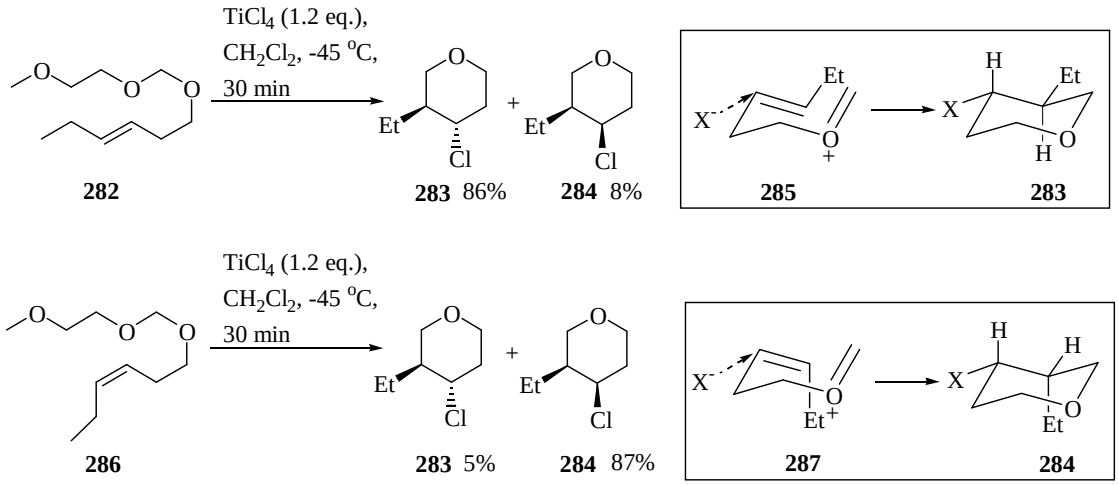


1.2.2.4 Coupling Reactions in the Presence of a Lewis Acid.

i. Lewis Acid Mediated Acetal-Alkene Cyclisation.

Alper *et al*. reported the stereospecific synthesis of tetrahydropyrans by reaction of alkene-acetals with Lewis acids such as titanium (IV) chloride or titanium (IV) bromide.[120] The *trans*-alkene **282** gave predominately the *trans*-tetrahydrofuran **283** while the *cis*-alkene **286** afforded the *cis*-heterocyclic ring **284** as the major product (**Scheme 65**). The stereoselectivity observed can be rationalised by the fact that the carbon-carbon bond formation occurred *via* a six-membered ring transition state (see intermediates **285** and **287**).

Scheme 65. Formation of Tetrahydropyran by Lewis Acid Mediated Acetal-Alkene Cyclisation.



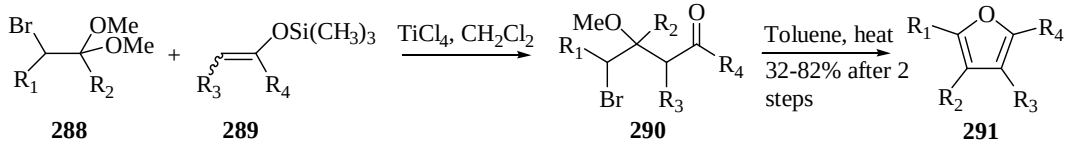
A similar strategy has been used for the synthesis eight-membered cyclic ethers, which are important structural motifs found for example in marine natural products such as brevetoxin A and laurencin.[121]

ii. Coupling Using Organosilane Reagents.[122]

* Aldol Reaction.

Dimethyl acetals **288** can undergo aldol reaction when treated with titanium (IV) chloride and silyl enol ether **289**.[123] The strong affinity of titanium with oxygen atom allowed the formation of the oxonium species, which subsequently reacted with the nucleophilic silyl enol ether. Upon heating, the γ-bromo ketones **290** generated from the aldol reaction could be converted into tetrasubstituted furans **291** (**Scheme 66**).

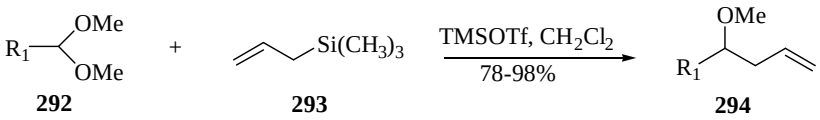
Scheme 66. Aldol Reaction.



* Alkylation.

Acetals can also be alkylated using allyl silane reagents (for instance, **293**). In order to generate the oxonium ion, Lewis acids such titanium tetrachloride or boron trifluoride etherate can be used. The reaction can also be performed using catalytic amount of trimethylsilyl trifluoromethansulfonate (**Scheme 67**), iodotrimethylsilane or tritylperchlorate or diphenylboryl triflate.[124, 125, 126]

Scheme 67. Alkylation.



292 **293** **294**

1.2.3 CONCLUSION.

Acetals are very versatile functional groups. They are stable for example to strong reducing agents, but on the other hand, they can be easily cleaved under mild acidic conditions. They are consequently widely used as diols or carbonyls protecting groups. More recently, the chemistry of acetals started to emerge, giving access to interesting applications, such as for example the chiral reduction of ketones using homochiral acetals as seen in **Section 1.2.2.2**.

Chapter 2 | RESULTS & DISCUSSION

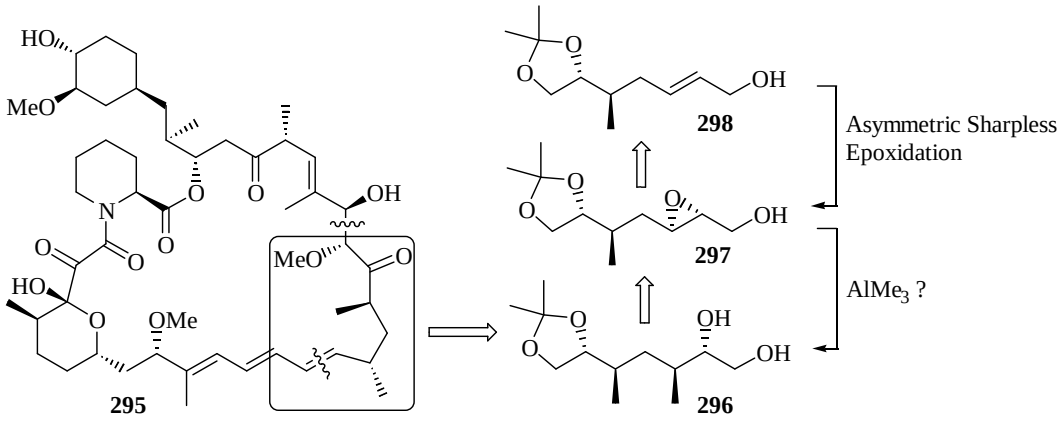
As seen in **Chapter 1**, due to their ambivalent properties, organoaluminium reagents can easily coordinate and subsequently react with acetals by transferring alkyl groups. We wish to report the development of a novel method for the synthesis of stereodefined heterocyclic rings, which could be used for the synthesis of natural products containing tetrahydrofurans, such as, for example, members of the pamamycin family. This novel cascade reaction involved the reaction of acetals with trialkylaluminium reagents, which was subsequently followed by a cyclisation reaction, consequently generating tetrahydrofuran (**Section 2.1**) or tetrahydropyran rings (**Section 2.2**). In addition, investigation towards the synthesis of pyrrolidines was also carried out and is summarised in **Section 2.3**.

2.1 SYNTHESIS OF STEREODEFINED TETRAHYDROFURANS.

2.1.1 PREVIOUS WORK AND AIM WITHIN THIS THESIS.

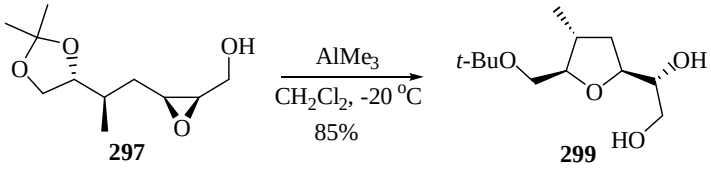
Previous work within the Parsons group towards the total synthesis of rapamycin **295**, also known as Sirolimus, a new immunosuppressant drug used to prevent rejection of organ transplant,[127] led to the discovery of some interesting results. It was hoped that synthesis of the bottom right part of rapamycin (boxed in **Scheme 68**) could be achieved by protecting group manipulations and functional group interconversions of fragment **296**.[128] This intermediate could be synthesised by a nucleophilic attack onto the epoxide group of epoxide **297**. Aluminium reagents have previously been employed to open epoxides[109] and as a result, trialkylaluminium seemed to be the reagent of choice to perform this reaction.

Scheme 68. Rapamycin **295**.



However, reaction of epoxy-acetal **297** with trimethylaluminium did not lead to the formation of diol **296** and, on the contrary tetrahydrofuran **299** was isolated in excellent yield and with control of all the stereocentres (**Scheme 69**).[129] As seen in **Chapter 1**, the control of the stereoselectivity can be a task difficult to achieve, and developing high selective methodologies is essential for the synthesis of natural products.

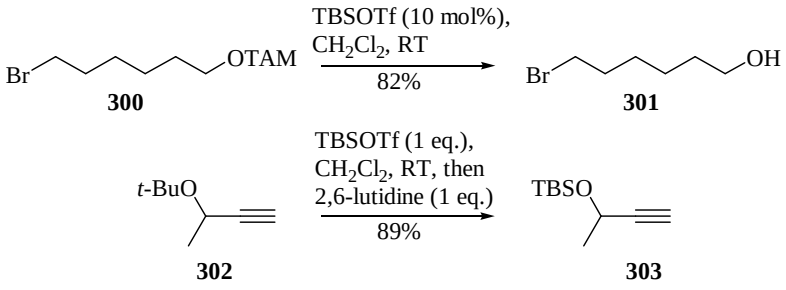
Scheme 69. Formation of Tetrahydrofuran **299**.



As seen in **Scheme 69**, tetrahydrofuran **299** possesses a *tert*-butyl ether and a 1,2-diol group, each being useful functionalities as synthetic handles in synthetic organic chemistry. A diol functionality can for instance be oxidatively cleaved to generate an aldehyde, which can then be further olefinated using phosphorus ylide reagents or reacted with Grignard reagents. In addition, *tert*-butyl group is an excellent protecting group for alcohols, being liberated to the corresponding alcohol by treatment with mild acid.

Figadère and co-workers showed that *tert*-butyl and *tert*-amyl groups could be cleaved under mild conditions.[130] Treatment with a catalytic amount of *tert*-butyldimethylsilyl triflate in dichloromethane at RT, could deprotect *tert*-butyl or *tert*-amyl groups (TAM) of protected alcohol **300** to give the corresponding free alcohols **301**. When one equivalent of *tert*-butyldimethylsilyl triflate was used in the presence of a base, 2,6-lutidine, the alcohol generated from the *t*ert-butyl ether **302** was subsequently protected as the corresponding TBS ether **303** (**Scheme 70**). The TAM protecting groups could be installed by reaction of the free alcohol with 2-methylbut-1-ene and a catalytic amount of boron trifluoride etherate in dichloromethane and at RT.[130]

Scheme 70. *tert*-Butyl and *tert*-Amyl Deprotections.



As a result, both sides of tetrahydrofuran **299** can be selectively extended through functional group interconversions and consequently, if this methodology could be further developed, this would give access to valuable building blocks for the synthesis of more complex tetrahydrofuran containing natural products.

Therefore, the aim of the project was to develop methodology for the synthesis of stereodefined heterocyclic rings such as tetrahydrofurans, tetrahydropyrans and pyrrolidines, based on the initial results obtained within the Parsons group (**Scheme 69**). Formation of stereodefined tetrahydrofurans was first focussed upon, and the developed

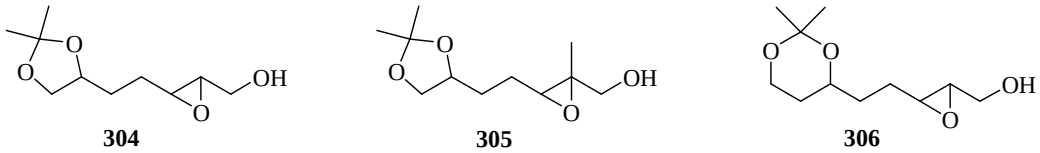
methodology was then employed for the synthesis of tetrahydropyrans (**Section 2.2**) and pyrrolidines (**Section 2.3**)

2.1.2 SYNTHESIS OF THE PRECURSORS.

2.1.2.1 Initial Target Molecules and Retrosyntheses.

In order to examine the scope and limitations of this cascade reaction, a range of epoxy-acetals were synthesised. Epoxy-acetal **304** was chosen, as without any substituents, it was the simplest of the possible precursors on which to develop this chemistry on. To supplement the initial study trisubstituted epoxide **305** as well as epoxy-1,3-acetal **306** were selected as target precursors (**Figure 6**).

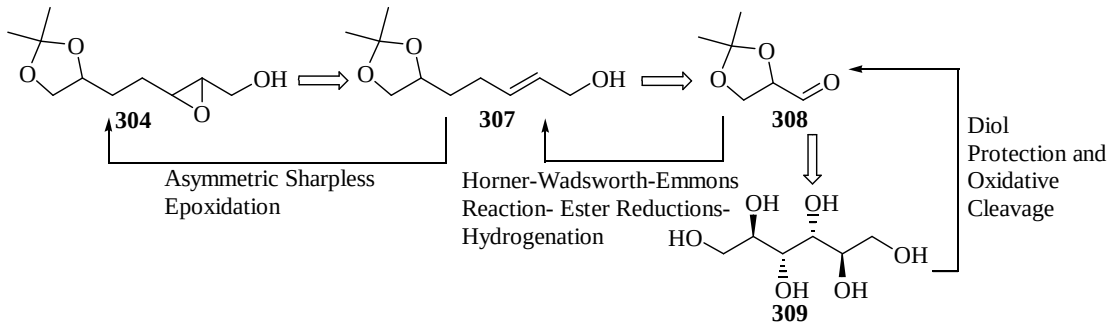
Figure 6. Initial Target Molecules.



Compound **304** had been previously synthesised by the group of Ley, and it was decided to use their synthesis as a guideline.[131, 132]

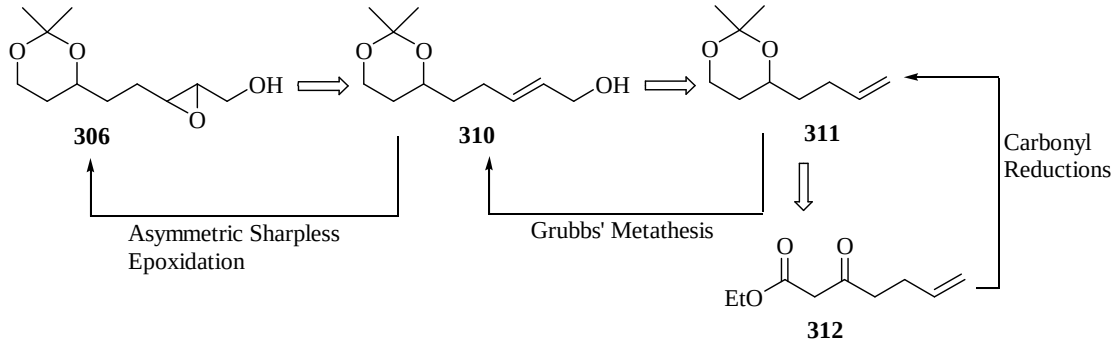
Compounds **304** and **305** could be synthesised from protected glyceraldehyde **308**, which in turn could be prepared from D-mannitol **309**, a cheap, already available and enantiopure starting material (**Scheme 71**). Extension of the chain to give allylic alcohol **307**, could be obtained by carrying out the following transformations from aldehyde **308**: a Horner-Wadsworth-Emmons olefination using triethyl phosphonoacetate and sodium hydride,[133-134] an alkene hydrogenation, an ester to aldehyde reduction, again an olefination using the same conditions and finally an ester to alcohol reduction. Finally, the epoxide moiety could then be introduced using the Sharpless asymmetric epoxidation procedure,[135] to afford the desired target precursors with high enantiomeric excess.

Scheme 71. Epoxy-Acetal **304**: Retrosynthetic Analysis.



Similarly, the epoxide group of epoxy-acetal **306** could be introduced using the Sharpless asymmetric epoxidation procedure on allylic alcohol **310**. The latter compound could have been obtained by a cross-metathesis reaction[136] between alkene **311** and methyl acrylate followed by an ester reduction. Finally, the 1,3-dioxane group could be obtained by a double reduction of the ketone and ester groups of keto-ester **312**. In addition, compound **306** could also be obtained as a single enantiomer if a chiral reduction of the ketone moiety was to be performed (a set of conditions known for the chiral reduction, see **Section 2.1.2.4**)[137].

Scheme 72. Epoxy-Acetal **306**. Retrosynthesis Analysis.

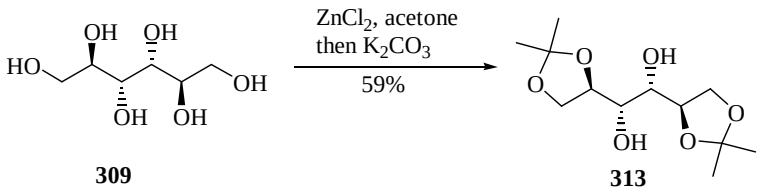


2.1.2.2 Synthesis of Epoxy-Acetals 304 and 305.

i. Formation of Protected Glyceraldehyde **308** from D-Mannitol **309**.

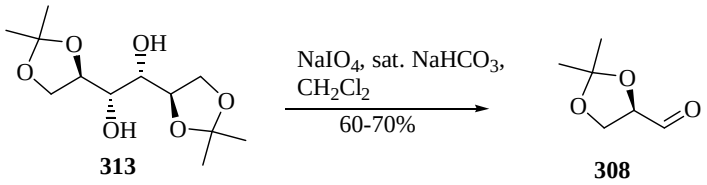
Protection of D-mannitol **309** was achieved by refluxing compound **309** in 2,2-dimethoxypropane and dimethyl ethylene glycol and in the presence of a catalytic amount of tin(II) chloride and pyridine.[138] However, it was observed by ^{1}H NMR analysis that *tris*-acetalisation of D-mannitol **309** occurred and that the corresponding product was difficult to remove from the desired product **313**. Higher purity of the desired product **313** was obtained when D-mannitol was treated with a saturated solution of anhydrous zinc chloride in acetone.[139] After a work-up with potassium carbonate and recrystallisation from dichloromethane and petroleum ether, *bis*-acetal **313** was afforded in 59% yield and as a white solid (**Scheme 73**).

Scheme 73. Protection of D-Mannitol **309**.



Cleavage of diol **313** with sodium *meta*-periodate in THF/water afforded the desired aldehyde **308** in 82% yield (crude) on a 5 g scale.[140] On a 25 g scale, the crude yield tended to decrease dramatically and aldehyde **308** was generally obtained in 10-40% yield. Using this method, we found issues with reproducibility between reaction runs. Cleavage of diol **313** could also be achieved with sodium *meta*-periodate in CH_2Cl_2 or diethyl ether and water in presence of silica.[141] However, aldehyde **308** was still obtained in a moderate yield of 40%. Finally, the best result was achieved when diol **313** was treated by sodium *meta*-periodate in dichloromethane and in the presence of sodium hydrogen carbonate, and after purification by distillation, aldehyde **308** could be isolated in 60-70% yield (**Scheme 74**).[142] Under these conditions, the reaction was reliable, even on large scale synthesis (the reaction was tested on a 30 g scale).

Scheme 74. Cleavage of Diol **313**.



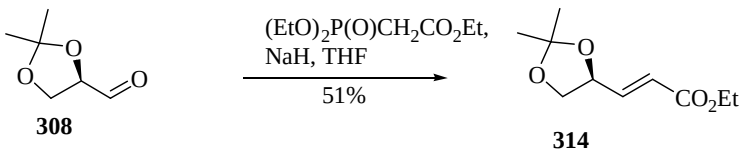
313 **308**

Although aldehyde **308** was stable, it was usually reacted straightaway to avoid decomposition and/or racemisation. The next steps of the synthesis consisted in elongating the chain of four carbons and are described in the following sections.

ii. Olefination of Aldehyde **308** and Hydrogenation.

Using the Horner-Wadsworth-Emmons reaction, olefination of the glyceraldehyde derivative **308** was carried out. The phosphorus ylide was initially formed by deprotonation of triethyl phosphonoacetate with sodium hydride (60% *w/w* in mineral oil) in dry THF at 0 ^{o}C and a solution of aldehyde **308** was then added to the reaction mixture. The corresponding ester **314** was afforded in 51% yield and mainly as the *trans*-isomer (**Scheme 75**).[133, 134]

Scheme 75. Reaction of Aldehyde **308** with Triethyl Phosphonoacetate.



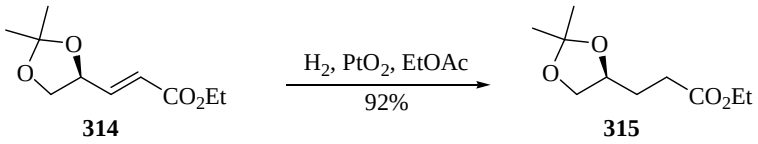
308 **314**

Ester **314** could also be obtained, when reacted with (carbothoxymethylene)-triphenylphosphorane in dichloromethane at RT, in a yield of 68% and as 1:1.2 mixture

of *cis* and *trans*-isomers.[131, 132] Stabilised phosphorus ylides when reacted with aldehydes under the Wittig conditions, usually produce *E*-alkenes. However, the presence of the chiral centre in the case of aldehyde **308** favoured the formation of the *cis*-alkene. Finally, it should be noted that no defined stereochemistry was required at this point, as hydrogenation of the double bond would remove this stereochemistry information.

Thus, ester **314** was treated with platinum (IV) oxide in ethyl acetate in a flask fitted with a balloon of hydrogen at RT for 20 h.[131] The corresponding saturated ester **315** was afforded in 92% yield (**Scheme 76**).

Scheme 76. Hydrogenation of Unsaturated Ester **315**.



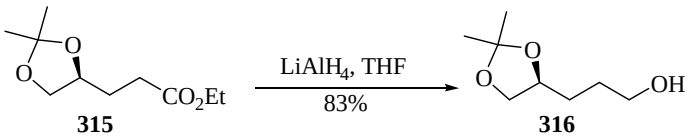
314 **315**

iii. Formation of Ester **318**.

Several routes were tested in order to synthesise ester **318** as a key precursor for the synthesis of the epoxy-acetals required for the development of this new chemistry. Ester **315** was either reduced to the free alcohol **316**, oxidised to the corresponding aldehyde **317** and then further olefinated, or alternatively ester **315** was reduced directly to the aldehyde **317** before being olefinated as before. Although the three step route gave better overall yield, in this synthesis, the second route was preferred as it was more convenient (shorter reaction time and easy purification) even if the desired ester **318** was afforded in a lower overall yield (24% *versus* 38%). Problems were encountered during the oxidation step and, although this was overcome by using the second route, we gained insight on the chemistry of these compounds, which proved to be useful later on for the synthesis of similar substrates. Hence for that reason, both routes will be described.

Starting with the first route, ester **315** was reduced using lithium aluminium hydride in dry THF to give alcohol **316** in 83% yield.[131]

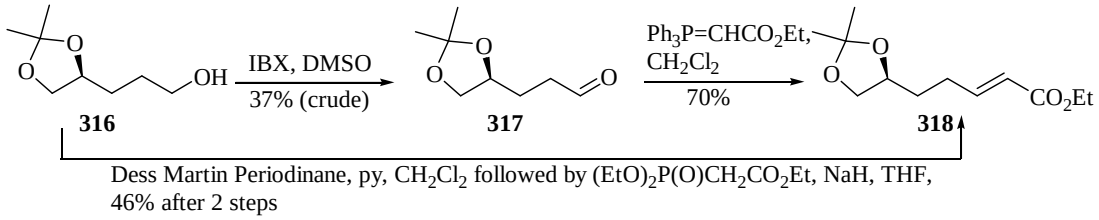
Scheme 77. Reduction of Ester **315** with Lithium Aluminium Hydride.



315 **316**

Oxidation of alcohol **316** with IBX in DMSO afforded the corresponding aldehyde **317** in a disappointing yield of 37% (yield of the crude material).[131] Aldehyde **317** was not purified and subsequently olefinated using (carbothoxymethylene)triphenylphosphorane to give ester **318** in 70% yield. Alcohol **316** could be also oxidised using the Dess-Martin periodinane in the presence of pyridine in dichloromethane to give aldehyde **317**, which was subsequently reacted without any purification with triethyl phosphonoacetate and sodium hydride in dry THF to afford ester **318**, as the *trans*-isomer only, in 46% yield after two steps (**Scheme 78**).

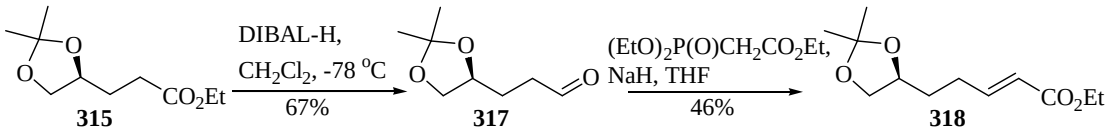
Scheme 78. Oxidation of Alcohol **316** Followed by Olefination.



As can be seen, the IBX reagent afforded aldehyde **317** in a disappointing yield, but could be improved through the use of the Dess-Martin periodinane. However, the use of pyridine and also the cost of the Dess-Martin periodinane reagent were the major drawbacks to this reaction and, as a result, these two methods were abandoned and, instead, a two-step in one transformation was employed.

Therefore, reduction of ester **315** using DIBAL-H (1 M, hexanes) in dichloromethane and at -78 ^{o}C afforded aldehyde **317** in 67% yield after purification by flash column chromatography. Ester **318** was then obtained in 46% yield and as the *trans*-isomer using the Horner-Wadsworth-Emmons procedure (**Scheme 79**).[133, 134]

Scheme 79. DIBAL-H Reduction Followed by Horner-Wadsworth-Emmons Olefination.

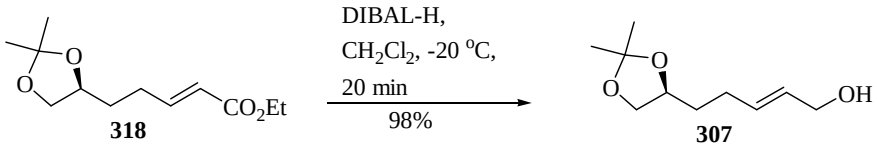


iv. Formation of Epoxy-Acetals **304a**/**b**.

Ester **318** was reduced using DIBAL-H (1 M, hexanes) in dry dichloromethane (-20 ^{o}C to RT, 3 h) and the corresponding alcohol **307** was obtained in 57% yield.[131] The yield

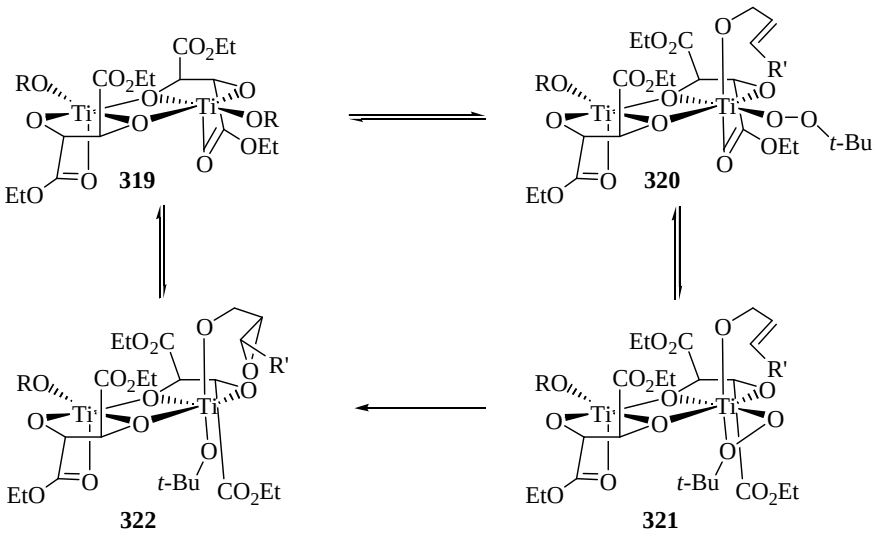
of the reaction was improved when ester **318** was reduced at -20 ^{o}C for 20 minutes and allylic alcohol **307** was afforded in 98% yield (**Scheme 80**).

Scheme 80. Reduction of Ester **318** Using DIBAL-H.



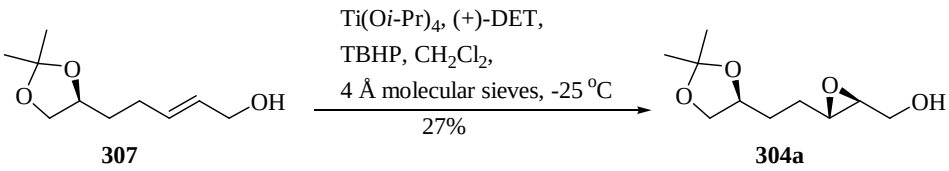
Finally, the desired epoxy-acetals were synthesised by utilising the Sharpless asymmetric epoxidation methodology using catalytic titanium (IV) isopropoxide, (+)-diethyl tartrate or (-)-diisopropyl tartrate, a solution of *tert*-butyl hydroperoxide in dichloromethane and in the presence of activated 4 Å molecular sieves.[135] The Sharpless epoxidation is an enantioselective reaction, which produces the corresponding epoxides with high e.e.. The catalyst has a dimeric structure (structure **319**) as shown in **Scheme 81**. The mechanism of the reaction can be described as follows: there is first a ligand exchange with the allylic alcohol and *tert*-butyl hydroperoxide to give intermediate **320**. This is then followed by activation of *tert*-butyl hydroperoxide and the transfer of an oxygen atom with liberation of the product and regeneration of the catalyst **319** (see **Scheme 82**).[143, 144]

Scheme 81. Asymmetric Sharpless Epoxidation.



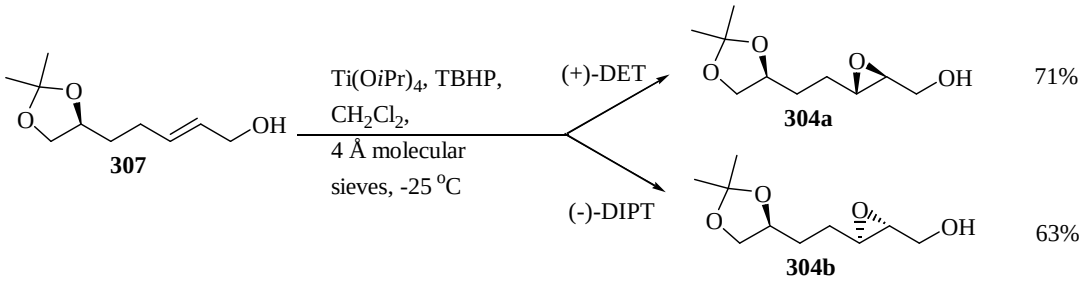
As a result, following the literature procedure, the desired epoxy-acetal **304a** was afforded in 27% (**Scheme 82**).[135]

Scheme 82. Sharpless Asymmetric Epoxidation.



The reaction was sluggish, affording the corresponding epoxide in low yield. This was probably due to a wet solution of *tert*-butyl hydroperoxide in dichloromethane, which consequently deteriorated the titanium complex and led to the recovery of the stating material. In addition, the product seemed to be sensitive to the work-up conditions. In the case, of compound **304a**, a mixture of iron sulfate and tartaric acid were used, followed by dilute sodium hydroxide in brine. However, it is believed that the acetal groups of the starting material and product were cleaved when the compounds were treated with tartaric acid and hence the low yield observed for compound **304a**. As a result, the crude material was only treated with iron sulfate in order to remove the excess of *tert*-butyl hydroperoxide. The products were easily purified from the ligands and the unreacted starting material by flash column chromatography. As a result, the desired epoxy-acetals **304a** and **304b** were afforded in 71% and 63% when treated with (+)-DET and (-)-DIPT, respectively (**Scheme 83**).

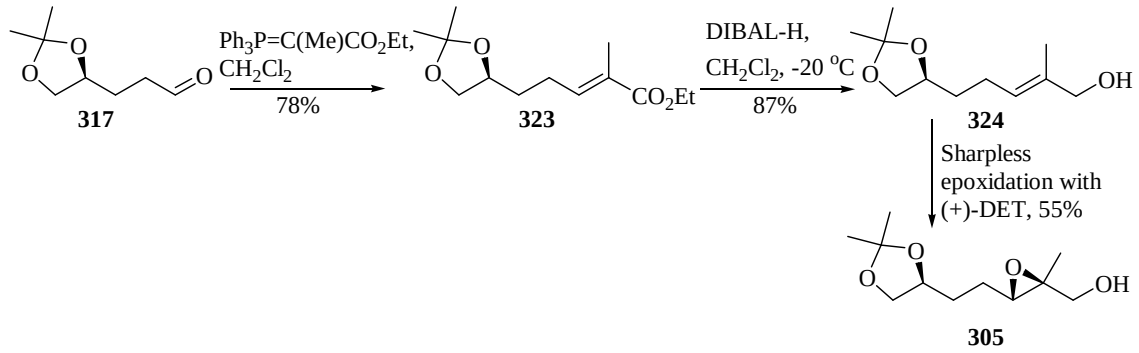
Scheme 83. Asymmetric Sharpless Epoxidations with a Modified Work-Up Procedure.



2.1.2.3 Synthesis of Epoxy-Acetal 305.

Following the same strategy for the synthesis of epoxy-acetals **304a**/**b**, aldehyde **317** was reacted with 1-carbethoxyethylidene triphenylphosphorane to give ester **323** in 78% yield. Reduction of the ester group with DIBAL-H (1M, hexanes) gave allylic alcohol **324** in 87% yield, which was then subjected to the Sharpless asymmetric epoxidation procedure using (+)-DET to give the corresponding epoxy-acetal **305** in 55% yield (**Scheme 84**).

Scheme 84. Synthesis of Epoxy-Acetal **305**.

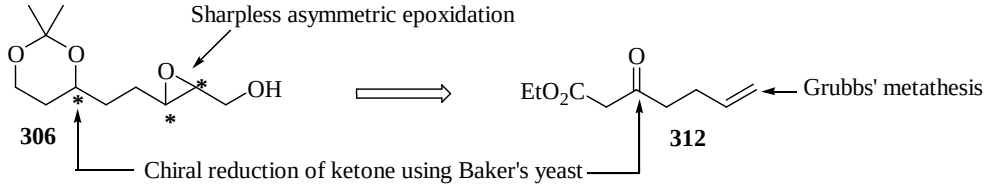


2.1.2.4 Synthesis of 1,3-Epoxy-Acetal 306.

i. Introduction.

As previously described in **Section 2.1.2.1**, the key steps of this reaction are: a cross coupling metathesis, a Sharpless asymmetric epoxidation and chiral reduction of the ketone group. The retrosynthesis is summarised in **Scheme 85**.

Scheme 85. Retrosynthetic Analysis of Epoxy-1,3-Acetal **306**.

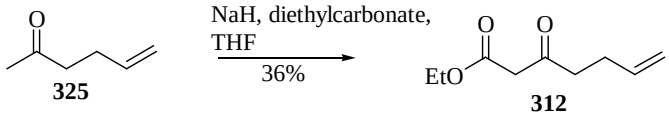


ii. Synthesis of Keto-Ester **312**.

* *Via* a Claisen Condensation.

Keto-ester **312** can be synthesised *via* a Claisen condensation. Reaction of hept-5-en-2-one **325** with diethyl carbonate and sodium hydride (60% *w*/*w* in mineral oil) afforded the product **312** in 36% yield (**Scheme 86**).[145]

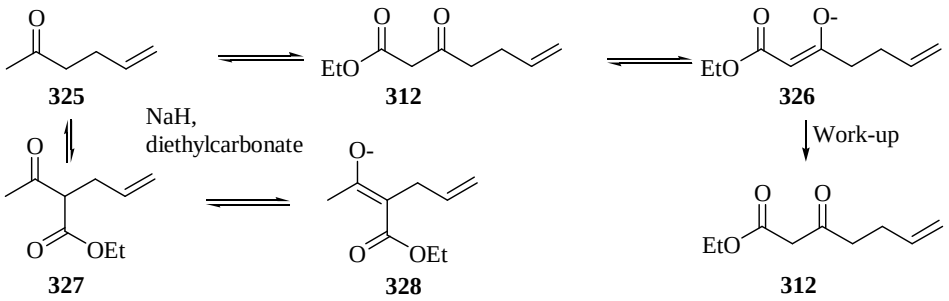
Scheme 86. Claisen Condensation.



The mechanism of the reaction is described in the **Scheme 87** and is as follows: sodium hydride can deprotonate the protons α to the ketone generating two possible anions. They both can react with diethyl carbonate to give the intermediates **312** and **327** and can also enolise to give compounds **326** and **328**. Because of the double bond, all the substituents have to fit in the same plane, and enolate **326**, which is less hindered than

enolate **328** is consequently the most stable. The reaction is therefore displaced in favour of the formation of the less substituted compound **312**.

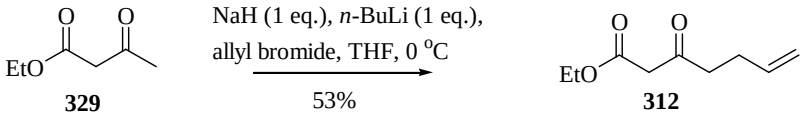
Scheme 87. Mechanism of Formation of Keto-Ester **312**.



* *Via* the Formation of the Dianion.

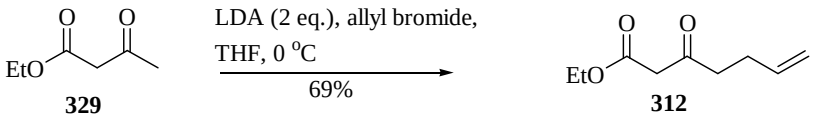
Keto-ester **312** can be also synthesised by reaction of ethyl acetoacetate **329** with sodium hydride followed by *n*-BuLi and reaction with allyl bromide.[146] This gave the product **312** in 53% yield (**Scheme 88**). The first equivalent of base (one equivalent of sodium hydride (60% *w*/*w* in mineral oil)) deprotonates the most acidic proton (proton in α to the ester moiety) and the second equivalent of base (one eq. of *n*-BuLi) deprotonates the methyl group to give the corresponding dianion, which is characterised by formation of an orange solution. The latter anion formed is the most reactive and is quenched by the addition of allyl bromide and consequently to generate the corresponding keto-ester **312**.

Scheme 88. Synthesis of Keto-Ester **312**.



Finally, the best result was obtained when two equivalents of LDA were used as base and compound **312** was afforded in 69% yield (**Scheme 89**).[147]

Scheme 89. Deprotonation with LDA.

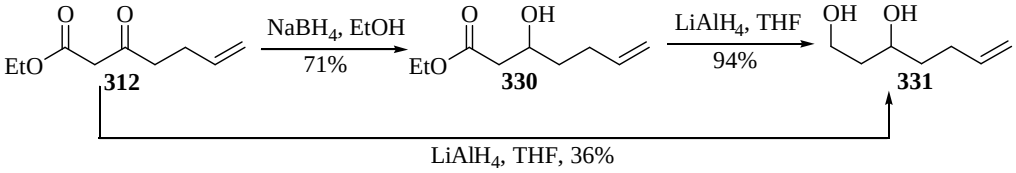


iii. Racemic Synthesis of Epoxy-Acetal **306**.

The synthesis of epoxy-acetal **306** was first tested and optimised on the racemic material. Thus, reduction of keto-ester **312** with lithium aluminium hydride under

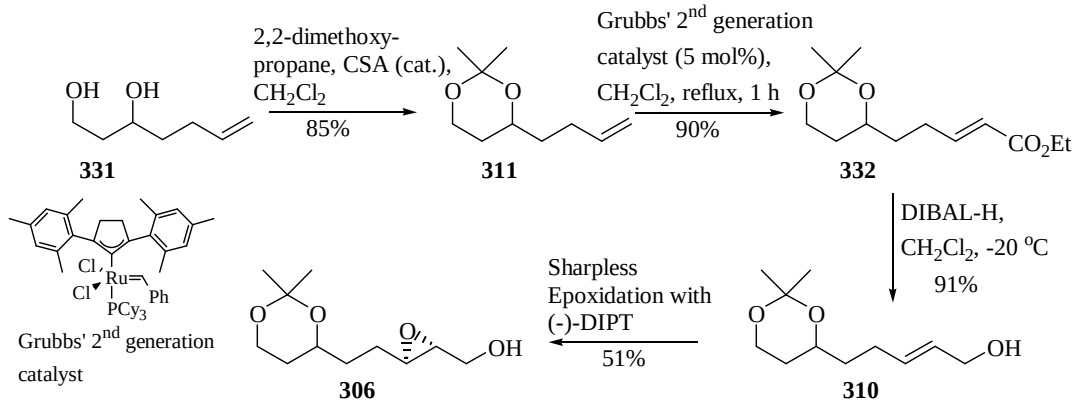
standard procedure gave diol **331** in 36% yield.[148] The formation of diol **331** was improved by using a two-step procedure: reduction of the ketone moiety of keto-ester **312** with sodium borohydride, followed by reduction of the ester moiety with lithium aluminium hydride and the corresponding diol **331** was afforded in 67% yield after two steps (**Scheme 90**).[148]

Scheme 90. Synthesis of Diol **331**.



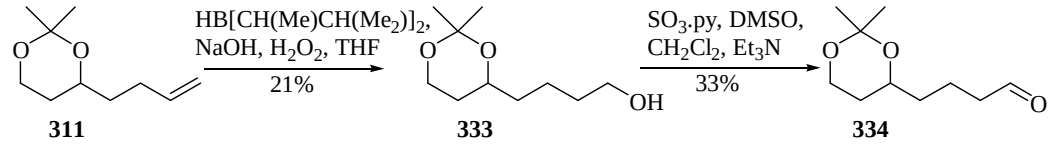
Diol **331** was then protected with an acetal group using 2,2-dimethoxypropane and a catalytic amount of camphorsulfonic acid in dichloromethane.[149] Acetal **311** was afforded in 85% yield. A Grubbs metathesis, using the second generation catalyst and ethyl acrylate was carried out and ester **332** was afforded in 90% yield.[133, 150] Finally, reduction with DIBAL-H gave allylic alcohol **310** in 91% yield, which was then subjected to a Sharpless asymmetric epoxidation to give the desired epoxy-acetal **306** in 51% yield (**Scheme 91**).

Scheme 91. Synthesis of Epoxy-Acetal **306**.



Hydroboration of alkene **311** using disiamylborane in THF with NaOH and H_2O_2,[151] followed by a Parikh-Doering oxidation[152] of alcohol **333** with SO_3-pyridine with Et_3N in DMSO/CH_2Cl_2 were performed in order to explore the possible formation a precursor for the synthesis of tetrahydropyrans (**Scheme 92**). These reactions were, however, not optimised.

Scheme 92. Chain Extension of Alkene **311** by Hydroboration and Oxidation.



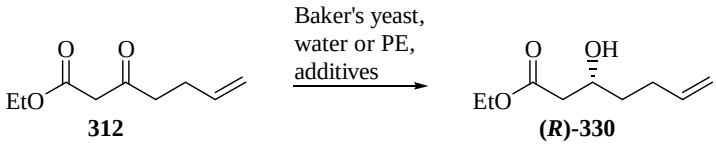
311 **333** **334**

iv. Chiral Reduction of Keto-Ester **312** with Baker's Yeast.

*** Introduction.**

Introducing another chiral centre would give access to a stereodefined precursor, which would consequently afford the desired tetrahydrofuran with a high degree of stereocontrol. As a result, the asymmetric reduction of the ketone group of keto-ester **312** was investigated and Baker's yeast (*Saccharomyces cerevisiae*) was chosen as it could offer an inexpensive way to achieve this goal (**Scheme 93**).

Scheme 93. Reduction of Keto-Ester **312** with Baker's Yeast.



312 **(*R*)-330**

*** Results.**

Three reactions following different literature procedures were carried out. The solvent (aqueous or organic), and the presence of glucose or additive such as methyl vinyl ketone have been varied in order to find the best conditions (compromise between yield and e.e.). The different conditions and yields are summarised in the table below.

Table 4. Results.

Entry	Conditions	T (^{o}C)	Yield	Reference
i	Yeast, glucose, KH_2PO_4, $MgSO_4$, water	30	49%	[153]
ii	Yeast, glucose, methyl vinyl ketone, water	28	47%	[154]
iii	Yeast, petroleum ether:water/ 50:1	30	30%	[155]

The poor yield obtained for entry iii led us to abandon this procedure and concentrate on entries i and ii, which gave much better yields. Optical rotatory power proved to be higher in the case of procedure ii. This was consistent with the literature and we decided to scale-up this reaction in order to continue the synthesis epoxy-acetal **306**. However,

scaling-up this reaction proved to be difficult due to the large amount biomass generated and in order to extract the product **(*R*)-330** of the reaction, a continuous extraction apparatus was used.

Enantiomeric excess of the two procedures and the different methods (use of a chiral NMR shift reagent and formation of the Mosher's esters) are described below:

Use of a Chiral NMR Shift Reagent.

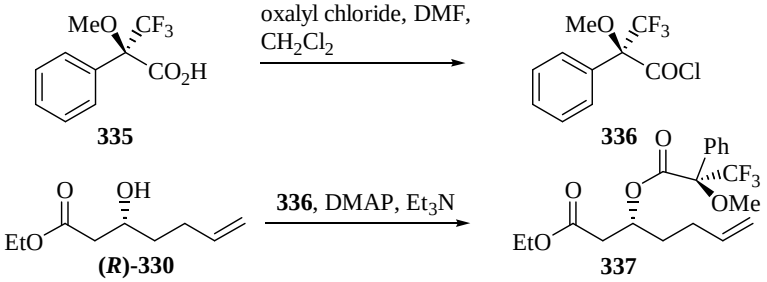
Europium *tris*[3-(trifluoro-methylhydroxymethylene)-(+)-camphorate)] was used as the chiral shift reagent in order to determine the enantiomeric excess e.e. of compound **(*R*)-330**.[156] A shift of the CH signal was observed by ^{1}H NMR. Unfortunately, the signal overlapped with the CH_2 signal of the ester, and consequently the determination of the e.e. was not possible.

Mosher's Esters.[157]

The introduction of another chiral centre to molecule **(*R*)-330** would form two diastereoisomers, which possess distinct ^{1}H NMR data. It is then possible, by integration of the different signals to give the diastereomeric excess, which is equal to the enantiomeric excess (e.e.) of the corresponding mixture of alcohols (given a pure reagent and complete reaction). Consequently, it was hoped that reaction of alcohol **(*R*)-330** with the (*S*)-Mosher's acid chloride would permit the determination of the e.e..

Thus, (*R*)-Mosher acid **335** was reacted with oxalyl chloride and a catalytic amount of DMF in CH_2Cl_2 in order to form the (*S*)-Mosher acid chloride, which was reacted directly with a solution of alcohol **(*R*)-330** in the presence of a catalytic amount of DMAP and triethylamine. This reaction was performed with alcohols **(*R*)-330** obtained from entry i and entry ii and the corresponding Mosher's esters were obtained in 77% and 81% yields respectively.

Scheme 94. Synthesis of the Corresponding Mosher's Esters.



Due to overlapping of the signals in the ^{1}H NMR spectra, the characterisation of the two diastereoisomers was difficult and the determination of the e.e. was not possible. However, accurate determination of the e.e. might be obtained by analysis of the Mosher's esters ^{19}F NMR spectra.

*** Discussion.**

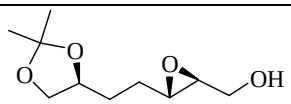
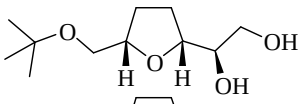
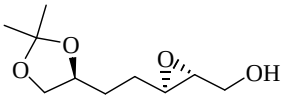
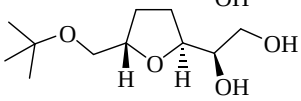
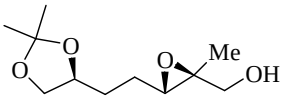
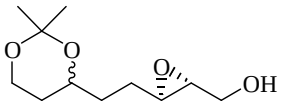
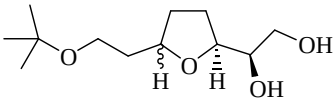
The stereochemistry obtained by microbial reduction depends on the substrates and is generally difficult to predict. Most of the time, a microbe/enzyme screening is necessary in order to establish the conditions for the formation of the desired chiral centre. However, in the case of ketones and keto-esters, an empirical rule also known as Prelog's rule, can predict the stereochemistry of the product.[158] It has been observed that the hydrogen transfer occurs on the *Re* face of the ketone. Consequently, reduction of keto-ester **312** afforded compound **(*R*)-330** with a (*R*)-configuration. Reduction of keto-esters using baker's yeast can often lead to alcohols with low enantiomeric excess. This can be explained by the opposite action of the different enzymes present in the whole cell (the first type leading to the (*R*)-alcohol whilst the second one giving the (*S*)-alcohol). Enhancement of the stereoselectivity can be achieved by for example modifying the substrate (by increasing the steric bulk of one of the substituent), adding additives such as glucose or immobilising the microbe in a hydrophobic network of polymer.[158] Nakamura *et al*. have observed that reduction of methyl 3-oxopentanoate with baker's yeast was obtained with high selectivity when glucose and methyl vinyl ketone where added during the fermentation step. They concluded that the glucose activated the enzymes producing the (*R*)-hydroxy-ester whilst methyl vinyl ketone inhibited the enzymes producing the opposite enantiomer.[154]

2.1.3 Results and Discussion.

2.1.3.1 Results.

Epoxy-acetals **304-306** were reacted at -20 ^{o}C with a 2 M solution of trimethylaluminium. We were delighted to observe the formation of the corresponding tetrahydrofurans **338a**, **338b** and **339** in 59%, 70% and 43%, respectively. Epoxy-acetal **305** did not react and only starting material was recovered (see **Table 5**).

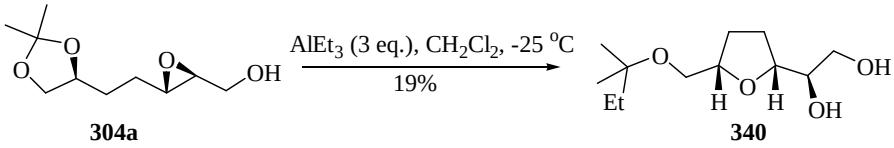
Table 5. Results.

	Starting Material		Product		Yield
i		**304a**		**338a**	59%
ii		**304b**		**338b**	70%
iii		**305**	-		
iv		**306**		**339**	43%

Conditions: $AlMe_3$ (3 eq.), CH_2Cl_2, -25 ^oC

The reaction of epoxy-acetal **304a** with triethylaluminium was also investigated and the desired tetrahydrofuran **340** was obtained in 19% yield (**Scheme 95**). Difficulties were encountered during the purification and the material required purification twice by flash columns chromatography to separate the product from the starting material. No optimisation was carried out on this reaction, but the low quality of the organoaluminium reagent was possibly responsible for the low yield obtained.

Scheme 95. Reaction of Epoxy-Acetal **304a** with Triethylaluminium.



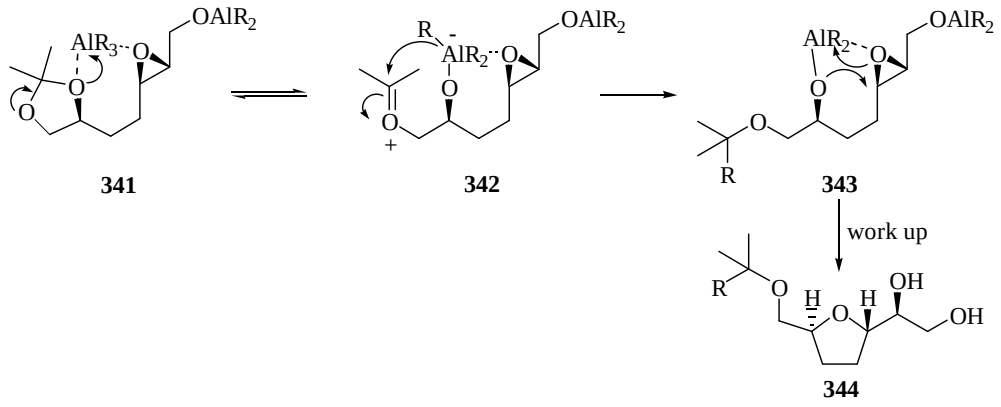
304a **340**

2.1.3.2 Regioselective Reaction and Proposed Mechanism.

The opening of the epoxide rings with trialkylaluminium and the subsequent formation a diol (see **Scheme 68**) was never observed and only the tetrahydrofuran rings were obtained. The reaction of organoaluminium reagents with acetals is well known in the literature[115, 116] and has been described for example by Takano and co-workers, who reported the deprotection of a range of acetal-alcohol with trimethylaluminium to give 1,2 diol, bearing a 3-*tert*-butyl group (see Takano, **Section 1.2.2.3**). We postulated that there was an association of the organoaluminium reagents with the oxygen atoms of the acetal and also with the epoxide. This consequently led to the cleavage of the ring and the formation of an oxonium species **342**. Then, after attack of a nucleophilic alkyl

group to the oxonium ion and attack of the epoxide by the alkoxide, the corresponding tetrahydrofuran could be obtained. The proposed mechanism is described in **Scheme 96**.

Scheme 96. Proposed Mechanism.



2.1.4 CONCLUSION.

To conclude, target molecules **304a/b-306** have been successfully synthesised and reacted with trimethyl and triethylaluminium. The corresponding tetrahydrofurans **338a/b-340** were isolated in good yield and we showed that the reaction was possible with 1,2-epoxy-acetals but also with 1,3-epoxy-acetal. Reaction with a more hindered epoxide (epoxy-acetal **305**) was however unsuccessful and the proposed mechanism described in **Scheme 96** does not explain recovery of the starting material **305**.

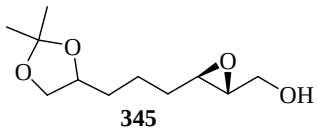
Overall the development of this methodology can easily be applied to the synthesis of natural products containing these motifs.

2.2 SYNTHESIS OF STEREODEFINED TETRAHYDROPYRANS.

2.2.1 SYNTHESIS OF EPOXY-ACETAL 345.

The promising results obtained with the formation of tetrahydrofurans led us to investigate the formation of tetrahydropyrans using the methodology developed so far. As before, we decided to focus initially on target molecules which were easy to construct in order to test the methodology. Based on this point of view, racemic epoxy-acetal **345,** with no substituent was chosen (**Figure 7**).

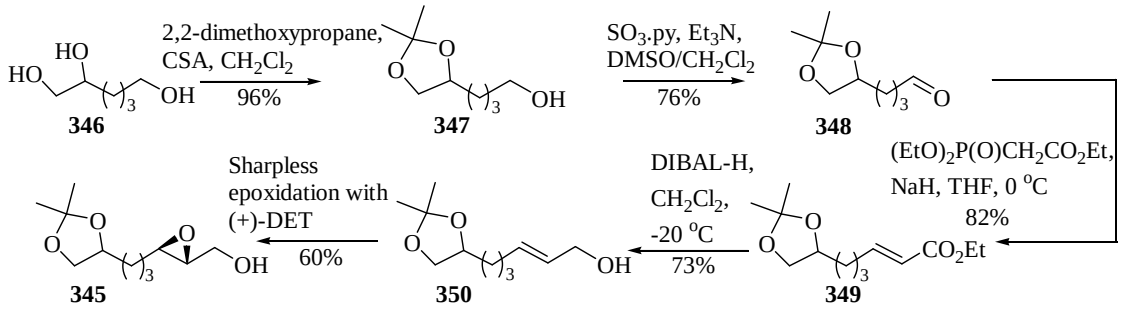
Figure 7. Target Molecule **345**.



345

The synthesis started with commercial available 1,2,6-hexan triol **346**. Protection of the diol functionality was achieved using 2,2-dimethoxypropane and a catalytic amount of camphorsulfonic acid in dichloromethane and the corresponding acetal **347** was afforded in 96% yield.[149] Oxidation of the primary alcohol was carried out using the Parikh-Doering procedure,[152] using sulfur trioxide-pyridinium complex, triethylamine in dichloromethane and DMSO. The corresponding aldehyde **348** was isolated in 76% yield. As seen in **Section 2.1.2.2**, the use of IBX or the Dess-Martin periodinane gave the products in moderate yield. For this type of substrates, the Parikh-Doering procedure was the most successful. Olefination of aldehyde **348** afforded the *trans*-ester **349** in 82% yield and the ester group was then reduced using DIBAL-H in dichloromethane at -20 ^{o}C to give the corresponding allylic alcohol **350** in 73% yield. Finally, the Sharpless asymmetric epoxidation procedure,[135] using (+)-DET was performed and the desired product **345** was afforded in 60% yield.

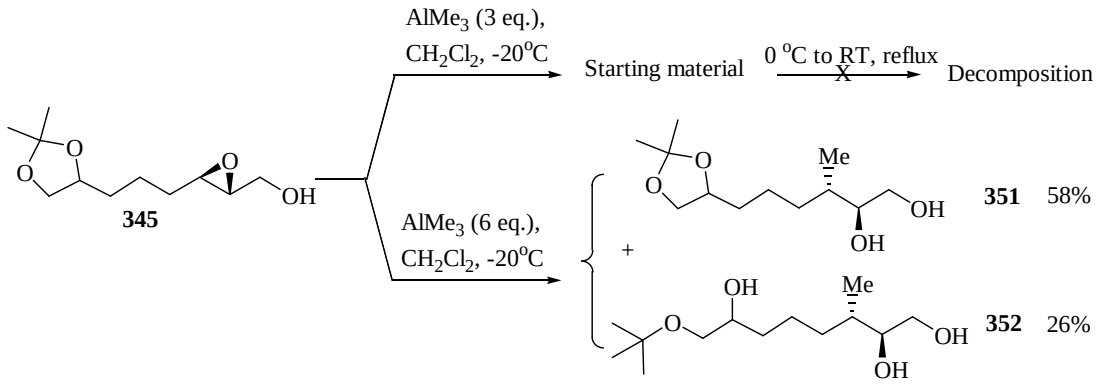
Scheme 97. Synthesis of Epoxy-Acetal **345**.



2.2.2 RESULTS.

Reaction of epoxy-acetal **345** with a 2 M solution of trimethylaluminium (3 eq.) at -20 °C for 2-3 h led only to the recovery of the unreacted starting material and upon warming to RT and then refluxing for few hours, the starting material decomposed. When an excess of trimethylaluminium was used (6 eq.), diol **351** and triol **32** were isolated in 58% and 26% yields, respectively, but the formation of the desired tetrahydropyran was not observed. The results are summarised in **Scheme 98**.

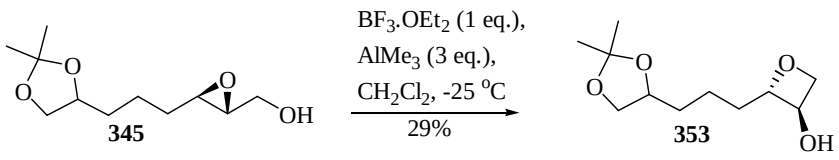
Scheme 98. Reaction of Epoxy-Acetal **345** with $AlMe_3$.



Consequently, the opening of the epoxide moiety was more favorable than those of the acetal group and diol **351** was the major product obtained. This showed that the distance between the epoxide and the acetal moieties was a critical factor for this reaction. A shorter distance may allow a better coordination of the organoaluminium reagent with the two oxygens and favour the intramolecular cyclisation.

In order to facilitate the opening of the acetal, we investigated the addition of a Lewis acid to the reaction mixture. Thus, by reaction of epoxy-acetal **345** with boron trifluoride etherate (1 eq.) and trimethylaluminium (3 eq.) at -30 °C in dichloromethane, we were not able to isolate the corresponding tetrahydropyran. However, a compound of same molecular weight of the starting material was isolated in 29% yield. The NMR analysis showed the presence of the acetal group, but the disappearance of the epoxide moiety. It was tentatively concluded, based on these data, that the free alcohol attacked the epoxide ring to give oxetane **353** (**Scheme 99**).

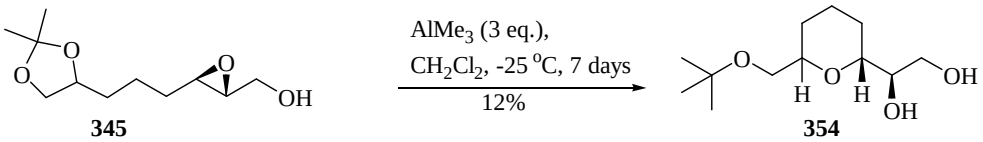
Scheme 99. Reaction of Epoxy-Acetal **345** with $BF_3.OEt_2$ and $AlMe_3$.



It is noteworthy that similar results were obtained when only boron trifluoride etherate (2 eq.) was reacted with epoxy-acetal **345**. We showed previously that trimethylaluminium probably reacted extremely slowly with the starting material and hence no reaction was observed after 2-3 h at low temperature. Consequently, in the reaction described in **Scheme 99**, boron trifluoride etherate seemed to be the only reagent responsible of the formation of the oxetane ring.

Finally, epoxy-acetal **345** was reacted with trimethylaluminium (3 eq.) in dichloromethane for 7 days at -25 ^{o}C. The starting material was mainly recovered but we were delighted to observe the formation of the desired tetrahydropyran **354**, but in a poor yield of 12% (**Scheme 100**).

Scheme 100. Formation of Tetrahydropyran **354**.



345 **354**

2.2.3 CONCLUSION.

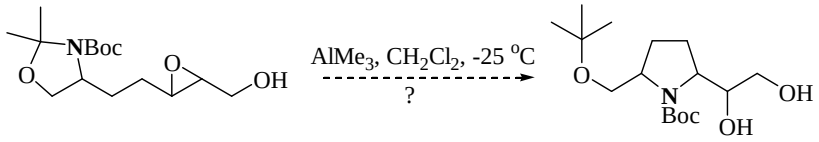
We showed that the formation of tetrahydropyrans using the methodology developed for the synthesis of tetrahydrofurans is possible, but is extremely slow and also low yielding. However, the yield and rate of this reaction could possibly be improved by adding substituents onto the chain. Utilising the Thorpe-Ingold effect,[159] the intramolecular cyclisation could therefore become more favourable leading to increased conversion of the starting material into tetrahydropyrans.

2.3 TOWARDS THE SYNTHESIS OF PYRROLIDINES.

2.3.1 TARGET MOLECULE AND RETROSYNTHESES.

We then focused our interest towards the formation of pyrrolidines using the strategy developed so far (**Scheme 101**). As previously seen, the formation of a five-membered ring was more favourable than the synthesis of the six-membered ring and consequently we hoped that the cyclisation could again be possible in this particular case. The choice of the protecting group on the nitrogen was essential and we opted for a Boc group. Due to the oxophilicity of organoaluminium reagent, the different oxygen atoms of the Boc group could coordinate to trimethylaluminium and possibly direct the opening of the acetal by the oxygen atom alone.

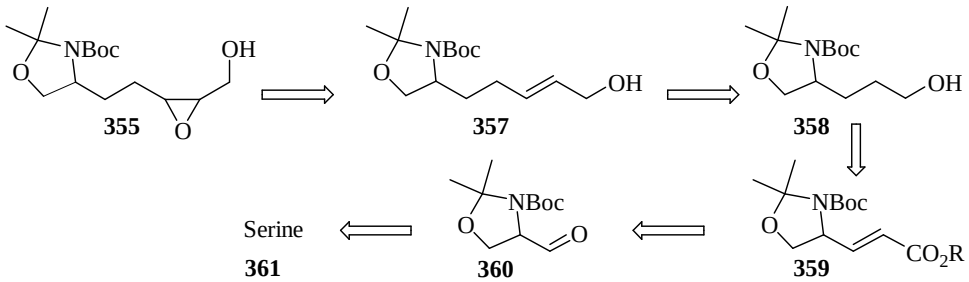
Scheme 101. Strategy.



355 **356**

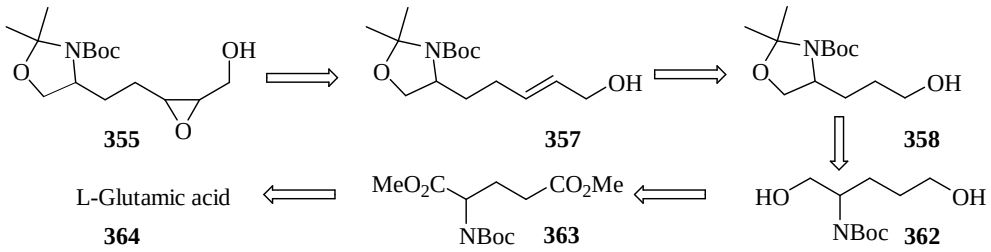
Synthesis of target molecule **355** can be achieved using a strategy similar to that of the tetrahydrofuran precursor. The epoxide group can be introduced by a Sharpless asymmetric epoxidation procedure of allylic alcohol **357**, which can be obtained by modification of the Garner aldehyde **360**. This chiral aldehyde can be synthesised from D or L-serine (**Scheme 102**).

Scheme 102. Retrosynthesis.



However, alcohol **358** could also be easily synthesised by modifications of L-glutamic acid, which is an inexpensive and an enantiopure starting material and we decided to proceed *via* this route. The retrosynthetic analysis is described in **Scheme 103**.

Scheme 103. Retrosynthetic Analysis.

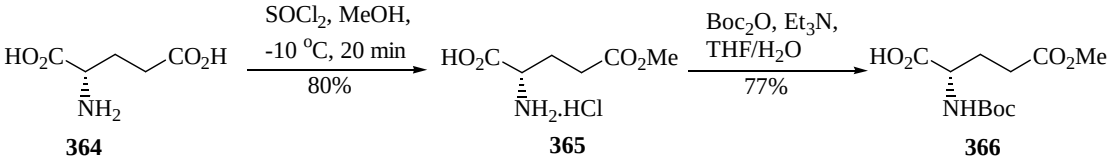


2.3.2 SYNTHESIS OF THE TARGET MOLECULE 355.

2.3.2.1 Synthesis of Alcohol 358: 1st Attempt.

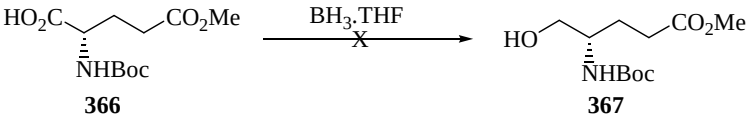
The synthesis started with the esterification of L-glutamic acid **364**, using methanol and thionyl chloride.[160] Reaction for 20 minutes at -10 °C afforded the mono-ester **365** in 80% yield. Because of the difference of reactivity between an ester and carboxylic acid group, it was hoped that the carboxylic acid could be selectively reduced to form the alcohol in order to synthesise the *N*,*O*-acetal group. Before attempting any reductions, the amine group was Boc-protected using Boc anhydride, triethylamine in THF and water giving carboxylic acid **366** in 77% yield (**Scheme 104**).[161]

Scheme 104. Formation of Carboxylic Acid **366**.



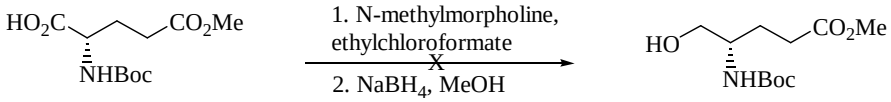
Different methods were investigated in order to selectively reduce the carboxylic acid group in the presence of the ester and carbamate groups. Borane is a very chemoselective reagent and can reduce very rapidly carboxylic acid even in the presence of esters. It reacts with the carboxylic acid to generate a triacylborate, which is very reactive as the lone pair of the oxygen atoms stabilises the empty p orbital of the boron atom. As a result, reduction of carboxylic acid **366** using a 1 M solution of borane in THF was attempted. However, no desired alcohol **367** was obtained (**Scheme 105**).[162]

Scheme 105. Reduction of Carboxylic Acid **366** with Borane in THF.



Formation of a mixed anhydride followed by its subsequent reduction is another way to reduce carboxylic acid. Consequently, the mixed anhydride was synthesised *in situ* by reaction of carboxylic acid **366** with *N*-methylmorpholine and ethylchloroformate in THF and was subsequently reacted with sodium borohydride in methanol (**Scheme 106**).[163] Unfortunately, no desired product was obtained after flash column chromatography.

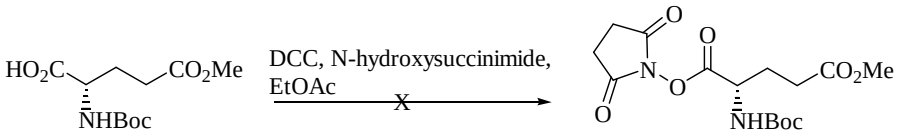
Scheme 106. Formation of Mixed Anhydride Followed by an *in situ* Reduction with $NaBH_4$.



366 **367**

Finally, carboxylic acid **366** was reacted with DCC and *N*-hydroxysuccinimide in ethyl acetate in order to give the succinate ester **368**, which was expected to be stable enough for purification (**Scheme 107**). Although dicyclohexylurea formed during the reaction (a white precipitate was observed), it was not clear if the formation of compound **368** had occurred.[164]

Scheme 107. Formation of Succinate Ester **368**.

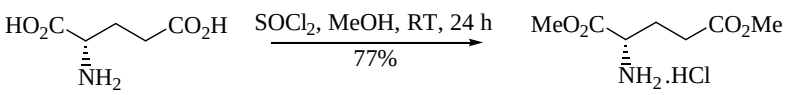


366 **368**

2.3.2.2 Synthesis of Alcohol 358: 2nd Attempt.

Reduction of the carboxylic acid seemed to be quite problematic and we therefore decided to change strategy. Instead, we decided to form dimethyl ester **369** from L-glutamic acid **364** using the Fischer procedure described previously.[165] By controlling the reaction conditions (time and temperature) it was possible to synthesise either the mono or diester. As seen previously, reaction of L-glutamic acid **364** with thionyl chloride and methanol at -10 ^{o}C for 20 minutes gave ester **365**. However, when it was reacted for 12 h at RT, dimethyl ester **369** was obtained in 77% yield (**Scheme 108**).

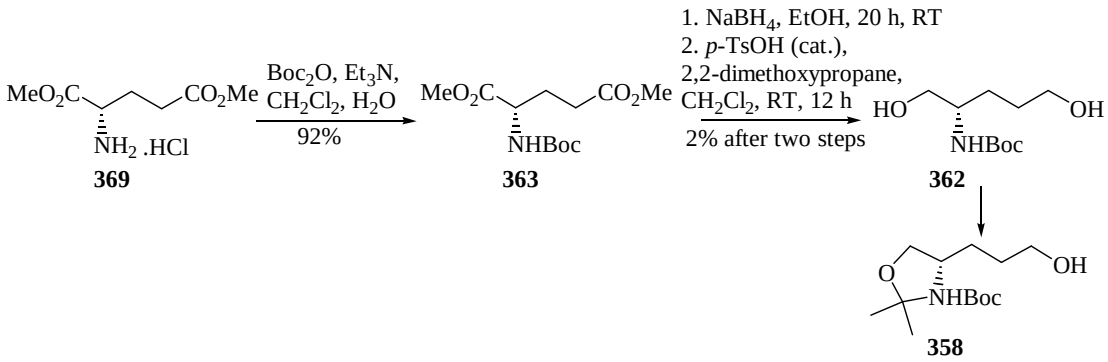
Scheme 108. Dimethyl Ester **369** Formation Using the Fischer Procedure.



364 **369**

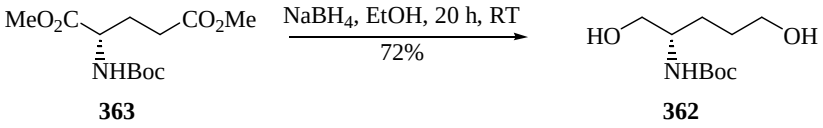
The amine group was then protected with a Boc group using Boc_2O, triethylamine in dichloromethane and water or in methanol.[166] The corresponding product **363** was obtained in 92% yield. Following the literature, the ester groups were reduced using sodium borohydride in ethanol to give the desired diol **362**, which without purification, was subsequently reacted with *p*-TsOH and 2,2-dimethoxypropane in dichloromethane at RT for 12 h. Alcohol **358** was obtained in only 2% yield after 2 steps (40% in the literature) (**Scheme 109**).[167]

Scheme 109. Formation of Alcohol **358**.



In order to improve the yield of the reactions, diol **362** was purified and was obtained as a white solid in 72% yield after recrystallisation (**Scheme 110**).

Scheme 110. Reduction of Dimethyl Ester **363** with $NaBH_4$.



Different reaction conditions were performed in order to introduce the acetal group. The addition of freshly activated 4 Å powdered molecular sieves in order to remove methanol formed during the reaction led to decomposition of the starting material and/or the products of the reaction and the yield observed was lower. When the reaction mixture was heated under reflux in toluene, the desired product was obtained in 30% yield. The best result was obtained when the reagents were heated under reflux in dichloromethane for 2 h. Acetal **358** was obtained in 74% yield on a 100 mg scale and ~60% on a 5 g scale (see **Table 6**).

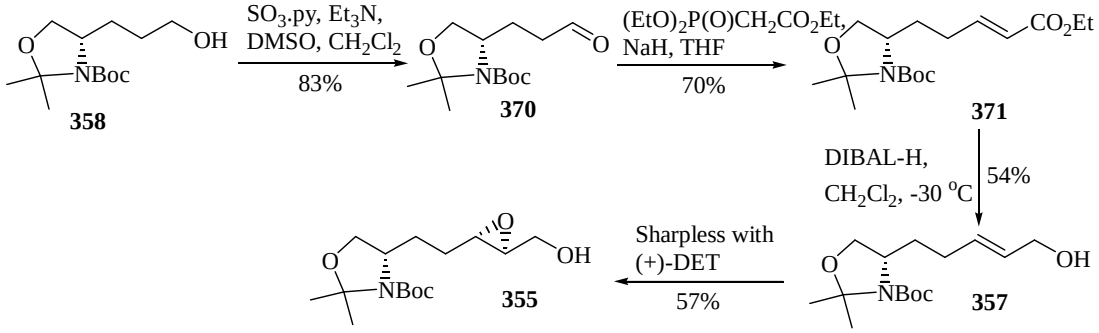
Table 6. Formation of *N,O*-Acetal **358**.

Entry	Conditions	Yield and Observations
i	Toluene, RT, 2 h	32% + starting material
ii	Toluene, reflux, 30 minutes	30% + slight decomposition
iii	Toluene, reflux, 4 Å ms, 30 minutes	13% + decomposition
iv	CH_2Cl_2, reflux, 2 h, 100 mg	74%
v	CH_2Cl_2, reflux, 2 h, 5 g	60%

2.3.2.3 Synthesis of Epoxy-*N,O*-Acetal 355.

To complete the synthesis, the primary alcohol **358** was then oxidised to the corresponding aldehyde **370** using the Parikh-Doering procedure and using sulfur trioxide pyridinium complex, triethylamine in DMSO and dichloromethane.[152] The corresponding aldehyde **370** was afforded in 83% yield. This was followed by a Horner-Wadsworth-Emmons reaction using sodium hydride (60% *w/w* in mineral oil) and triethyl phosphonoacetate in dry THF to give ester **371** in 70% yield.[133] Reduction of the ester moiety was achieved using a 2 M solution of DIBAL-H in dichloromethane to give allylic alcohol **357** in 54% yield. Finally, a Sharpless asymmetric epoxidation was carried out with 4 Å molecular sieves, (+)-DET, *tert*-butyl hydrogen peroxide and titanium isopropoxide in dry CH_2Cl_2 to give epoxy-*N,O*-acetal **355** in 57% yield (**Scheme 111**).[135]

Scheme 111. Formation of Epoxy-*N,O*-Acetal **355**.

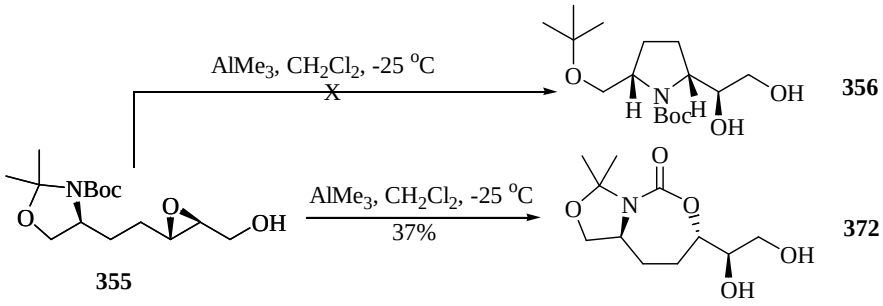


2.3.3 RESULTS.

2.3.3.1 Reaction of Epoxy-*N,O*-Acetal 355 with Trimethylaluminium.

Epoxy-acetal **355** was reacted with trimethylaluminium (3 eq.) for 24 h at -25 °C. Unfortunately, the desired compound, pyrrolidine **356**, was not isolated, but, on the contrary, we observed the formation of a seven-membered carbamate **372**, which was obtained in 37% yield (**Scheme 112**).

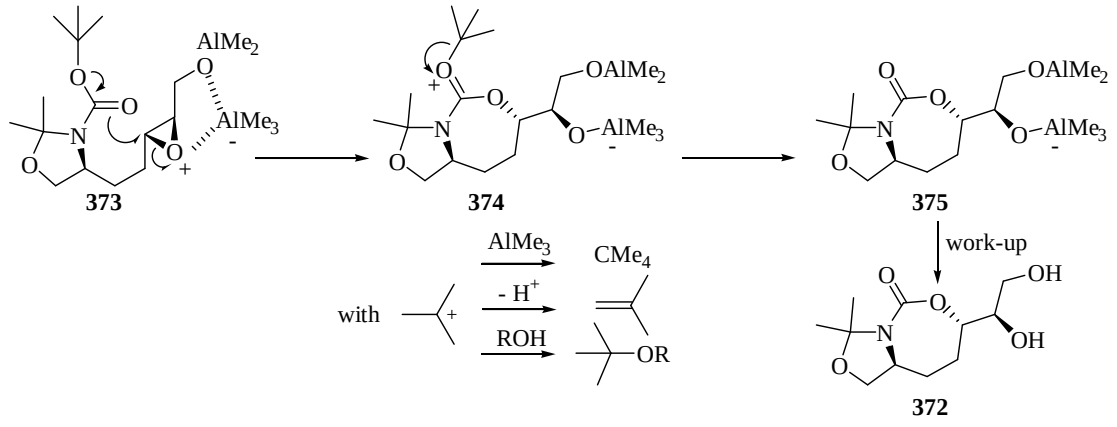
Scheme 112. Carbamate Formation.



2.3.3.2 Proposed Mechanism.

The result obtained can be explained by the attack of the epoxide ring by the oxygen atom of the carbamate followed by the loss of the *tert*-butyl group. The proposed mechanism is described in **Scheme 113**.

Scheme 113. Proposed Mechanism.



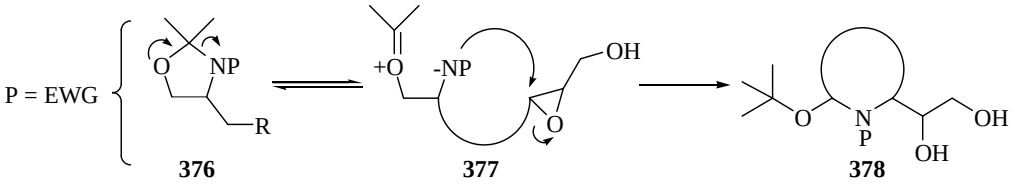
2.3.3.3 Protecting Group Screening.

i. Choice of the Protecting Group.

This result led us to revisit the protection of the amine in order to synthesise the desired pyrrolidine ring. As previously seen, an electron withdrawing group on the nitrogen seemed to be the best option to perform the reaction as it could lead to the opening of

the mixed acetal from the oxygen atom (formation of intermediate **377**) (**Scheme 114**). However, as seen in the previous section, having a Boc group introduced too much stability on the acetal ring and consequently its cleavage was not observed when reacted with trimethylaluminium.

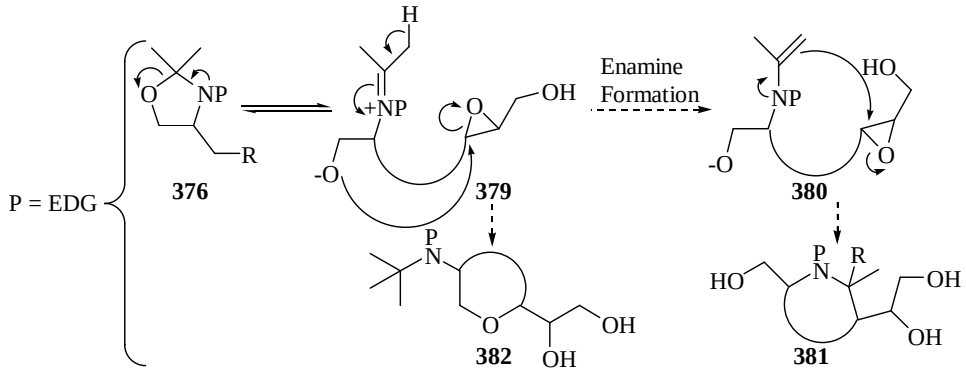
Scheme 114. Electron-Withdrawing Protecting Group.



376 **377** **378**

Conversely, having an electron-donating group could destabilise the ring, leading to its cleavage, but possibly by the nitrogen atom and hence few reaction paths are consequently possible (**Scheme 115**). The alkoxide can attack the epoxide and lead to the formation of an heterocyclic ring containing an oxygen atom (compound **382**). However, as seen in the case of the tetrahydropyran, the intramolecular cyclisation can be difficult. The formation of an enamine species **380** could also be possible and could lead to the nucleophilic attack of the epoxide giving in this case, an heterocyclic ring containing a nitrogen atom (compound **381**) (see **Scheme 115**).

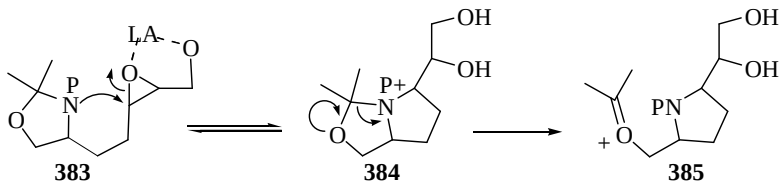
Scheme 115. Electron-Donating Protecting Group and Possible Outcome.



376 **379** **380** **382** **381**

Finally, another possibility could happen if the reaction is carried out in the presence of a mild Lewis acid. The presence of this epoxide might be a driving for the opening of the acetal ring (**Scheme 116**).

Scheme 116. Electron-Donating Protecting Group.



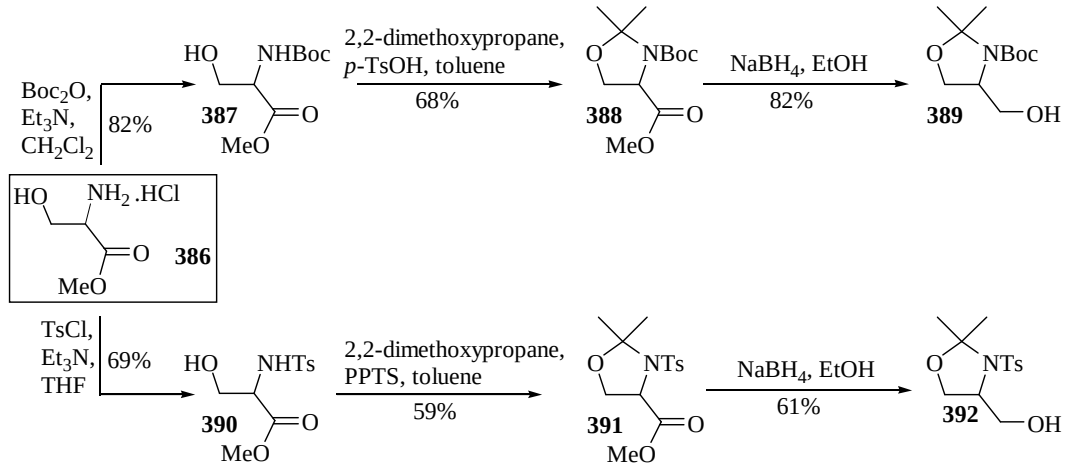
383 **384** **385**

ii. Protecting Group Models.

In order to verify these hypotheses, a model study based on serine derivatives was carried out. The compounds were synthesised with different protecting groups, Boc, tosyl and benzyl groups and reacted with trimethylaluminium.

The synthesis of compounds **389** and **392** started with racemic D,L-serine methyl ester **386**. Protection of the amine was carried out using Boc anhydride, triethylamine in dichloromethane to give Boc protected serine methyl ester **387** in 82% yield.[168] The acetal group was then installed using 2,2-dimethoxypropane, *para*-toluenesulfonic acid and when heated under reflux in toluene for 2 h.[168] Finally, reduction of the ester group of acetal **388** was achieved using sodium borohydride in ethanol to give alcohol **389** in 82% yield.[168] Simirlarly, D,L-serine methyl ester **386** could be protected with a tosyl group and the reaction was carried out using tosyl chloride, triethylamine in THF.[169] The formation of the mixed acetal was difficult and reaction with *para*-toluenesulfonic acid did not lead to the isolation of the desired product **391**. However, reaction using pyridinium *para*-toluenesulfonate gave the corresponding acetal **391** in 59% yield. Finally, reduction of the ester group was achieved using sodium borohydride in ethanol and compound **392** was obtained in 61% yield (**Scheme 117**).

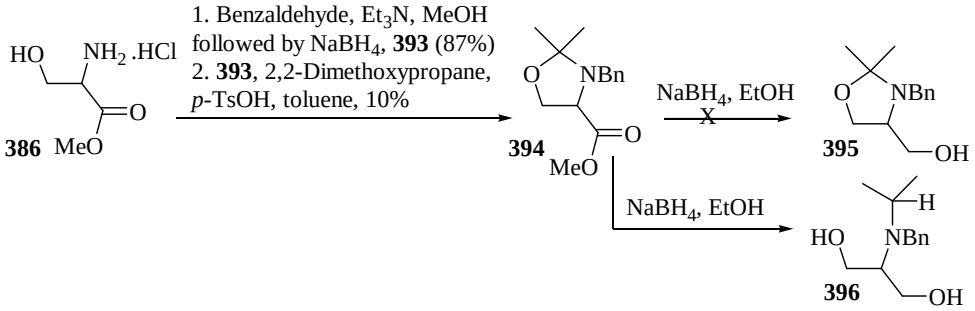
Scheme 117. Synthesis of Model Systems with Electron-Withdrawing Groups.



Introduction of a benzyl group on the amine was achieved by carrying out a reductive amination. D,L-Serine methyl ester **386** was reacted with benzaldehyde in the presence of triethylamine in methanol for 12 h and the reaction mixture was then treated with sodium borohydride to afford benzyl amine **393** in 87% yield.[170] Acetal formation was performed using 2,2-dimethoxypropane with *para*-toluene sulfonic acid in toluene and

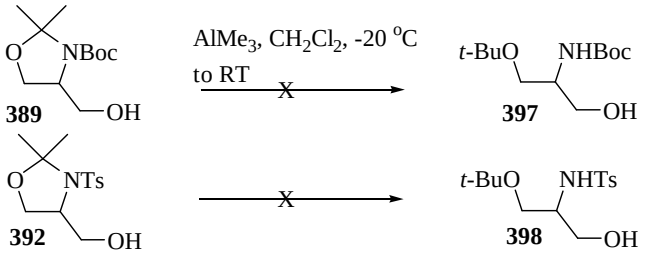
acetal **394** was obtained in 10% yield only.[170] Reduction of the ester group with sodium borohydride led mainly to the cleavage of the acetal ring (only formation of diol **396**) and the formation of compound **395** proved to be unsuccessful (**Scheme 118**).

Scheme 118. Synthesis of a Model System with an Electron-Donating Group.



Compounds **389** and **392** were then reacted with trimethylaluminium. As predicted, the presence of a Boc or tosyl group stabilised the acetal ring and no cleavage of the ring was observed (**Scheme 119**).

Scheme 119. Reaction with Trimethylaluminium.



It was observed that reaction of compound **394** with sodium borohydride led to the opening of the ring (**Scheme 118**). As a result, the presence of an electron donating group destabilised the acetal ring and favoured its opening. As expected, the opening was due to the action of the nitrogen atom and not of the oxygen atom as desired.

2.3.4 Conclusion.

The synthesis of pyrrolidines, using the methodology developed for the synthesis of tetrahydrofurans, was unsuccessful and led instead to the formation of a 7-membered carbamate **372**. This could be an efficient strategy to synthesise enantiopure 1,4-amino-alcohols upon cleavage of the carbamate group. As could be seen from the model study, the protecting group on the amine is the key element in this reaction and should be choose carefully for the reaction to proceed.

Chapter 3 | CONCLUSION & FUTURE WORK

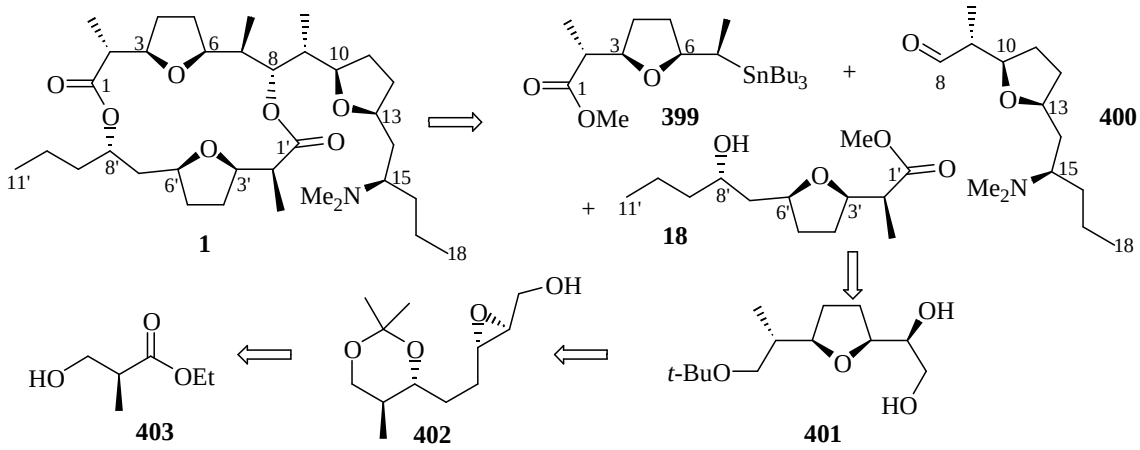
To conclude, the desired epoxy-acetals **304a**/**b**, **305** and **306** were successfully synthesised and we were delighted to observe to the formation of the corresponding tetrahydrofurans **338a/8**, **339** and **340** in good yield when reacted with trialkylaluminium reagents. We showed that 1,2 and 1,3-acetals could both be opened under these conditions.

The formation of tetrahydropyran **354** from epoxy-acetal **345** was also successful although the product was obtained in low yield.

Finally, reaction of epoxy-*N*,*O*-acetal **355** with trimethylaluminium led to the formation of a 7-membered carbamate **372**. This could provide, after removal of the carbamate group, an useful methodology for the synthesis of stereocontrolled 1,4-amino-alcohols.

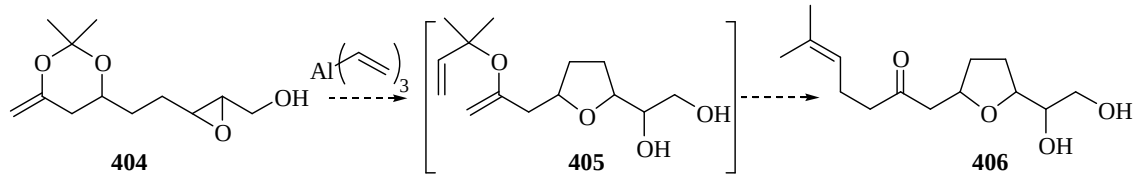
Future work could include the total synthesis of pamamycin 607 **1** in order to apply the method having been developed. The retrosynthesis is outlined in **Scheme 120**. Cleavage of the ester bonds gives fragments **399**, **400** and **18**. Theses intermediates coud be synthesised from the common tetrahydrofuran **401**, which could be obtained by treatment of epoxy-acetal **402** with trimethylaluminium. Epoxy-acetal **402** could be synthesised from the commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate **403**.

Scheme 120. Pamamycin 607 **1** Retrosynthesis.



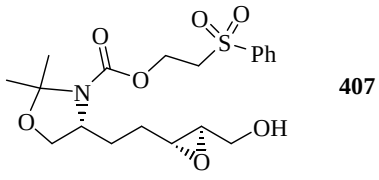
Other type of epoxy-acetals such as compound **404** shown in **Scheme 121** could also be investigated. Reaction with trivinylaluminium could generate tetrahydrofuran **405**, which upon heating could undergo a Claisen rearrangement to give advanced precursor **406**.

Scheme 121. Tandem Cyclisation-Claisen Rearrangement.



Further work on the serine derivatives could also be performed in order to find a suitable protecting group. As seen in **Section 2.3.3.3**, the protecting group on the amine should be chosen carefully in order to be able to synthesise the corresponding pyrrolidines. A carbamate protecting group stabilises the acetal ring and makes it unreactive. It should then be possible to synthesise the target molecule without loss of the acetal. However, the protecting should be easily and selectively removable in order to activate the acetal group and allow the cyclisation to take place. As a result, the use of a sulfone ethylene carbamate protecting group (target molecule **407** shown in **Figure 8**) could possibly be investigated. This protecting group could be easily removed under basic conditions.

Figure 8. Sulfone Ethylene Carbamate Protecting Group.



Chapter 4 | EXPERIMENTAL

Except where specified, all reagents were purchased from commercial sources and were used without further purification. When necessary, diethyl ether and THF were distilled from sodium/benzophenone immediately before use and dichloromethane from calcium hydride. Petroleum ether refers to the fraction with boiling range 40-60 ^{o}C.

Reaction were monitored by tlc, using Merck glass backed tlc plates pre-coated with a 250 μm layer of 60 F$_{254}$ silica gel containing a fluorescent indicator and visualised with ultraviolet light at 254 nm and/or $KMnO_4$ or vanillin dips. Flash column chromatography was carried out using Merck Kiesel gel 60 silica gel, 35-70 μm, using the eluent specified.

Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

Infra-red (IR) spectra were recorded on a Perkin Elmer 1710 Fourier transform spectrometer with NaCl plates. Optical rotations were recorded using a Perkin Elmer 241 polarimeter with a 1 cm-path length cell. The solution concentrations are given in g.100mL^{-1} and optical rotations of a mixture of diastereoisomers were not recorded. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Brüker Advance AC-300 at 300 MHz and 75 MHz respectively or a Varian-500 at 500 MHz and 125 MHz respectively. Chemical shifts are quoted in ppm, using residual solvent peaks as internal standards (δ_H 7.26 for $CDCl_3$ and δ_C 77.0 for $CDCl_3$). Full proton and carbon assignment has been made when possible, however where signal identity is ambiguous no assignment is offered. Mass spectra were recorded on a Fison VG autospec mass spectrometer (low resolution EI) or on a Bruker Daltonics APEX III (ESI).

4.1 GENERAL PROCEDURES.

Procedure 1: Hydrogenation of Alkene.

A solution of alkene (1.0 mmol) in ethyl acetate (5 mL) was treated by platinum oxide PtO_2 (2 mmol) under a ballon of H_2 and the reaction mixture was stirred at RT for 20 h. The solution was filtered through Celite®, the residue washed with ethyl acetate (10 mL), the solution evaporated under reduced pressure, and the crude material purified by flash column chromatography.

Procedure 2: Ester Reduction Using Lithium Aluminium Hydride.

To a suspension of lithium aluminium hydride (2.76 mmol) in dry THF (25 mL) under an atmosphere of nitrogen was added at 0 ^oC a solution of ester (2.76 mmol) in dry THF (5 mL) and the resulting mixture was stirred at 0 ^oC for 1 h. Water (0.5 mL), followed by a 15% aqueous solution of sodium hydroxide (0.1 mL) and water (1 mL) were added and the reaction mixture was stirred at RT for a further 4 h. The solution was filtered and partitioned between water (5 mL) and diethyl ether (20 mL). The aqueous layer further extracted with diethyl ether (3 x 20 mL) and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and purified by flash column chromatography.

Procedure 3: Reduction with DIBAL-H.

To a solution of ester (0.25 mmol) in dry CH_2Cl_2 (2 mL) under an atmosphere of nitrogen was added at -20 ^oC a 1 M solution of DIBALH in hexanes (0.55 mmol) and the reaction mixture was stirred for 1 h at this temperature. An aqueous solution of potassium-sodium tartrate (600 mg in 2 mL of water) was added and the reaction mixture was stirred at RT overnight. The reaction mixture was partitioned between CH_2Cl_2 and the aqueous layer and the aqueous layer was further extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, evaporated under reduced pressure and purified by flash column chromatography

Procedure 4: Acetal protection.

To a solution of diol (11.75 mmol) in dry CH_2Cl_2 (30 mL) was added freshly distilled 2,2-dimethoxypropane (14.10 mmol) and a catalytic amount of camphorsulfonic acid or

p-toluenesulfonic acid. The solution was stirred under nitrogen at RT for 1.5 days, evaporated under reduced pressure and purified by flash column chromatography.

Procedure 5: Reaction with Organoaluminium Reagent.

To a solution of epoxy-acetal (0.77 mmol) in dry CH_2Cl_2 (6 mL) under an atmosphere of nitrogen was added at -20 ^oC a 2 M solution of trimethylaluminium in heptanes (2.30 mmol) and the reaction mixture was stirred for 2 h at -20 ^oC. A saturated solution of $MgSO_4$ was added (2 mL), the reaction mixture was diluted with CH_2Cl_2 (15 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and purified by flash column chromatography.

Procedure 6: Horner-Wadsworth-Emmons Reactions.

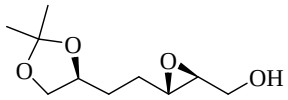
To a suspension of sodium hydride (60% *w/w* in mineral oil; 401 mg, 16.70 mmol) in dry THF (40 mL) under an atmosphere of nitrogen was added triethyl phosphonoacetate (3.75 g, 16.70 mmol) at 0 ^oC and the reaction mixture was stirred for 40 minutes at this temperature. To the solution was added a solution of aldehyde (2.40 g, 15.19 mmol) in dry THF (30 mL) and the reaction mixture was stirred 2 h at 0 ^oC and for a further 2 h at RT. A saturated solution of $NaHCO_3$ (10 mL) and water (30 mL) were added, the solution partitioned between water and THF and the aqueous layer further extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, evaporated under reduced pressure and purified by flash column chromatography.

Procedure 7: Ester Reduction Using Sodium Borohydride.

To a solution of ester (37.2 mmol) in EtOH (150 mL) under an atmosphere of nitrogen was added at 0 ^oC sodium borohydride (297.7 mmol) and the reaction mixture was stirred for 2 h at this temperature. The reaction mixture was quenched with brine (100 mL), filtered and the residue washed with Et_2O (100 mL). The reaction mixture was then partitioned between water and ether and the aqueous layer was further extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by flash column chromatography or recrystallisation.

4.2 EXPERIMENTAL.

(2*S*,3*S*,6*S*)-{3-[2-(2,2-Dimethyl-[1,3] dioxolan-4yl)-ethyl]-oxiranyl}-methanol



304a

To a suspension of freshly activated 4 Å powdered molecular sieves (20 mg) in dry CH_2Cl_2 (5 mL) under an atmosphere of nitrogen was added (+)-DET (34 mg, 0.17 mmol) followed by titanium isopropoxide (40 mg, 0.14 mmol) and a 6 M solution of *tert*-butyl hydroperoxide in CH_2Cl_2 (0.35 mL, 2.09 mmol) at -30 ^oC and the resulting reaction mixture was stirred for 30 minutes at this temperature in order to age the catalyst. A solution of **307** (259 mg, 1.39 mmol) in CH_2Cl_2 (2 mL) was added and the reaction mixture was kept at -25^oC for a further 16 h. The solution was warmed to 0 ^oC and a solution of ferrous sulphate was added. The resulting mixture was partitioned between water and CH_2Cl_2 and the organic layer was further extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:2 to afford the title compound **304a** as a pale yellow oil (200 mg, 71%). Spectroscopic data in agreement with the literature values.[131]

$[\alpha]_D^{22.2}$ = -56.3 ($CHCl_3$, *c* 1.83).

HRMS (+ESI) $[MNa]^+$ $C_{10}H_{18}O_4Na$ requires 225.1097. Found 225.1090 (3.1 ppm error).

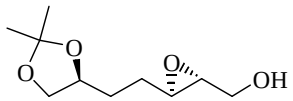
IR (neat, cm^{-1}) ν_{max} 3436, 2984, 2925, 2870, 1749, 1456, 1380, 1371, 1248, 1216, 1160, 1096, 1063, 982, 926, 881, 857, 792, 721, 666.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.20-4.08 (1H, m, C*H*) 4.08-4.00 (1H, m, OC*H*H'CHO), 3.93-3.84 (1H, m, C*H*H'OH), 3.68-3.58 (1H, m, CH*H'*OH), 3.56-3.46 (1H, m, OCH*H'*CHO), 3.05-2.97 (1H, m, CHC*H*CH_2OH), 2.97-2.91 (1H, m,

C*H*CHCH$_2$OH), 1.77-1.59 (4H, m, C*H*$_2$CH$_2$ and CH$_2$C*H*$_2$), 1.40 (3H, s, C*H*$_3$), 1.34 (3H, s, C*H*$_3$), O*H* not observed.

^{13}C NMR (CDCl$_3$, 75 MHz) δ_C 109.3 (*C*), 75.6 (*C*HO), 69.6 (*C*H$_2$O), 62.0 (*C*H$_2$OH), 58.7 (*C*H), 55.7 (*C*H), 30.1 (*C*H$_2$CH$_2$CHOCH), 28.1 (CH$_2$*C*H$_2$CHOCH), 27.3 (*C*H$_3$), 26.0 (*C*H$_3$).

(2*R*,3*R*,6*S*)-{3-[2-(2,2-Dimethyl-[1,3] dioxolan-4yl)-ethyl]-oxiranyl}-methanol



304b

To a suspension of freshly activated 4 Å powdered molecular sieves (200 mg) in dry CH$_2$Cl$_2$ (10 mL) under an atmosphere of nitrogen was added (-)-D-DIPT (42 mg, 0.18 mmol) followed by titanium isopropoxide (45 mg, 0.16 mmol) and a 4.6 M solution of *tert*-butyl hydroperoxide in CH$_2$Cl$_2$ (0.77 mL, 3.54 mmol) at -30 ^{o}C and the resulting reaction mixture was stirred for 30 minutes at this temperature. A solution of **307** (300 mg, 1.61 mmol) in CH$_2$Cl$_2$ (5 mL) was added and the reaction mixture was stirred at -25 ^{o}C for 2 days. The solution was warmed to 0 ^{o}C and a solution of ferrous sulphate (4 g) and tartaric acid (1.2 g) in water (10 mL) was added. The resulting mixture was stirred for 1 h at 0 ^{o}C and partitioned between water and CH$_2$Cl$_2$. The organic layer was removed and the organic layer was further extracted with CH$_2$Cl$_2$ (4 x 20 mL). The combined organic extracts were treated by a 30% aqueous solution of NaOH in brine, partitioned between brine and CH$_2$Cl$_2$ and the aqueous layer was further extracted with CH$_2$Cl$_2$ (4 x 10mL). The combined organic extracts were dried (MgSO$_4$), filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:2 to afford the title compound **304b** as a pale yellow oil (205 mg, 63%). Spectroscopic data in agreement with the literature values.[131]

$[\alpha]_D^{23.5}$ = 20.2 (CHCl$_3$, *c* 2.31).

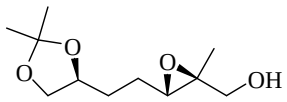
HRMS (+ESI) $[MNa]^+$ $C_{10}H_{18}O_4Na$ requires 225.1097. Found 225.1098 (0.4 ppm error).

IR (neat, cm^{-1}) ν_{max} 3436, 2985, 2930, 2871, 1733, 1456, 1377, 1371, 1246, 1216, 1160, 1093, 1063, 980, 920, 876, 857, 793, 721.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.15-4.01 (2H, m, C*H* and OC*H*H'CHO), 3.89-3.81 (1H, m, C*H*H'OH), 3.69-3.60 (1H, m, CH*H'*OH), 3.53 (1H, dd, *J* 7.5, 6.6 Hz, OCH*H'*CHO), 3.00-2.91 (2H, C*H*CHCH$_2$OH and CHC*H*CH$_2$OH), 1.80-1.56 (4H, m, CH_2CH$_2$ and CH$_2$CH_2), 1.40 (3H, s, CH_3), 1.34 (3H, s, CH_3), O*H* not observed.

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 109.4 (*C*), 76.2 (*C*HO), 69.8 (*C*H$_2$O), 62.1 (*C*H$_2$OH), 58.9 (*C*H), 56.2 (*C*H), 30.5 (*C*H$_2$CH$_2$CHOCH), 28.8 (CH$_2$*C*H$_2$CHOCH), 27.3 (*C*H$_3$), 26.1 (*C*H$_3$).

(2*S*,3*S*,6*S*)-{3-[2-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-ethyl]-2-methyl-oxiranyl}-methanol



305

To a suspension of freshly activated 4 Å powdered molecular sieves (200 mg) in dry CH_2Cl_2 (5 mL) under an atmosphere of nitrogen was added (+)-DET (107 mg, 0.52 mmol) followed by titanium isopropoxide (134 mg, 0.47 mmol) and a 4.6 M solution of *tert*-butyl hydroperoxide in CH_2Cl_2 (0.22 mL, 1.03 mmol) at -30 ^oC and the reaction mixture was stirred for 30 minutes at this temperature. A solution of **324** (94 mg, 0.47 mmol) in CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred at -25 ^oC for 5 days. The solution was warmed to 0 ^oC and a solution of ferrous sulphate (4 g) and tartaric acid (1.2 g) in water (10 mL) was added. The resulting mixture was stirred for 1 h at 0 ^oC and partitioned between water and CH_2Cl_2 and the organic layer was further extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were treated by a 30% aqueous solution of NaOH in brine, partitioned between brine and CH_2Cl_2 and the

aqueous layer was further extracted with CH_2Cl_2 (4 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:2 to afford the title compound **305** as a colourless oil (57 mg, 55%).

$[\alpha]_D^{22}$ = 51.2 ($CHCl_3$, *c* 0.41).

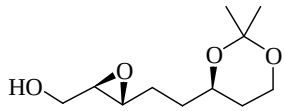
HRMS (+ESI) $[MNa]^+$ $C_{11}H_{20}O_4Na$ requires 239.1254. Found 239.1249 (1.9 ppm error).

IR (neat, cm^{-1}) ν_{max} 3453, 2984, 2926, 2871, 2856, 1457, 1380, 1371, 1259, 1216, 1159, 1064, 858, 737.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 4.19-4.09 (1H, m, OCH_2CHO), 4.05 (1H, dd, *J* 7.6, 6.0 Hz, $OCHH'CHO$), 3.71-3.62 (1H, m, $CHH'OH$), 3.61-3.55 (1H, m, $CHH'OH$), 3.53 (1H, dd, *J* 7.6, 7.2 Hz, $OCHH'CHO$), 3.07 (1H, t, *J* 5.3 Hz, CHO), 1.92-1.58 (4H, m, CH_2CH_2 and CH_2CH_2), 1.40 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.29 (3H, s, CH_3C), O*H* not observed.

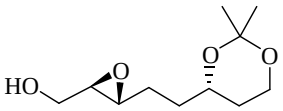
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 109.4 (*C*), 75.6 (*C*HO), 69.6 (CH_2O), 65.7 (CCH_2OH), 61.4 (*C*), 59.9 (*C*H), 30.7 (CH_2CH_2CH=C), 27.3 (CH_3), 26.0 (CH_3), 24.8 (CH_2CH_2CH=C), 14.6 (CH_3).

(2*R*,3*R*,6*R*)-{3-[2-(2,2)-Dimethyl-[1,3] dioxan-4-yl)-ethyl] oxiranyl}methanol



(2*R*,3*R*,6*R*)-306

(2*R*,3*R*,6*S*)-{3-[2-(2,2)-Dimethyl-[1,3] dioxan-4-yl)-ethyl] oxiranyl}methanol



(2*R*,3*R*,6*S*)-306

To a suspension of freshly activated 4 Å powdered molecular sieves in dry CH_2Cl_2 (15 mL) under an atmosphere of nitrogen was added (-)-D-DIPT (58 mg, 0.22 mmol) followed by titanium isopropoxide (57 mg, 0.20 mmol) and a 4.6 M solution of *tert*-

butyl hydroperoxide in CH_2Cl_2 (0.96 mL, 4.4 mmol) at -30 ^oC and the resulting reaction mixture was stirred for 45 minutes at this temperature. A solution of **310** (400 mg, 2.00 mmol) in CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred at -25^oC for 2 days. The solution was warmed to 0 ^oC and a solution of ferrous sulphate (4 g) and tartaric acid (1.2 g) in water (10 mL) was added. The resulting mixture was stirred for 1 h at 0 ^oC, partitioned between water and CH_2Cl_2 and the organic layer was further extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:2 to afford the title compound **306** as a pale yellow oil (220 mg, 51%) and as a 1:1 inseparable mixture of two diastereoisomers.

HRMS (+ESI) $[MNa]^+$ $C_{11}H_{20}O_4Na$ requires 239.1254. Found 239.1252 (0.6 ppm error).

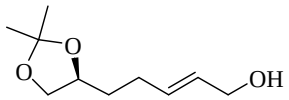
IR (neat, cm^{-1}) ν_{max} 3436 (OH), 2995, 2951, 2873, 2250, 1459, 1448, 1383, 1372, 1275, 1239, 1200, 1165, 1101, 909, 732, 649.

There was difficulty in assigning signals to a given isomer, but the following was observed:

^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.00-3.75 (4H, m, C*H*O, C*H*$_2$O and C*H*H'OH)), 3.62-3.58 (1H, m, CH*H'*$_2$O), 2.98-2.90 (2H, m, C*H*-O-CHCH$_2$OH and CH-O-C*H*CH$_2$OH), 1.80-1.46 (6H, m, CHOC*H*$_2$CH$_2$O, C*H*$_2$CH$_2$CHO and CH$_2$C*H*$_2$CHO), 1.43 (3H, s, C*H*$_3$), 1.36 (3H, s, C*H*$_3$), O*H* not observed.

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 98.7 (*C*), 98.6 (*C*), 68.9 (*C*HO), 68.4 (*C*HO) 62.0 (*C*H$_2$), 60.3 (*C*H$_2$), 58.9 (*C*H), 58.8 (*C*H), 56.3 (*C*H), 56.0 (*C*H), 33.2 (*C*H$_2$), 32.8 (*C*H$_2$), 31.6 (*C*H$_2$), 31.5 (*C*H$_2$), 30.3 (*C*H$_3$), 27.8 (*C*H$_2$), 27.3 (*C*H$_2$), 19.6 (*C*H$_3$).

(2*E*,6*S*)-5-(2,2-Dimethyl-[1,3]-dioxolan-4-yl)-pent-2-en-1-ol



307

Following general **procedure 3**, ester **318** (53 mg, 0.25 mg) in dry CH_2Cl_2 (2 mL) under an atmosphere of nitrogen was reacted with a 1 M solution of DIBAL-H in hexanes (0.54 mL, 0.55 mmol) at -20 ^oC for 5 h and for a further 1 h at RT. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **307** as a colourless oil (26 mg, 57%). Spectroscopic data in agreement with the literature values.[131]

$[\alpha]_D^{24.5}$ = 17.7 ($CHCl_3$, *c* 2.01).

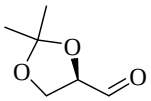
HRMS (+ESI) $[MNa]^+$ $C_{10}H_{18}O_3Na$ requires 209.1148. Found 209.1146 (1.2 ppm error).

IR (neat, cm^{-1}) ν_{max} 3412 (OH), 2987, 2930, 2868, 1671 (C=C), 1456, 1371, 1248, 1215, 1157, 1063, 1011, 969, 856, 791.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 5.71-5.61 (2H, m, C*H*=CHCH$_2$OH and CH=C*H*CH$_2$OH), 4.11-3.97 (2H, m, C*H* and OC*H*H'CHO), 3.50 (1H, dd, *J* 7.2, 6.9, OCH*H'*CHO), 2.23-2.00 (2H, m, C*H*$_2$OH), 1.79-1.49 (4H, m, C*H*$_2$CH$_2$ and CH$_2$C*H*$_2$), 1.39 (3H, s, C*H*$_3$), 1.34 (3H, s, C*H*$_3$), O*H* not observed.

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 132.3 (*C*H=CHCO$_2$Et), 130.0 (CH=*C*HCO$_2$Et), 109.1 (*C*), 75.9 (*C*HO), 69.7 (*C*H$_2$O), 63.9 (*C*H$_2$OH), 33.4 (*C*H$_2$CH$_2$CH=CHCH$_2$OH), 28.8 (CH$_2$*C*H$_2$CH=CHCH$_2$OH), 27.3 (*C*H$_3$), 26.1 (*C*H$_3$).

(2*S*)-2,2-Dimethyl-[1,3] dioxolane-4-carbaldehyde



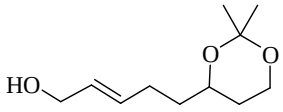
308

To a solution of 1,2-5,6-di-*O*-isopropylidene-D-mannitol **313** (10 g, 38.46 mmol) in dry CH_2Cl_2 (100 mL) was added a saturated solution of sodium hydrogen carbonate (3.6 mL). This was followed by the addition of sodium *meta*-periodate (16.45 g, 76.92 mmol), portionwise and over a period of 30 minutes. The reaction mixture was stirred for a further 2 h, then filtered and distilled at atmospheric pressure to give the title compound **308** as a colourless oil (6.67 g, 67%). Spectroscopic data in agreement with the literature values.[142]

b.p.= 150 ^{o}C, 760 Torr.

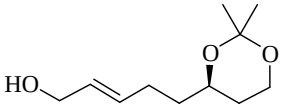
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.66 (1H, d, *J* 1.7 Hz, C*H*(O)), 4.31-4.28 (1H, m, C*H*CH(O)), 4.12-3.95 (2H, m, CH_2), 1.43 (3H, s, CH_3), 1.38 (3H, s, CH_3).

(+/-)-2*E*-5-(2,2-Dimethyl-1,3-dioxan-4-yl)pent-2-en-1-ol



310

(2*E*,6*R*)-5-(2,2-Dimethyl-1,3-dioxan-4-yl)pent-2-en-1-ol



(2*E*,6*R*)-310

Following general **procedure 3**, a solution of ester **332** (1.71 g, 7.51 mmol) in CH_2Cl_2 (40 mL) under an atmosphere of nitrogen was reacted with a 1 M solution of DIBALH in hexanes (22.53 mL, 22.53 mmol) for 50 minutes at -20 ^{o}C under nitrogen. The residue was purified by flash column chromatography eluting with petroleum ether:ethyl acetate/ 1:1 to afford the title compound **310** as a colourless oil (1.37 g, 91%).

$[\alpha]_D^{28}$ = 20.0 ($CHCl_3$, *c* 0.50). [**(2*E*,6*R*)-310**; obtained from **(2*E*,6*R*)-332**].

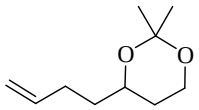
HRMS (+ESI) $[MNa]^+$ $C_{11}H_{20}O_3Na$ requires 223.1305. Found 223.1305 (0.4 ppm error).

IR (neat, cm^{-1}) ν_{max} 3400 (OH), 2993, 2940, 2868, 1670, 1456, 1434, 1382, 1371, 1272, 1252, 1237, 1200, 1162, 1124, 1096, 1058, 1001, 970, 934, 870, 846.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 5.68-5.63 (2H, m, C*H*=CH and CH=C*H*), 4.08 (2H, d, *J* 4.5 Hz, CH_2OH), 4.00-3.78 (3H, m, C*H*O and CH_2O), 2.17-2.02 (2H, m, CHOCH_2CH_2O), 1.76-1.70 (1H, brs, O*H*), 1.64-1.30 (4H, m, CHOCH_2CH_2 and CHOCH_2CH_2), 1.43 (3H, s, CH_3), 1.37 (3H, s, CH_3).

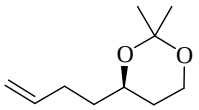
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 132.9 (*C*H), 129.8 (*C*H), 98.7 (*C*), 68.5 (*C*HO), 64.1 (*C*H_2OH), 60.4 (*C*H_2O), 36.0 (CHO*C*H_2CH_2O), 31.6 (CO*C*H_2CH_2), 30.4 (*C*H_3), 28.0 (COCH_2*C*H_2), 19.7 (*C*H_3).

(+/-)-4-But-3-en-1-yl-2,2-dimethyl-1,3-dioxane



311

(3*R*)-4-But-3-en-1-yl-2,2-dimethyl-1,3-dioxane



(3*R*)-311

Following general **procedure 4**, a solution of diol **331** (1.53 g, 11.75 mmol) in dry CH_2Cl_2 (30 mL) was reacted with 2,2-dimethoxypropane (1.47 g, 14.10 mmol) and a catalytic amount of camphorsulfonic acid for 1.5 days at RT. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 13:1 to afford the title compound **311** as a colourless oil (1.70 g) in 85% yield.

$[\alpha]_D^{23}$ = 12.4 ($CHCl_3$, *c* 1.61). [**(3*R*)-311**; obtained from **(3*R*)-331**].

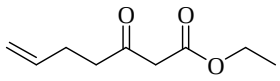
HRMS (+ESI): obtained wrong mass.

IR (neat, cm^{-1}) ν_{max} 2994, 2944, 2866, 1641 (C=C), 1458, 1444, 1381, 1370, 1273, 1251, 1237, 1200, 1168, 1113, 1100, 1057, 994, 972, 912, 845, 757.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 5.79 (1H, ddt, *J* 16.8, 10.2, 6.6 Hz, C*H*=CH_2), 5.00 (1H, dd, *J* 16.8, 1.2 Hz, CH=CH_{trans}H), 4.94 (1H, dd, *J* 10.2, 1.2 Hz, CH=CHH_{cis}), 4.00-3.74 (3H, m, C*H*O and CH_2O), 2.20-2.04 (2H, m, CHOCH_2CH_2O), 1.66-1.35 (4H, m, CHOCH_2CH_2 and CHOCH_2CH_2), 1.43 (3H, s, CH_3), 1.37 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 138.7 (*C*H=CH_2), 115.1 (CH=*C*H_2), 98.6 (*C*), 68.4 (*C*HO), 60.4 (*C*H_2O), 35.8 (CHO*C*H_2CH_2O), 31.6 (CO*C*H_2CH_2), 30.4 (*C*H_3), 29.5 (COCH_2*C*H_2), 19.6 (*C*H_3).

Ethyl 3-oxo-hept-6-enoate



312

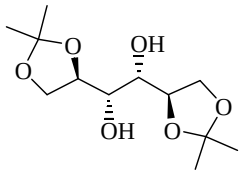
To a suspension of sodium hydride (60% *w/w* in mineral oil; 1.54g, 38.4 mmol) in dry THF (40 mL) under an atmosphere of nitrogen was added at 0 ^oC a solution of ethyl acetoacetate (5.0 g, 38.4 mmol) in dry THF (10 mL) and the reaction mixture was stirred for 30 minutes at this temperature. A 2.05 M solution of *n*-BuLi in hexanes was added dropwise and the reaction mixture was stirred for a further 30 minutes at 0 ^oC. Freshly distilled allyl bromide (4.65 g, 38.4 mmol) was added and the reaction mixture was stirred for a further 4 h at RT. An aqueous solution of hydrochloric acid (2 mL in 50 mL of water) was added, the reaction mixture was partitioned between water and ether and the aqueous layer was further extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 10:1 to afford the title compound **312** as a pale yellow oil (3.47 g, 53%).

IR (neat, cm^{-1}) ν_{max} 3080, 2982, 2936, 2913, 1743 (CO ester), 1717 (CO ketone), 1643, 1446, 1412, 1368, 1317, 1242, 1200, 1157, 1116, 1096, 1034, 1001, 917, 737.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 5.78 (1H, ddt, *J* 16.8, 10.2, 6.6 Hz, C*H*=CH_2), 5.03 (1H, dd, *J* 16.8, 1.2 Hz, CH=C*H*$_{trans}$H$_{cis}$), 4.98 (1H, dd, *J* 10.2, 1.2 Hz, CH=CH$_{trans}$*H*$_{cis}$), 4.19 (2H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 3.43 (2H, s, $COCH_2CO_2Et$), 2.64 (2H, t, *J* 7.5 Hz, $COCH_2CH_2$), 2.33 (2H, dt, *J* 7.5, 6.6 Hz, $COCH_2CH_2$), 1.26 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 207.0 (*C*O), 167.5 (CO_2Et), 136.9 (*C*H=CH_2), 115.9 (CH=*C*H$_2$), 61.8 ($CO_2CH_2CH_3$), 49.7 ($COCH_2CO_2Et$), 42.4 ($COCH_2CH_2$), 27.8 ($COCH_2CH_2$), 14.5 ($CO_2CH_2CH_3$).

(2*S*,3*S*,4*S*,5*S*)-1,2-5,6-Di-O-isopropylidene-D-mannitol



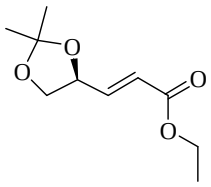
313

To D-mannitol **309** (18.22 g, 100.0 mmol) under an atmosphere of nitrogen was added a filtered solution of $ZnCl_2$ (35.44 g, 260 mmol) in acetone (180 mL) and the solution was stirred at RT for 17 h. An aqueous solution of potassium carbonate (1:1 *w*/*w*, 40 mL) was added, the mixture was filtered and the solution evaporated under reduced pressure to give a white solid. The white precipitate was washed with CH_2Cl_2 (100 mL) and the filtrate used to dissolve the white solid. The solution was partitioned between water and CH_2Cl_2 and the aqueous layer further extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The title compound **313** was recrystallised from petroleum ether: ethyl acetate/ 45:5 and isolated as a white solid (15.51 g, 59%). Spectroscopic data in agreement with the literature values.[139]

HRMS (+ESI) $[MNa]^+$ $C_{12}H_{22}O_6Na$ requires 285.1314. Found 285.1309 (1.8 ppm error).

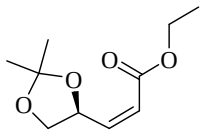
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 4.09 (4H, m, CH_2 x 2), 3.98 (2H, dd, *J* 8.3, 5.6 Hz, C*H*CH(OH) x 2), 3.74 (2H, d, *J* 6.3 Hz, C*H*(OH) x 2), 2.17 (2H, s, O*H*), 1.42 (6H, s, CH_3 x 2), 1.36 (6H, s, CH_3 x 2).

(2*E*,4*S*)-Ethyl 3-(2,2-dimethyl-[1,3]-dioxolan-4-yl)acrylate



***trans*-314**

(2*Z*,4*S*)-Ethyl 3-(2,2-dimethyl-[1,3]-dioxolan-4-yl)acrylate



***cis*-314**

To aldehyde **308** (2.48 g, 19.09 mmol) in CH_2Cl_2 (300 mL) under an atmosphere of nitrogen was added (carbethoxymethylene) triphenylphosphorane (15.96 g, 45.80 mmol) and the resulting reaction mixture was stirred at RT for 2.5 days. The reaction mixture was evaporated under reduced pressure and the residue purified by flash column chromatography eluting with ethyl acetate: petroleum ether/ 1:10 to afford the title compounds in a 1:1.2 mixture of *cis* and *trans*-alkene (2.59 g, 68%). Spectroscopic data in agreement with the literature values.[131]

***cis*-314:**

HRMS (+ESI) $[MNa]^+$ $C_{10}H_{16}O_4Na$ requires 223.0941. Found 223.0938 (1.3 ppm error).

IR (neat, cm^{-1}) ν_{max} 2983, 2926, 2851, 1720 (CO), 1644 (C=C), 1454, 1380, 1370, 1256, 1188, 1155, 1061, 1029, 829, 817, 666.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 6.36 (1H, dd, *J* 11.5, 6.6 Hz, CH=CH), 5.84 (1H, dd, *J* 11.5, 6.6 Hz, CH=CH), 5.49 (1H, ddd, *J* 13.5, 6.9, 1.5 Hz, C*H*), 4.38 (1H, dd, *J* 8.4, 7.2 Hz, CH_2), 4.16 (2H, q, *J* 7.2 Hz, OCH_2CH$_3$), 3.62 (1H, dd, *J* 8.1, 6.9 Hz, CH_2), 1.45 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.29 (3H, t, *J* 7.2 Hz, OCH$_2$CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 166.0 (*C*O), 149.6 (*C*H=CHCO$_2$Et), 121.1 (CH=*C*HCO$_2$Et), 110.0 (*C*), 73.9 (*C*HO), 69.7 (*C*H$_2$O), 60.8 (O*C*H$_2$CH$_3$), 26.9 (*C*H$_3$), 25.7 (*C*H$_3$), 14.5 (OCH$_2$*C*H$_3$).

***trans*-314:**

$[\alpha]_D^{22}$ = 41.0 ($CHCl_3$, *c* 3.7).

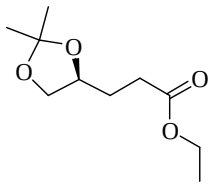
HRMS (+ESI) $[MNa]^+$ $C_{10}H_{16}O_4Na$ requires 223.0941. Found 223.0935 (2.5 ppm error).

IR (neat, cm^{-1}) ν_{max} 2987, 2935, 2873, 1724 (CO), 1663 (C=C), 1372, 1303, 1261, 1217, 1178, 1155, 1063, 1034, 978.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 6.86 (1H, dd, *J* 15.6, 5.7 Hz, C*H*=CHCO$_2$Et), 6.09 (1H, dd, *J* 15.6, 1.2 Hz, CH=C*H*CO$_2$Et), 4.69-4.62 (1H, m, C*H*), 4.19 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 4.16 (1H, dd, *J* 7.2, 2.1 Hz, C*H*H'), 3.66 (1H, dd, *J* 8.1, 7.2 Hz, CH*H*'), 1.44 (3H, s, C*H*$_3$), 1.40 (3H, s, C*H*$_3$), 1.28 (3H, t, *J* 7.2 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 166.4 (*C*O), 145.0 (*C*H=CHCO$_2$Et), 122.8 (CH=*C*HCO$_2$Et), 110.6 (*C*), 75.3 (*C*HO), 69.2 (*C*H$_2$O), 61.0 (O*C*H$_2$CH$_3$), 26.8 (*C*H$_3$), 26.1 (*C*H$_3$), 14.6 (OCH$_2$*C*H$_3$).

(4*S*)-3-(2,2-Dimethyl-[1,3]-dioxolan-4-yl) propionic acid ethyl ester



315

Following general **procedure 1**, ester **314** (120 mg, 0.6 mmol) in ethyl acetate (3 mL) was treated by platinum oxide PtO_2 (3 mg, 0.013 mmol) under a balloon of H_2 for 3 h. The residue was purified by flash column chromatography eluting with ethyl acetate:

petroleum ether/ 1:10 to afford the title compound **315** as a colourless oil (115 mg, 92%). Spectroscopic data in agreement with the literature values.[131]

$[\alpha]_D^{28}$ = 0.2 ($CHCl_3$, *c* 2.0).

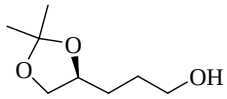
HRMS (+ESI) $[MNa]^+$ $C_{10}H_{18}O_4Na$ requires 225.1097. Found 225.1084 (6.0 ppm error).

IR (neat, cm^{-1}) ν_{max} 2986, 2936, 1736 (CO), 1371, 1303, 1256, 1214, 1178, 1157, 1075.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.12 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.10-4.02 (2H, m, OC*H*H'CHO and C*H*), 3.55 (1H, dd, *J* 7.8, 6.6 Hz, OCH*H'*CHO), 2.51-2.33 (2H, m, CH_2CO_2Et), 1.91-1.82 (2H, m, $CH_2CH_2CO_2Et$), 1.40 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.25 (3H, t, *J* 7.2 Hz, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 173.6 (*C*O), 109.4 (*C*), 75.3 (*C*HO), 69.4 (CH_2O), 60.8 ($CO_2CH_2CH_3$), 30.8 ($CH_2CH_2CO_2Et$), 29.1 ($CH_2CH_2CO_2Et$), 27.3 (CH_3), 26.0 (CH_3), 14.6 ($CO_2CH_2CH_3$).

(4*S*)-3-(2,2-Dimethyl-[1,3]-dioxolan-4-yl) propan-1-ol



316

Following **general procedure 2**, a solution of ester **315** (557 mg, 2.76 mmol) in dry THF (5 mL) under an atmosphere of nitrogen was reacted with lithium aluminium hydride (105 mg, 2.76 mmol) in dry THF (25 mL) at 0°C for 1 h and for a further 3 h at RT. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 followed by 5:1 to afford the title compound **316** as a colourless oil (368 mg, 83%). Spectroscopic data in agreement with the literature values.[131]

$[\alpha]_D^{25.3}$ = 16.7 ($CHCl_3$, *c* 1.67).

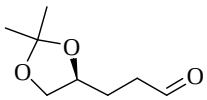
HRMS (+ESI) $[MNa]^+$ $C_8H_{16}O_3Na$ requires 183.0992. Found 183.0991 (0.6 ppm error).

IR (neat, cm^{-1}) ν_{max} 3427 (OH), 2986, 2937, 2872, 1377, 1303, 1248, 1216, 1158, 1057, 995, 851.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.13-4.02 (2H, m, C*H* and OC*H*H'CHO), 3.68-3.64 (2H, m, C$H_2$$CH_2CH_2OH$), 3.52 (1H, dd, *J* 7.5, 7.2 Hz, OCH*H'*CHO), 2.36-2.26 (1H, brs, O*H*), 1.70-1.55 (4H, m, C$H_2$$CH_2OH$ and $CH_2C$$H_2$OH), 1.40 (3H, s, C$H_3$), 1.35 (3H, s, C$H_3$).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 109.4 (*C*), 77.0 (*C*HO), 69.9 (*C*H_2O), 63.0 (*C*H_2OH), 30.6 (*C*$H_2CH_2CO_2Et$), 29.6 (CH_2*C*H_2CO_2Et), 27.3 (*C*H_3), 26.1 (*C*H_3).

(4*S*)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-propionaldehyde



317

To a solution of the Dess-Martin periodinane (10.14 g, 23.9 mmol) in dry CH_2Cl_2 (100 mL) under an atmosphere of nitrogen was added pyridine (10 mL, 123.6 mmol) and a solution of alcohol **316** (3.48 g, 21.8 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC and the resulting reaction mixture was stirred at this temperature for 3 h. Diethyl ether (180 mL) and a saturated solution of $Na_2S_2O_3$ (25 mL) were added, the solution was partitioned between water and CH_2Cl_2 and the aqueous layer was further extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Aldehyde **317** was not purified and used directly for the next step. Spectroscopic data in agreement with the literature values.[131]

$[\alpha]_D^{19}$ = -1.0 ($CHCl_3$, *c* 3.3).

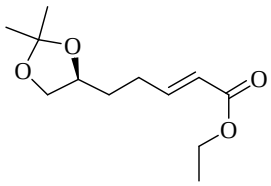
HRMS (+ESI) $[MNa]^+$ $C_8H_{14}O_3Na$ requires 181.0835. Found 181.0833 (1.0 ppm error).

IR (neat, cm^{-1}) ν_{max} 2987, 2935, 2874, 1726 (CO), 1380, 1371, 1245, 1215, 1158, 1088, 1059, 735, 666.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.79 (1H, s, COH), 4.16-4.08 (1H, m, C*H*), 4.05 (1H, dd, *J* 7.5, 6.3 Hz, OC*H*H'CHO), 3.54 (1H, dd, *J* 7.8, 6.3 Hz, OCH*H'*CHO), 2.63-2.55 (2H, m, C$H_2$$CH_2$CHO), 2.00-1.75 (2H, m, CH_2CH_2CHO), 1.39 (3H, s, CH_3), 1.33 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 207.4 (*C*O), 104.0 (*C*), 80.1 (*C*HO), 69.9 (*C*H_2O), 67.7 (*C*H_2OH), 34.2 (*C*$H_2$$CH_2$$CO_2$Et), 31.3 (*C*$H_3$ x 2), 23.8 (CH_2*C*$H_2$$CO_2$Et).

(2*E*,6*S*)-5-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-pent-2-enoic acid ethyl ester



318

Following general **procedure 6**, aldehyde **317** (2.40 g, 15.19 mmol) in dry THF (30 mL) was reacted with a solution of sodium hydride (60% *w/w* in mineral oil; 401 mg, 16.70 mmol) and triethyl phosphonoacetate (3.75 g, 16.70 mmol) in dry THF (40 mL). The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 10:1 to afford the title compound **318** as a colourless oil (1.71 g, 46% after two steps). Spectroscopic data in agreement with the literature values.[131]

$[\alpha]_D^{31}$ = 9.9 ($CHCl_3$, *c* 3.27).

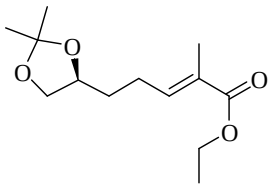
HRMS (+ESI) $[MNa]^+$ $C_{12}H_{20}O_4Na$ requires 251.1254. Found 251.1251 (1.0 ppm error).

IR (neat, cm^{-1}) ν_{max} 2985, 2936, 2874, 1719 (CO), 1656 (C=), 1455, 1447, 1380, 1369, 1308, 1265, 1211, 1158, 1065, 1046, 986, 860.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 6.95 (1H, dt, *J* 15.6, 6.9 Hz, C*H*=CHCO$_2$Et), 5.83 (1H, dt, *J* 15.6, 1.2 Hz, CH=C*H*CO$_2$Et), 4.17 (2H, q, *J* 7.2 Hz, CO$_2$C*H*$_2$CH$_3$), 4.12-4.00 (2H, m, C*H* and OC*H*H'CHO), 3.52 (1H, dd, *J* 7.2, 6.9 Hz, OCH*H'*CHO), 2.43-2.17 (2H, m, CHOC*H*$_2$CH$_2$), 1.82-1.55 (2H, m, CHOCH$_2$C*H*$_2$), 1.40 (3H, s, C*H*$_3$), 1.34 (3H, s, C*H*$_3$), 1.27 (3H, t, *J* 7.2 Hz, CO$_2$CH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 167.4 (*C*O), 148.4 (*C*H=CHCO$_2$Et), 122.2 (CH=*C*HCO$_2$Et), 109.4 (*C*), 75.5 (*C*HO), 69.6 (*C*H$_2$O), 60.6 (CO$_2$*C*H$_2$CH$_3$), 32.4 (*C*H$_2$CH$_2$CH=CHCO$_2$Et), 28.8 (CH$_2$*C*H$_2$CH=CHCO$_2$Et), 27.3 (*C*H$_3$), 26.0 (*C*H$_3$), 14.7 (CO$_2$CH$_2$*C*H$_3$).

(2*E*,6*S*)-5-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2 methyl pent-2-enoic acid ethyl ester



323

To a solution of aldehyde **317** (184 mg, 1.16 mmol) in CH_2Cl_2 (10 mL) under an atmosphere of nitrogen was added (carbethoxyethylidene)triphenylphosphorane (504 mg, 1.39 mmol) at 0 ^{o}C. The reaction mixture was stirred for 17 h at RT, evaporated under reduced pressure and purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 6:1 to afford the title compound **323** as a colourless oil (220 mg, 78%).

$[\alpha]_D^{26}$ = -19.3 ($CHCl_3$, *c* 3.08).

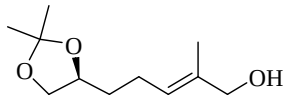
HRMS (+ESI) $[MNa]^+$ $C_{13}H_{22}O_4Na$ requires 265.1410. Found 265.1392 (6.8 ppm error).

IR (neat, cm^{-1}) ν_{max} 2985, 2935, 2868, 1711 (CO), 1651 (C=C), 1456, 1377, 1369, 1264, 1240, 1217, 1189, 1155, 1134, 1068, 858, 746, 666.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 6.74 (1H, dd, *J* 7.2, 6.3 Hz, C*H*=(Me)CO_2Et), 4.18 (2H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 4.12-4.00 (2H, m, C*H* and OC*H*H'CHO), 3.53 (1H, dd, *J* 7.2, 6.6 Hz, OCH*H'*CHO), 2.36-2.18 (2H, m, CHOCH_2CH_2), 1.83 (3H, s, CH_3), 1.78-1.57 (2H, m, $CHOCH_2CH_2$), 1.41 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.28 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 168.5 (*C*O), 141.2 (*C*HC), 128.9 (*C*), 109.3 (*C*), 75.7 (*C*HO), 69.6 (CH_2O), 60.9 ($CO_2CH_2CH_3$), 32.9 (CH_2CH_2CHC), 27.3 (CH_3), 26.1 (CH_3), 25.4 (CH_2CH_2CHC), 14.7 (CH_3), 12.7 ($CO_2CH_2CH_3$).

(2*E*,6*S*)-5-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2-methyl-pent-2-en-1-ol



324

Following general **procedure 3**, ester **323** (185 mg, 0.76 mmol) in dry CH_2Cl_2 (5 mL) under an atmosphere of nitrogen was reacted with a 1 M solution of DIBALH in hexanes (1.7 mL, 1.68 mmol) for 2 h at -20 ^{o}C. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **324** as a pale yellow oil (132 mg, 87%).

$[\alpha]_D^{27.8}$ = 24.0 ($CHCl_3$, *c* 1.7).

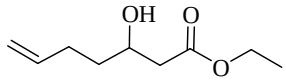
HRMS (+ESI) $[MNa]^+$ $C_{11}H_{20}O_3Na$ requires 22.1305. Found 223.1300 (2.2 ppm error).

IR (neat, cm^{-1}) ν_{max} 3413 (OH), 2986, 2934, 2868, 1671 (C=C), 1455, 1377, 1370, 1243, 1216, 1155, 1101, 1068, 1015, 858, 666.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 5.41 (1H, t, *J* 7.2 Hz, C*H*=C), 4.11-4.01 (2H, m, C*H*H'O and C*H*O), 4.00 (2H, s, CCH_2OH), 3.52 (1H, dd, *J* 7.5, 6.9 Hz, CH*H'*O), 2.20-2.04 (2H, m, CH_2CH_2C), 1.76-1.44 (3H, m, CH_2CH_2C and O*H*), 1.66 (3H, s, CH_3C), 1.41 (3H, s, CH_3), 1.34 (3H, s, CH_3).

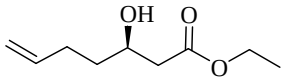
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 135.9 (*C*), 125.3 (*C*H=C), 109.1 (*C*), 76.0 (*C*HO), 69.8 (*C*H_2O), 60.2 (*C*H_2OH), 33.8 (*C*$H_2$$CH_2$CH=C), 27.4 (*C*$H_3$), 26.1 (*C*$H_3$), 24.3 ($CH_2$*C*$H_2$CH=C), 14.1 (*C*$H_3$).

(+/-)-Ethyl 3-hydroxy-hept-6-enoate



330

(3*R*)-Ethyl 3-hydroxy-hept-6-enoate



(3*R*)-330

● Reduction with sodium borohydride.

To a solution of keto-ester **312** (3.09, 18.18 mmol) in EtOH under an atmosphere of nitrogen was added at 0 ^{o}C a suspension of sodium borohydride (690 mg, 18.24 mmol) in EtOH over a period of 20 minutes. The reaction mixture was stirred for a further 10 minutes at this temperature and a saturated solution of ammonium chloride (10 mL) followed by a 1 N aqueous solution of hydrochloric acid (5 mL) were added. The reaction mixture was partitioned between water and ether and the aqueous layer was further extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 3:1 to afford the title compound **330** as a colourless oil (2.23g, 71%).

● Chiral reduction with Baker's yeast.

To Backer's yeast (22 g) was added water (600 mL), D-glucose (22 g) and methyl vinylketone (400 mg, 5.71 mmol) and the reaction mixture was stirred for 2 h at RT. A solution of keto-ester **312** (2.2 g, 12.94 mmol) in ethyl acetate (3 mL) was added and the reaction mixture was stirred for 3 days at RT (18-20 ^{o}C). The mixture was then continuously extracted with diethyl ether for 5 days, the organic extract was evaporated under reduced pressure and the residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 3:1 to afford the title compound **(*R*)-330** as a pale yellow oil (1.13 g, 51%).

$[\alpha]_D^{28.5}$ = -21.7 ($CHCl_3$, *c* 2.07).

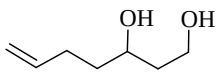
HRMS (+ESI) $[MNa]^+$ $C_9H_{16}O_3Na$ requires 195.0992. Found 195.0994 (1.3 ppm error).

IR (neat, cm^{-1}) ν_{max} 3445 (OH), 3079, 2980, 2934, 1734 (CO), 1641 (C=C), 1446, 1416, 1374, 1302, 1180, 1118, 1094, 1061, 1032, 996, 914.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 5.82 (1H, ddt, *J* 16.8, 10.2, 6.6 Hz, C*H*=CH_2), 5.05 (1H, dd, *J* 16.8, 1.2 Hz, CH=CH_{trans}H), 4.98 (1H, dd, *J* 10.2, 1.2 Hz, CH=CHH_{cis}), 4.17 (2H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 4.07-3.97 (1H, m, C*H*O), 2.60-2.50 (1H, brs, O*H*), 2.51 (1H, dd, *J* 16.5, 3.3 Hz, CHOC*H*H'CH_2O), 2.41 (1H, dd, *J* 16.5, 9.0 Hz, CHOCH*H'*CH_2O), 2.28-2.04 (2H, m, CHOCH_2CH_2), 1.67-1.52 (2H, m, $CHOCH_2CH_2$), 1.27 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$).

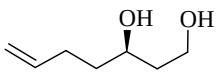
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 173.4 (*C*O), 138.5 (*C*H=CH_2), 115.4 (CH=*C*H_2), 67.8 (*C*HO), 61.1 ($CO_2CH_2CH_3$), 41.6 ($COCH_2CO_2Et$), 35.9 ($COCH_2CH_2$), 30.1 ($COCH_2CH_2$), 14.6 ($CO_2CH_2CH_3$).

(+/-)-Hept-6-ene-1,3-diol



331

(3*R*)-Hept-6-ene-1,3-diol



(3*R*)-331

Following general **procedure 2**, a solution alcohol **330** (2.20 g, 12.8 mmol) in dry THF (20 mL) was reacted with lithium aluminium hydride (971 mg, 35.6 mmol) in dry THF (30 mL) at 0 ^oC for 40 minutes. The residue was purified by flash column chromatography eluting with 100% diethyl ether to afford the title compound **331** as a colourless oil (1.56 g, 94%).

$[\alpha]_D^{28}$ = 7.1 ($CHCl_3$, *c* 0.42). [**(3*R*)-331**; obtained from **(3*R*)-330**].

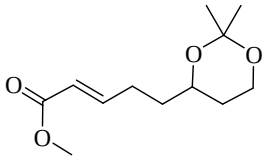
HRMS (+ESI) $[MNa]^+$ $C_7H_{14}O_2Na$ requires 153.0886. Found 153.0871 (9.9 ppm error).

IR (neat, cm^{-1}) ν_{max} 3350, 2937, 2884, 1641, 1445, 1417, 1375, 1340, 1267, 1098, 1059, 996, 975, 912, 738.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 5.83 (1H, ddt, *J* 16.8, 9.9, 6.6 Hz, C*H*=CH_2), 5.05 (1H, dt, *J* 16.8, 1.5 Hz, CH=$CH_{cis}H_{trans}$), 4.97 (1H, dd, *J* 9.9, 1.5 Hz, CH=C$H_{cis}H_{trans}$), 3.93-3.75 (3H, m, C*H*OH and CH_2OH), 2.64 (2H, brs, O*H* x 2), 2.26-2.04 (2H, m, CH_2(OH)CH_2CH(OH)), 1.72-1.66 (2H, m, CH_2CH_2CH=CH_2), 1.66-1.52 (2H, m, CH_2CH_2CH=CH_2).

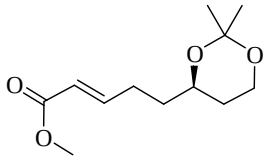
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 138.5 (*C*H=CH_2), 115.3 (CH=*C*H_2), 72.1 (*C*HOH), 62.1 (*C*H_2OH), 38.6 (*C*H_2), 37.1 (*C*H_2), 30.3 (*C*H_2).

(+/-)-Methyl (2*E*)-5-(2,2-dimethyl-1,3-dioxan-4-yl)pent-2-enoate



332

(2*E*,6*R*)-Methyl-5-(2,2-dimethyl-1,3-dioxan-4-yl)pent-2-enoate



(2*E*,6*R*)-332

To a solution of **311** (1.45 g, 8.53 mmol) in dry CH_2Cl_2 (30 mL) was added freshly distilled methyl acrylate (2.94 g, 34.12 mmol) followed by the 2nd generation of Grubb's catalyst (88 mg, 0.10 mmol). The reaction mixture was heated under reflux for 1 h, evaporated under reduced pressure and purification by flash column chromatography eluting with petroleum ether: ethyl acetate/ 7:1 to afford the title compound **332** as a colourless oil (1.75 g, 90%).

$[\alpha]_D^{21.5}$ = 26.3 ($CHCl_3$, *c* 1.64). [**(2*E*,6*R*)-332**; obtained from **(3*R*)-311**].

HRMS (+ESI) $[MNa]^+$ $C_{12}H_{20}O_4Na$ requires 251.1254. Found 251.1245 (3.7 ppm error).

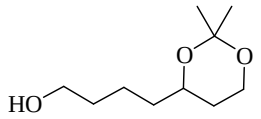
IR (neat, cm^{-1}) ν_{max} 2993, 2950, 2867, 1727 (CO), 1657 (C=C), 1459, 1437, 1381, 1371, 1325, 1312, 1273, 1250, 1238, 1199, 1173, 1163, 1126, 1107, 1043, 972, 836.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 6.96 (1H, dt, *J* 15.6, 6.9 Hz, C*H*=CHCO_2Me), 5.82 (1H, dd, *J* 15.6, 1.2 Hz, CH=C*H*CO_2Me), 4.00-3.91 (1H, m, C*H*H'O), 4.85-3.78 (2H, m,

C*H*O and CH*H'*O), 3.72 (3H, s, CO_2CH_3), 2.41-2.18 (2H, m, $CHOCH_2CH_2O$), 1.75-1.48 (4H, m, $CHOCH_2CH_2$ and $CHOCH_2CH_2$), 1.42 (3H, s, CH_3), 1.37 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 167.5 (*C*O), 149.4 (*C*H=CHCO$_2$Me), 121.6 (CH=*C*HCO$_2$Me), 98.7 (*C*), 68.2 (*C*HO), 60.3 (*C*H$_2$O), 51.8 (CO_2CH_3), 34.9 ($CHOCH_2CH_2O$), 31.6 ($COCH_2CH_2$), 30.3 (CH_3), 28.1 ($COCH_2CH_2$), 19.6 (CH_3).

(+/-)-4-(2,2-Dimethyl-1,3-dioxan-4-yl)butan-1-ol



333

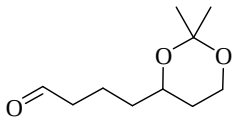
To a 1 M solution of borane in THF (6.0 mL, 6.0 mmol) under an atmosphere of nitrogen was added a 2 M solution of 2-methyl-2-butene in THF (6.0 mL, 12.0 mmol) at -5 ^{o}C and the resulting mixture was stirred for 2 h at 0 ^{o}C. To the solution of disiamylborane in THF previously made was added a solution of alkene **311** (882 mg, 5.18 mmol) in dry THF (3 mL) and the reaction was stirred at 0 ^{o}C for 1 h and for a further 1.5 h at RT. A 3 N aqueous solution of sodium hydroxide (2.0 mL, 6.0 mmol) followed by a 35% *v/v* aqueous solution of hydrogen peroxide (0.40 mL, 6.0 mmol) were added, the reaction mixture partitioned between water and diethyl ether and the aqueous layer further extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with 100% diethyl ether to afford the title compound **333** as a colourless oil (216 mg, 21%).

HRMS (+ESI) $[MNa]^+$ $C_{10}H_{20}O_3Na$ requires 211.1305. Found 211.1305 (0.2 ppm error).

IR (neat, cm^{-1}) ν_{max} 3401 (OH), 2993, 2940, 2865, 1478, 1461, 1429, 1381, 1369, 1273, 1244, 1199, 1164, 1101, 1062, 971, 947, 869, 852, 755.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 4.00-3.60 (5H, m, C*H*O, CH_2O and CH_2OH), 1.60-1.40 (8H, m, CH_2 x 4), 1.43 (3H, s, CH_3), 1.37 (3H, s, CH_3), O*H* not observed.
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 98.6 (*C*), 69.3 (*C*HO), 63.1 (*C*H_2O), 60.4 (*C*H_2OH), 36.5 (*C*H_2), 32.9 (*C*H_2), 31.6 (*C*H_2), 30.4 (*C*H_3), 21.6 (*C*H_2), 19.6 (*C*H_3).

(+/-)-4-(2,2-Dimethyl-1,3-dioxan-4-yl)butanal



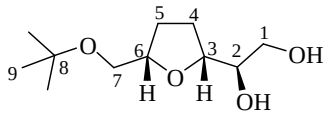
334

To a solution of alcohol **333** (176 mg, 0.94 mmol) in CH_2Cl_2 (1.41 mL) under an atmosphere of nitrogen was added DMSO (1.34 mL, 18.87 mmol) followed by triethylamine (0.72 mL, 4.7 mmol) and SO_3-pyridine (748 mg, 4.7 mmol) at 0 ^{o}C. The reaction mixture was stirred for 45 minutes at this temperature, diluted by diethyl ether (10 mL), quenched with water (10 mL) and partitioned between water and diethyl ether. The aqueous layer was further extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 3:1 to afford the title compound **334** as a pale yellow oil (58 mg, 33%). Spectroscopic data in agreement with the literature values.[171]

IR (neat, cm^{-1}) ν_{max} 2993, 2945, 2868, 1725 (CO), 1450, 1436, 1411, 1381, 1370, 1271, 1199, 1163, 1132, 1101, 1062, 970, 948, 912, 871, 852, 839.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.76 (1H, t, *J* 1.2 Hz, C*H*O), 4.00-3.76 (3H, m, C*H*O, CH_2O), 2.45-2.42 (2H, m, CH_2CHO), 1.73-1.36 (8H, m, CH_2 x 4), 1.43 (3H, s, CH_3), 1.37 (3H, s, CH_3).

(2*R*,3*R*,6*S*)-1-(5-*tert*-Butoxymethyl-tetrahydro-furan-2-yl)-ethane-1,2-diol



338a

Following general **procedure 5**, epoxy-acetal **304a** (68 mg, 0.34 mmol) was reacted with a 2 M solution of $AlMe_3$ (0.52 mL, 1.04 mmol) in dry CH_2Cl_2 (2 mL) for 3 h at -20 ^oC under an atmosphere of nitrogen. The residue was purified by flash column chromatography eluting with hexane: ethyl acetate/ 1:1 followed by 1:2 to afford the title compound **338a** as a colourless oil (43 mg, 59%).

$[\alpha]_D^{29}$= 7.2 ($CHCl_3$, *c* 0.6).

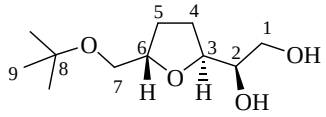
HRMS (+ESI) $[MNa]^+$ $C_{11}H_{22}O_4Na$ requires 241.1410. Found 241.1403 (2.9 ppm error).

IR (neat, cm^{-1}) ν_{max} 3401, 2975, 2934, 2876, 1725, 1464, 1391, 1365, 1255, 1237, 1197, 1072, 1028, 888, 736, 702.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.15-4.09 (1H, m, H-6), 4.08-4.01 (1H, m, H-3), 3.89-3.83 (1H, m, H-2), 3.60 (2H, d, *J* 5.4 Hz, H-7), 3.63-3.58 (1H, m, H-1), 3.32 (1H, dd, *J* 9.6, 2.7 Hz, H-1'), 2.96 (2H, brs, O*H* x 2), 2.03-1.83 (4H, m, H-4 and H-5), 1.21 (9H, s, H-9).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 81.8 (C-3), 78.7 (C-6), 74.0 (C-8), 73.9 (C-2), 64.1 and 64.0 (C-1 and C-7), 28.3 (C-4 or C-5), 27.7 (C-9), 26.6 (C-4 or C-5).

(2*R*,3*S*,6*S*)-1-(5-*tert*-Butoxymethyl-tetrahydro-furan-2-yl)-ethane-1,2-diol



338b

Following general **procedure 5**, epoxy-acetal **304b** (158 mg, 0.78 mmol) was reacted with a 2 M solution of $AlMe_3$ (1.20 mL, 2.39 mmol) in dry CH_2Cl_2 for 3 h at -20 ^oC under an atmosphere of nitrogen. The residue was purification by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **338b** as a colourless oil (120 mg, 70%).

$[\alpha]_D^{29}$ = -8.2 ($CHCl_3$, *c* 0.82).

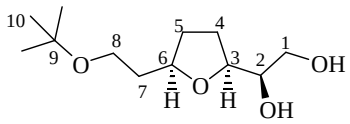
HRMS (+ESI) $[MNa]^+$ $C_{11}H_{22}O_4Na$ requires 241.1410. Found 241.1407 (1.3 ppm error).

IR (neat, cm^{-1}) ν_{max} 3401, 2974, 2925, 2872, 1728, 1463, 1388, 1365, 1264, 1235, 1198, 1069, 1026, 887, 737, 702, 666.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.15-4.06 (1H, m, H-6), 3.99-3.92 (1H, m, H-3), 3.81-3.75 (1H, m, H-2), 3.69 (1H, dd, *J* 11.4, 3.6 Hz, C-1), 3.60 (1H, dd, *J* 11.4, 6.5 Hz, H-1'), 3.39-3.27 (2H, m, H-7), 2.81 (2H, brs, O*H* x 2), 2.06-1.80 (2H, m, H-4 or H-5), 1.71-1.61 (2H, m, H-4 or H-5), 1.18 (9H, s, H-9).

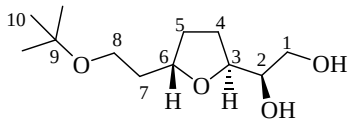
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 80.3 (C-3), 79.2 (C-6), 73.6 and 73.5 (C-2 and C-8), 65.1 and 64.2 (C-1 and C-7), 29.0 and 27.2 (C-4 and C-5), 27.8 (C-9).

(2*R*,3*S*,6*R*)-1-(5-(2-*tert*-Buthoxy)-tetrahydro-furan-2-yl]-ethane-1,2-diol



(2*R*,3*S*,6*R*)-339

(2*R*,3*S*,6*S*)-1-(5-(2-*tert*-Buthoxy)-tetrahydro-furan-2-yl]-ethane-1,2-diol



(2*R*,3*S*,6*S*)-339

Following general **procedure 5**, epoxy-acetal **306** (178 mg, 0.82 mmol) was reacted with a 2 M solution of $AlMe_3$ (1.24 mL, 2.47 mmol) in dry CH_2Cl_2 (10 mL) for 3 h at -20 ^oC under an atmosphere of nitrogen. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:3 to afford the title compound **339** as a colourless oil (82 mg, 43%) and as a 1:1 unseparable mixture of both diastereoisomers.

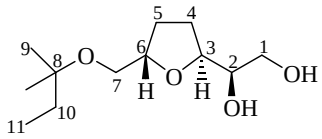
HRMS (+ESI) $[MNa]^+$ $C_{12}H_{24}O_4Na$ requires 255.1567. Found 255.1555 (4.7 ppm error).

IR (neat, cm^{-1}) ν_{max} 3400, 2973, 2936, 2874, 1649, 1464, 1446, 1391, 1363, 1251, 1233, 1198, 1073, 1023, 937, 905, 875, 734.

^1H NMR ($CDCl_3$, 300 MHz) δ_H (Due to overlapping signals, there was difficulty in assigning signals to a given isomer, but the following was observed) 4.10-3.85 (4H, m, H-3 x 2 and H-6 x 2), 3.80-3.39 (6H, m, H-1 x 2 and H-2 x 2), 3.46 (3H, t, *J* 6.3 Hz, H-8), 3.42 (3H, t, *J* 6.3 Hz, H-8), 2.55 (4H, brs, O*H* x 4), 2.06-1.52 (12H, m, H-4 x 2, H-5 x 2, H-7 x 2), 1.18 (9H, s, H-10), 1.17 (9H, s, H-10).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 81.0 (*C*H), 80.1 (*C*H), 78.1 (*C*H), 77.6 (*C*H), 73.6 (CH_2), 73.4 (CH_2), 73.2 (CH_2), 73.1 (CH_2), 64.5 (CH_2), 64.2 (CH_2), 59.5 (CH_2), 59.1 (CH_2), 37.1 (CH_2 x 2), 32.5 (CH_2), 31.7 (CH_2), 28.1 (CH_2), 27.9 (C-9), 27.8 (C-9), 26.3 (CH_2).

(2*R*, 3*S*,6*S*)-1-[5-(1,1-Dimethyl-propoxymethyl)-tetrahydrofuran-2-yl]-ethane-1,2-diol



340

Following general **procedure 5**, epoxy-acetal **304a** (200 mg, 1.0 mmol) was reacted with a 1 M solution of triethylaluminium (3.0 mL, 3.0 mmol) in dry CH_2Cl_2 (10 mL) for 24 h at -20 ^oC under an atmosphere of nitrogen. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:2 then by a second flash column chromatography eluting with methanol: chloroform/ 1:30 to afford the title compound **340** as a pale yellow oil (45 mg, 19%).

$[\alpha]_D^{23}$ = 6.0 ($CHCl_3$, *c* 1.1).

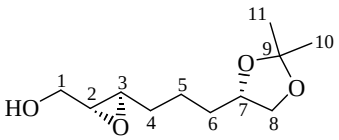
HRMS (+ESI) $[MNa]^+$ $C_{12}H_{24}O_4Na$ requires 255.1567. Found 255.1564 (0.9 ppm error).

IR (neat, cm^{-1}) ν_{max} 3400, 2971, 2923, 2878, 1463, 1380, 1364, 1396, 1241, 1193, 1179, 1158, 1069, 1058, 1000, 930, 917, 893, 865.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 4.17-4.10 (1H, m, H-6), 4.10-4.02 (1H, m, H-3), 3.91 (1H, m, H-2), 3.68-3.58 (2H, app. brs, H-1), 3.57 (1H, app. d, *J* 9.7 Hz, H-7), 3.30 (1H, app. d, *J* 9.7 Hz, H-7'), 2.41-2.20 (1H, brs, O*H*), 2.08-1.82 (4H, m, H-4 and H-5), 1.79-1.51 (1H, brs, O*H*), 1.51 (2H, q, *J* 7.3 Hz, H-10), 1.15 (6H, s, H-9 x 2), 0.88 (3H, t, *J* 7.3 Hz, H-11).

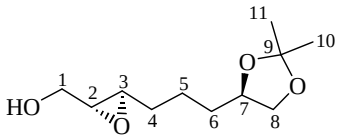
^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 81.5 (C-3), 78.7 (C-6), 75.6 (C-8), 73.5 (C-2), 63.7 and 63.2 (C-1 and C-7), 32.4 (C-10), 27.9 (C-5), 26.3 (C-4), 24.9 (C-9), 24.7 (C-9), 8.2 (C-11).

(2*R*,3*R*,7*S*)-{3-[3-(2,2-Dimethyl-[1,3] dioxolan-4-yl)-propyl]-oxiranyl}-methanol



(2*R*,3*R*,7*S*)-345

(2*R*,3*R*,7*R*)-{3-[3-(2,2-Dimethyl-[1,3] dioxolan-4-yl)-propyl]-oxiranyl}-methanol



(2*R*,3*R*,7*R*)-345

To a suspension of freshly activated 4 Å powdered molecular sieves in dry CH_2Cl_2 (15 mL) under an atmosphere of nitrogen was added (+)-DET (34 mg, 0.17 mmol) followed by titanium *iso*-propoxide (43 mg, 0.15 mmol) and a 4.6 M solution of *tert*-butyl hydroperoxide in CH_2Cl_2 (0.72 mL, 3.30 mmol) at -30 ^oC and the reaction mixture was stirred for 45 minutes at this temperature. A solution of **350** (300 mg, 1.50 mmol) in CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred at -25 ^oC for 1 day. The solution was warmed to 0 ^oC and a solution of ferrous sulphate (4 g) in water (10 mL) was added. The resulting mixture was stirred for 1 h at 0 ^oC, partitioned between water and CH_2Cl_2 and the organic layer was further extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:2 to afford the title compounds **(2*R*,3*R*,7*S*) and (2*R*,3*R*,7*R*)-345** as a pale yellow oil (196 mg, 60%).

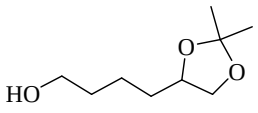
HRMS (+ESI) $[MNa]^+$ $C_{11}H_{20}O_4Na$ requires 239.1254. Found 239.1253 (0.3 ppm error).

IR (neat, cm^{-1}) ν_{max} 3436, 2986, 2936, 2867, 1457, 1434, 1379, 1370, 1249, 1216, 1159, 1095, 1062, 990, 887, 858.

^1H NMR ($CDCl_3$, 500 MHz) δ_H 4.10-3.98 (2H, m, H-7 and H-8), 3.91-3.82 (1H, m, H-8'), 3.64-3.54 (1H, m, H-1), 3.52-3.45 (1H, m, H-1'), 2.97-2.86 (2H, m, H-2 and H-3), 2.21 (1H, brs, O*H*), 1.72-1.42 (6H, m, H-4, H-5, H-6), 1.38 (3H, s, H-10 or H-11), 1.32 (3H, s, H-10 or H-11).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 108.7 (*C*), 75.8 and 75.7 (C-7), 69.31 and 69.30 (C-8), 61.7 and 61.6 (C-1), 58.4 and 58.3 (C-2 or C-3), 55.7 and 55.6 (C-2 or C-3), 33.3 and 33.1 (C-4 or C-6), 31.5 and 31.4 (C-4 or C-6), 26.8 and 25.6 (C-10 and C-11), 22.3 and 22.2 (C-5).

(+/-)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)butan-1-ol



347

Following general **procedure 4**, 1,2,6-trihydroxyhexane **346** (1.34 g, 10.0 mmol) in dry CH_2Cl_2 (20 mL) under an atmosphere of nitrogen was reacted with 2,2-dimethoxypropane (1.56 g, 15.0 mmol) and a catalytic amount of camphorsulfonic acid at RT for 2 h. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **347** as a colourless oil (1.49 g, 96%). Spectroscopic data in agreement with the literature values.[172]

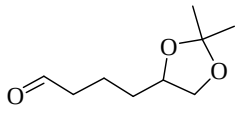
HRMS (+ESI) $[MNa]^+$ $C_9H_{18}O_3Na$ requires 197.1148. Found 197.1150 (1.0 ppm error).

IR (neat, cm^{-1}) ν_{max} 3401, 2986, 2940, 2937, 2867, 1457, 1379, 1370, 1248, 1216, 1248, 1216, 1157, 1092, 1080, 856.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 4.12-4.05 (1H, m, C*H*O), 4.02 (1H, dd, *J* 7.2, 6.9 Hz, C*H*H'O), 3.64 (2H, t, *J* 6.4 Hz, CH_2OH), 3.50 (1H, dd, *J* 7.2, 6.9 Hz, CH*H*'O), 1.46 (1H, brs, O*H*), 1.75-1.21 (6H, m, CH_2 x 3), 1.39 (3H, s, CH_3), 1.34 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 109.1 (*C*), 76.4 (*C*HO), 69.8 (*C*H_2O), 63.0 (*C*H_2OH), 33.6 (*C*H_2), 33.0 (*C*H_2), 27.3 (*C*H_3), 26.1 (*C*H_3), 22.4 (*C*H_2).

(+/-)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)butanal



348

To a solution of alcohol **347** (1.39 g, 7.99 mmol) in DMSO (11 mL) CH_2Cl_2 (12 mL)under an atmosphere of nitrogen was added triethylamine (5.6 mL, 39.95 mmol) and SO_3-py (6.36 g, 39.95 mmol) at 0 ^oC and the resulting reaction mixture was stirred for 1 h at this temperature. The reaction mixture was diluted with diethyl ether (100 mL) and water (40 mL), partitioned between ether and water and the aqueous layer was further extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (1 x 40 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purification by flash column chromatography eluting with petroleum ether: ethyl acetate/ 3:1 to afford the title compound **348** as a pale yellow oil (1.05 g, 76%). Spectroscopic data in agreement with the literature values.[172]

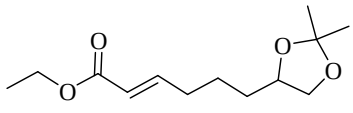
HRMS (+ESI) $[MNa]^+$ $C_9H_{16}O_3Na$ requires 195.0992. Found 195.0992 (0 ppm error).

IR (neat, cm^{-1}) ν_{max} 2986, 2937, 2872, 2724, 1727 (CO), 1457, 1412, 1380, 1370, 1249, 1216, 1158, 1095, 1060, 856.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.12-4.05 (1H, t, *J* 1.2 Hz, C*H*=O), 4.11-3.99 (2H, m, C*H*O and C*H*H'O), 3.50 (1H, dd, *J* 7.2, 6.9 Hz, CH*H*'O), 2.25 (2H, dt, *J* 7.2, 1.2 Hz, CH_2CH=O), 1.60-1.28 (4H, m, CH_2 x 2), 1.38 (3H, s, CH_3), 1.32 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 202.5 (*C*O), 109.2 (*C*), 76.0 (*C*HO), 69.6 (*C*H_2O), 44.0 (*C*H_2), 33.2 (*C*H_2), 27.3 (*C*H_3), 26.0 (*C*H_3), 18.7 (*C*H_2).

(+/-)-Ethyl (2*E*)-6-(2,2-dimethyl-1,3-dioxolan-4-yl)hex-2-enoate



349

Following general **procedure 6**, aldehyde **348** (0.99 g, 5.76 mmol) in dry THF (5 mL) was reacted with sodium hydride (60% *w/w* in mineral oil; 276 mg, 6.91 mmol) and triethyl phosphonoacetate (1.55 g, 6.91 mmol) in dry THF (40 mL). The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 5:1 to afford the title compound **349** as a pale yellow oil (1.15 g, 82%).

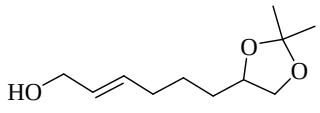
HRMS (+ESI) $[MNa]^+$ $C_{13}H_{22}O_4Na$ requires 265.1410. Found 265.1408 (1.0 ppm error).

IR (neat, cm^{-1}) ν_{max} 2985, 2937, 2870, 1721 (CO), 1655 (C=C), 1458, 1379, 1369, 1267, 1212, 1193, 1163, 1057, 1049, 982, 854.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 6.92 (1H, dt, *J* 15.4, 6.9 Hz, C*H*=CHCO$_2$Et), 5.80 (1H, dd, *J* 15.4, 0.9 Hz, CH=C*H*CO$_2$Et), 4.16 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 4.12-4.01 (1H, m, C*H*O), 4.01 (1H, dd, *J* 7.2, 6.6 Hz, C*H*H'O), 3.49 (1H, dd, *J* 7.2, 6.6 Hz, CH*H'*O), 2.23 (2H, dt, *J* 6.9, 6.8 Hz, C*H*$_2$CH=CHCO$_2$Et), 1.67-1.43 (4H, m, C*H*$_2$ x 2), 1.39 (3H, s, C*H*$_3$), 1.33 (3H, s, C*H*$_3$), 1.27 (3H, t, *J* 7.2 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 167.0 (*C*O), 148.9 (*C*H=CHCO$_2$Et), 122.1 (CH=*C*HCO$_2$Et), 109.2 (*C*), 76.1 (*C*HO), 69.9 (*C*H$_2$O), 60.6 (O*C*H$_2$CH$_3$), 33.3 (*C*H$_2$), 32.4 (*C*H$_2$), 27.3 (*C*H$_3$), 26.1 (*C*H$_3$), 22.6 (*C*H$_2$), 14.6 (OCH$_2$*C*H$_3$).

(+/-)-(2*E*)-6-(2,2-Dimethyl-1,3-dioxolan-4-yl)hex-2-en-1-ol



350

Following general **procedure 3**, a solution of compound **349** (1.04 g, 4.31 mmol) in dry CH_2Cl_2 (5 mL) under an atmosphere of nitrogen was reacted at -20 ^oC with a 1 M solution of DIBAL-H in hexanes (12.92 mL, 12.92 mmol) for 45 minutes. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **350** as a colourless oil (630 mg, 73%).

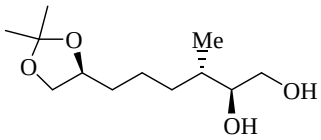
HRMS (+ESI) $[MNa]^+$ $C_{11}H_{20}O_3Na$ requires 223.1305. Found 223.1305 (0.3 ppm error).

IR (neat, cm^{-1}) ν_{max} 3401 (OH), 2986, 2935, 2865, 1670, 1457, 1438, 1379, 1371, 1249, 1216, 1156, 1086, 1059, 1002, 971, 859.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 5.66-5.62 (2H, m, C*H*=CHCH$_2$OH and CH=C*H*CH$_2$OH), 4.07-3.99 (4H, m, C*H*O, C*H*H'O and CH_2OH), 3.49 (1H, t, *J* 7.1 Hz, CH*H*'O), 2.10-2.03 (2H, m, CH_2), 2.00-1.98 (2H, m, CH_2), 1.55-1.40 (2H, m, CH_2), 1.39 (3H, s, CH_3), 1.34 (3H, s, CH_3), O*H* not observed.

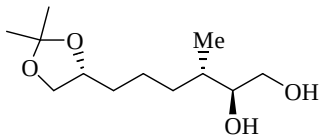
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 132.9 (*C*H), 129.8 (*C*H), 109.1 (*C*), 76.3 (*C*HO), 69.8 (*C*H$_2$O), 64.0 (*C*H$_2$OH), 33.3 (*C*H$_2$), 32.5 (*C*H$_2$), 27.3 (*C*H$_3$), 26.1 (*C*H$_3$), 25.6 (*C*H$_2$).

(2*S*,3*S*,7*R*)-6-(2,2-Dimethyl-[1,3] dioxolan-4-yl)-3-methyl-hexane-1,2-diol



(2*S*,3*S*,7*R*)-351

(2*S*,3*S*,7*S*)-6-(2,2-Dimethyl-[1,3] dioxolan-4-yl)-3-methyl-hexane-1,2-diol



(2*S*,3*S*,7*S*)-351

Following general **procedure 5**, epoxy-acetal **345** (166 mg, 0.77 mmol) under an atmosphere of nitrogen was reacted with a 2 M solution of trimethylaluminium (2.30 mL, 4.60 mmol) in dry CH_2Cl_2 (6 mL) for 1.5 h at -20 ^oC. The residue was purified by flash column chromatography eluting with petroleum ether:ethyl acetate/ 1:3 to afford the title compound **351** as a colourless oil (104 mg, 58%) and as an unseparable mixture of both diastereoisomers.

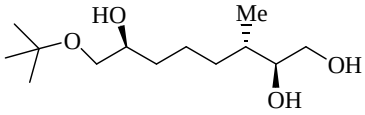
HRMS (+ESI) $[MNa]^+$ $C_{12}H_{24}O_4Na$ requires 255.1567. Found 255.1562 (1.8 ppm error).

IR (neat, cm^{-1}) ν_{max} 3401, 2982, 2935, 2869, 1647, 1456, 1382, 1370, 1320, 1249, 1216, 1160, 1063, 982, 958, 861, 666.

^1H NMR (d_6-DMSO, 300 MHz) δ_H 4.41-4.19 (1H, m, C*H*O), 4.08-3.79 (1H, m, C*H*H'O), 3.45-3.05 (4H, m, CH*H'*O, CH_2OH, C*H*OH), 1.61-1.10 (7H, m, CH_2 x 3, C*H*), 1.29 (3H, s, CH_3), 1.24 (3H, s, CH_3), 0.80 (3H, d, *J* 6.5 Hz, CH_3), O*H* not observed.

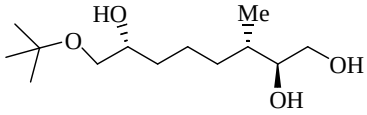
^{13}C NMR (d_6-DMSO, 75 MHz) δ_C 108.1 (*C*), 75.8 (*C*HO), 75.4 (*C*HO), 69.1 (*C*H_2O), 63.8 (*C*H_2O), 35.5 (*C*H), 33.9 (*C*H_2), 31.5 (*C*H_2), 27.2 (*C*H_3), 26.0 (*C*H_3), 23.4 (*C*H_2), 16.1 (*C*H_3).

(2*S*,3*S*,7*R*)-8-*tert*-Butoxy-3-methyl-octane-1,2,7-triol



(2*S*,3*S*,7*R*)-352

(2*S*,3*S*,7*S*)-8-*tert*-Butoxy-3-methyl-octane-1,2,7-triol



(2*S*,3*S*,7*S*)-352

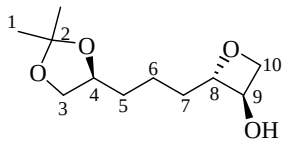
Following general **procedure 5**, epoxy-acetal **345** (166 mg, 0.77 mmol) under an atmosphere of nitrogen was reacted with a 2 M solution of trimethylaluminium (2.30 mL, 4.60 mmol) in dry CH_2Cl_2 (6 mL) for 1.5 h at -20 ^oC. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:3 to afford the title compound **352** as a colourless oil (50 mg, 26%) and as a unseparable mixture of both diastereoisomers.

HRMS (+ESI) $[MNa]^+$ $C_{13}H_{28}O_4Na$ requires 271.1880. Found 271.1878 (0.8 ppm error).

^1H NMR ($CDCl_3$, 300 MHz) δ_H 3.72-3.35 (6H, m, C*H*$_2$OH, C*H*$_2$O*t*-Bu, C*H*OH x 2), 3.20-2.90 (3H, brs, O*H* x 3), 1.63-1.27 (7H, m, C*H*$_2$ x 3, C*H*), 1.19 (9H, s, C*H*$_3$), 0.85 (3H, d, *J* 6.9 Hz, C*H*$_3$).

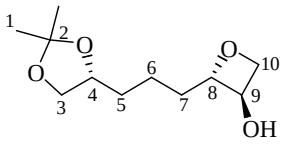
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 76.4 (*C*HO), 76.3 (*C*HO), 74.4 (*C*), 71.9 (*C*HO), 71.8 (*C*HO), 65.6 (*C*H$_2$O), 65.5 (*C*H$_2$O), 64.9 (*C*H$_2$O), 36.3 (*C*H), 36.2 (*C*H), 33.9 (*C*H$_2$), 33.0 (*C*H$_2$), 29.0 (*C*H$_3$), 23.1 (*C*H$_2$), 15.7 (*C*H$_3$), 15.6 (*C*H$_3$).

(2*R*,3*S*,7*R*)-2-[3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-propyl]-oxetan-3-ol



(2*R*,3*S*,7*R*)-353

(2*R*,3*S*,7*S*)-2-[3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-propyl]-oxetan-3-ol



(2*R*,3*S*,7*S*)-353

To a solution of epoxy-acetal **345** (103 mg, 0.47 mmol) in CH_2Cl_2 (2 mL) under an atmosphere of nitrogen was added at -30 ^oC boron trifluoride etherate (67 mg, 0.47 mmol) followed by a 2 M solution of trimethylaluminium in heptanes (0.71 mL, 1.42 mmol) and the reaction mixture was stirred for 30 minutes at this temperature. The reaction mixture was quenched with water (2 mL) and a few drops of concentrated hydrogen chloride, diluted with CH_2Cl_2 (5 mL), partitioned between water and dichloromethane and the aqueous layer was further extracted with dichloromethane (3 x 5 mL). the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **353** as a colourless oil (30 mg, 29%) and as an unseparable mixture of both diastereoisomers.

HRMS (+ESI) $[MNa]^+$ $C_{11}H_{20}O_4Na$ requires 239.1254. Found 239.1253 (0.4 ppm error).

IR (neat, cm^{-1}) ν_{max} 3403, 2992, 2930, 2863, 2243, 1458, 1439, 1380, 1370, 1256, 1212, 1153, 1099, 1068, 1047, 910, 731.

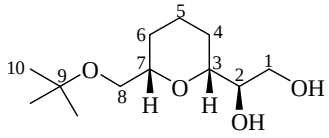
The title compound was obtained as a mixture of two diastereoisomers. The following was observed:

^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.21-3.20 (14H, m, H-3, H-4, H-8, H-9, H-10), 2.00-1.30 (14H, m, H-5, H-6, H-7, O*H*), 1.40 (3H, s, H-1), 1.39 (3H, s, H-1), 1.36 (3H, s, H-1), 1.35 (3H, s, H-1).

^{13}C NMR ($CDCl_3$, 75 MHz) 1st diastereoisomer: δ_C 109.8 (C-2), 75.8, 73.1, 73.0 (C-4, C-8, C-9), 67.6, 63.9 (C-3, C-10), 27.1 and 25.8 (C-1), 26.5, 26.3, 18.5 (C-5, C-6, C-7).

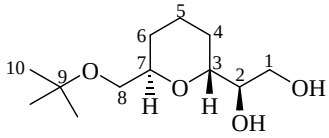
2nd diastereoisomer: δ_C 109.7 (C-2), 78.9, 78.6, 78.5 (C-4, C-8, C-9), 67.2, 66.5 (C-3, C-10), 28.1, 27.4, 22.8 (C-5, C-6, C-7), 27.0 and 25.7 (C-1).

(2*R*,3*R*,7*S*)-1-(6-*tert*-Butoxymethyl-tetrahydro-pyran-2-yl)-ethane-1,2-diol



(2*R*,3*R*,7*S*)-354

(2*R*,3*R*,7*R*)-1-(6-*tert*-Butoxymethyl-tetrahydro-pyran-2-yl)-ethane-1,2-diol



(2*R*,3*R*,7*R*)-354

Following general **procedure 5**, epoxy-acetal **345** (300 mg, 1.39 mmol) under an atmosphere of nitrogen was reacted with a 2 M solution of trimethylaluminium (2.08 mL, 4.17 mmol) in dry CH_2Cl_2 (5 mL) for 7 days at -20 ^oC. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:2 to afford the title compound **354** as a colourless oil (40 mg, 12%) and as an unseparable mixture of both diastereoisomers.

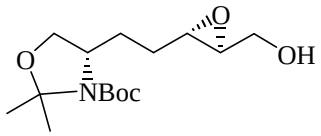
HRMS (+ESI) $[MNa]^+$ $C_{12}H_{24}O_4Na$ requires 255.1567. Found 255.1573 (2.5 ppm error).

IR (neat, cm^{-1}) ν_{max} 3401, 2964, 2924, 2868, 1458, 1442, 1385, 1365, 1256, 1231, 1196, 1114, 1085, 1048, 1031, 877.

^1H NMR ($CDCl_3$, 500 MHz) δ_H 3.96-3.90 (1H, m, H-7), 3.90-3.84 (1H, m, H-3), 3.73-3.59 (4H, m, H-1, H-2, H-3), 3.28 (1H, dd, *J* 5.7, 2.8 Hz, H-1'), 2.87 (1H, t, *J* 4.0 Hz, O*H*), 2.06 (1H, d, *J* 4.0 Hz, O*H*), 1.80-1.50 (6H, m, H-4, H-5, H-6), 1.21 (9H, s, H-10).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 73.3 (C-9), 72.9, 72.4, 71.9 (C-2, C-3, C-7), 65.1, 61.5 (C-1, C-5), 27.5 (C-10), 26.5, 26.0 (C-4, C-7), 18.8 (C-5).

(2*R*,3*S*,5*S*)-4-[2-(3-Hydroxymethyl-oxiranyl)-ethyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester



355

To a suspension of freshly activated 4 Å powdered molecular sieves in dry CH_2Cl_2 (2 mL) under an atmosphere of nitrogen was added (+)-DET (4 mg, 0.11 mmol) followed by titanium *iso*propoxide (5 mg, 0.11 mmol) and a 4.35 M solution of *tert*-butyl hydroperoxide in CH_2Cl_2 (74 µL, 2.0 mmol) at -30 ^oC and the reaction mixture was stirred for 45 minutes at this temperature. A solution of **357** (46 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred at -25 ^oC for 1 day. The solution was warmed to 0 ^oC, a saturated solution of ferrous sulphate was added, the resulting mixture stirred for 30 minutes at 0 ^oC and partitioned between water and CH_2Cl_2 and the organic layer was further extracted with CH_2Cl_2 (4 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **355** as a pale yellow oil (27 mg, 57%).

$[\alpha]_D^{32}$ = 5.1 ($CHCl_3$, 0.6).

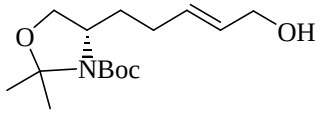
HRMS (+ESI) $[MNa]^+$ $C_{15}H_{27}NO_5Na$ requires 324.1781. Found 324.1779 (0.8 ppm error).

IR (neat, cm^{-1}) ν_{max} 3419, 2979, 2930, 2871, 1695, 1677, 1481, 1456, 1393, 1313, 1257, 1208, 1174, 1092, 1049, 847, 770.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.00-3.54 (5H, m, C*H*$_2$O, C*H* and C*H*$_2$OH), 3.02-2.86 (2H, m, C*H*OCH and CHOC*H*), 2.05-1.99 (1H, m, C*H*H'), 1.92-1.77 (1H, m, CH*H'*), 1.68-1.38 (17H, C*H*$_3$ x 2, O(C*H*$_3$)$_3$, C*H*$_2$), O*H* not observed.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 152.7 (*C*O), 94.2 and 93.7 (*C*), 80.7 and 80.0 (*C*), 67.1 (*C*H_2OH), 62.3 and 61.9 (*C*H_2O), 58.3 (*C*H), 57.2 (*C*H), 56.2 (*C*HNBoc), 30.5 and 29.8 (*C*H_2), 28.8 (*C*H_3 x 3), 28.5 (*C*H_2), 27.1 and 26.4 (*C*H_3), 24.8 and 23.5 (*C*H_3).

(2*E*,6*S*)-4-(5-Hydroxy-pent-3-enyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester



357

Following general **procedure 3**, a solution of ester **371** (110 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) under an atmosphere of nitrogen was reacted at -30 ^oC with a 1 M solution of DIBAL-H in hexanes (0.81 mL, 0.81 mmol) for 45 minutes. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **357** as a colourless oil (53 mg, 54%).

$[\alpha]_D^{29}$ = 21.1 ($CHCl_3$, 2.3).

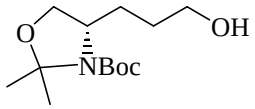
HRMS (+ESI) $[MNa]^+$ $C_{15}H_{27}NO_4Na$ requires 308.1832. Found 308.1829 (0.9 ppm error).

IR (neat, cm^{-1}) ν_{max} 3416, 2980, 2936, 2863, 1694, 1672, 1476, 1456, 1393, 1313, 1258, 1208, 1175, 1148, 1090, 1021, 972, 846, 806, 769.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.64 (2H, m, C*H*=CHCH_2OH and CH=C*H*CH_2OH), 4.10-3.66 (5H, m, CH_2O, C*H* and CH_2OH), 2.11-1.94 (4H, m, CH_2 x 2), 1.60-1.33 (16H, CH_3 x 2, O(CH_3)$_3$, O*H*).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 152.7 (*C*O), 132.1 (*C*H), 130.1 (*C*H), 94.0 and 93.6 (*C*), 80.5 and 79.9 (*C*), 67.2 and 66.9 (*C*H_2O), 63.8 (*C*H_2), 57.4 and 57.2 (*C*H), 33.3 and 32.4 (*C*H_2), 29.3 (*C*H_2), 28.8 (*C*H_3 x 3), 27.1 and 26.6 (*C*H_3), 24.8 and 23.6 (*C*H_3).

(2*S*)-4-(3-Hydroxy-propyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester



358

Following general **procedure 4**, a solution of **362** (5.0 g, 22.83 mmol) in CH_2Cl_2 (50 mL), *p*-toluene sulfonic acid (434 mg, 2.28 mmol) and 2,2-dimethoxypropane (2.7 mL, 22.23 mmol) under an atmosphere of nitrogen was heated under reflux for 2 h. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **358** as a colourless oil (3.45 g, 58%). Spectroscopic data in agreement with the literature values.[173]

$[\alpha]_D^{26}$ = 29.8 ($CHCl_3$, *c* 1.3)

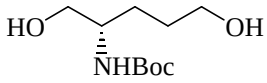
HRMS (+ESI) $[MNa]^+$ $C_{13}H_{25}NO_4Na$ requires 282.1676. Found 282.1660 (5.6 ppm error).

IR (neat, cm^{-1}) ν_{max} 3436, 2979, 2939, 2871, 1693, 1479, 1456, 1392, 1370, 1315, 1258, 1207, 1175, 1148, 1087, 1030, 845, 769.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.00-3.61 (5H, m, C*H*$_2$OC, C*H*, C*H*$_2$OH), 1.83 (1H, brs, O*H*), 1.65-1.32 (10H, m, C*H*$_2$ x 2 and C*H*$_3$ x 2), 1.46 (9H, s, C*H*$_3$ x 3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 152.9 and 152.4 (*C*O), 93.6 and 93.2 (*C*$(CH_3)_2$), 80.2 and 79.5 (*C*), 66.9 (*C*H_2O), 62.3 and 62.1 (*C*H_2OH), 57.1 (*C*H), 30.0 and 29.5 (*C*H_2), 29.3 and 28.9 (*C*H_2), 28.4 and 28.3 (C(*C*$H_3)_3$), 27.5 and 26.7 (*C*H_3), 24.5 and 23.2 (*C*H_3).

(2*S*)-(4-Hydroxy-1-hydroxymethyl-butyl)-carbamic acid *tert*-butyl ester



362

Following general **procedure 7**, a solution of ester **363** (10.23 g, 37.2 mmol) in EtOH (150 mL) under an atmosphere of nitrogen was treated by sodium borohydride (11.26 g, 297.7 mmol) at 0 ^{o}C and the reaction mixture was stirred for 2 h at this temperature and for a further 2 days at RT. The crude oil was dissolved with Et_2O and petroleum ether was added in order to induce the crystallisation. The solid was filtered and washed with petroleum ether to afford the title compound **362** as a white solid (5.9 g, 72%). Data in agreement with literature values.[174]

m.p.: 62-63 ^{o}C

$[\alpha]_D^{22}$ = -13.6 ($CHCl_3$, *c* 2.1).

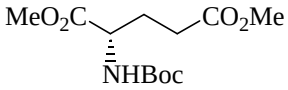
HRMS (+ESI) $[MNa]^+$ $C_{10}H_{21}NO_4Na$ requires 242.1363. Found 242.1351 (5.0 ppm error).

IR (nujol, cm^{-1}) ν_{max} 3344, 1680, 1530, 1367, 1315, 1299, 1252, 1167, 1074, 1005, 989, 902, 871.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.03 (1H, brs, N*H*), 3.70-3.11 (7H, m, CH_2OH x 2, C*H* and O*H* x 2), 1.70-1.33 (4H, m, CH_2 x 2), 1.42 (9H, s, CH_3 x 3).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 156.9 (*C*O), 80.0 (*C*), 65.4 (*C*H_2O), 62.6 (*C*H_2OH), 52.6 (*C*H), 29.1 (*C*H_2), 28.8 (*C*H_3 x 3), 28.3 (*C*H_2).

(2*S*)-2-*tert*-Butoxycarbonylamino-pentanedioic acid dimethyl ester.



363

To a solution of **369** (10 g, 50.66 mmol) in CH_2Cl_2 (60 mL) was added triethylamine (21.2 mL, 151.98 mmol), water (10 mL) and Boc_2O (12.16 g, 55.72 mmol) and the reaction mixture was stirred for 20 h at RT. The reaction mixture was partitioned between water and dichloromethane and the aqueous layer was further extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **363** as a pale yellow oil (12.8 g, 92%). Data in agreement with literature values.[166]

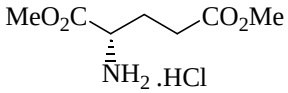
$[\alpha]_D^{26}$ = 13.7 ($CHCl_3$, *c* 1.8)

HRMS (+ESI) $[MNa]^+$ $C_{12}H_{21}NO_6Na$ requires 298.1267. Found 298.1238 (9.7 ppm error).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.10 (1H, brs, N*H*), 4.39-4.27 (1H, m, C*H*), 3.74 (3H, s, CO_2CH_3), 3.67 (3H, s, CO_2CH_3), 2.44-2.37 (2H, m, CH_2CO_2Me), 2.33-2.11 (1H, m, C*H*H'), 1.97-1.87 (1H, m, CH*H'*).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 173.6 (*C*O), 173.1 (*C*O), 80.4 (*C*), 53.2 (*C*H), 52.8 (CH_3), 52.2 (CH_3), 30.4 (CH_2), 28.7 (CH_3 x 3), 28.2 (CH_2), (*C*O of Boc group not observed).

(2*S*)-2-Amino-pentanedioic acid dimethyl ester hydrochloride



369

To a flask containing MeOH (100 mL) was added dropwise thionyl chloride (24.8 mL, 339.90 mmol) at -30 ^{o}C. L-Glutamic acid **364** (10 g, 67.98 mmol) was added in one portion and the reaction mixture stirred at RT for 16 h and concentrated under reduced pressure. Triturating the viscous oil with acetone and diethyl ether induced the crystallisation of the product. The title compound **369** was then recrystallised from acetone and diethyl ether and isolated as a white solid (13.77g, 77%). Data in agreement with literature values.[165]

m.p.: 92-93 ^{o}C

$[\alpha]_D^{21}$ = 24.3 (H_2O, *c* 0.6)

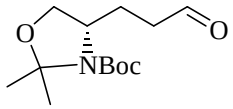
HRMS (+ESI) $[MH]^+$ $C_7H_{14}NO_4$ requires 176.0923. Found 176.0903 (11.4 ppm error).

IR (nujol, cm^{-1}) ν_{max} 2014, 1728, 1638, 1606, 1589, 1416, 1348, 1234, 1117, 1045, 994, 974, 953, 918, 889, 849, 806, 768, 747.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.92 (2H, brs, N*H*$_2$), 4.33 (1H, brs, C*H*), 3.81 (CO_2CH_3), 3.66 (CO_2CH_3), 2.86-2.28 (4H, m, C*H*$_2$ x 2).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C poorly soluble in $CDCl_3$.

(2*S*)-2,2-Dimethyl-4-(3-oxo-propyl)-oxazolidine-3-carboxylic acid *tert*-butyl ester



370

To a solution of **358** (3.0 g, 11.58 mmol) in CH_2Cl_2 (50 mL) and DMSO (15 mL) under an atmosphere of nitrogen was added Et_3N (8.1 mL, 57.92 mmol) followed by SO_3.py (9.2 g, 57.92 mmol) at 0 ^oC and the reaction mixture was stirred for 1 h at this temperature. The reaction mixture was then partitioned between ether and water and the aqueous layer was further extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 4:1 to afford the title compound **370** as a colourless oil (2.46 g, 83%). Spectroscopic data in agreement with the literature values.[173]

$[\alpha]_D^{21}$ = 19.9 ($CHCl_3$, *c* 1.2)

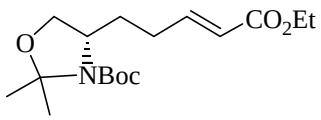
HRMS (+ESI) $[MNa]^+$ $C_{13}H_{23}NO_4Na$ requires 280.1519. Found 280.1500 (7.0 ppm error).

IR (neat, cm^{-1}) ν_{max} 2980, 2937, 2877, 1725, 1694, 1479, 1455, 1390, 1367, 1309, 1258, 1207, 1175, 1150, 1084, 1053, 846, 770.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 9.77 (1H, brs, C*H*O), 4.00-3.65 (3H, CH_2O, CH), 2.52-2.43 (2H, CH_2CHO), 2.02-1.82 (2H, m, CH_2), 1.59 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.46 (9H, s, CH_3 x 3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 202.0 (CHO), 80.7 (*C*-acetal), 80.0 (*C*-Boc), 67.4 (*C*H_2), 57.0 and 56.7 (*C*H), 40.9 (*C*H_2), 28.8 (*C*H_3 x 3), 28.0 (*C*H_3), 27.1 (*C*H_2), 26.3 (*C*H_3), 24.8 (*C*H_3).

(2*E*,6*S*)-4-(4-Ethoxycarbonyl-but-3-enyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester



371

Following general **procedure 6**, aldehyde **370** (2.0 g, 7.78 mmol) in dry THF (10 mL) under an atmosphere of nitrogen was reacted sodium hydride (60% *w/w* in mineral oil; 375 mg, 9.34 mmol) and triethyl phosphonoacetate (2.09 g, 9.34 mmol) in dry THF (30 mL). The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 4:1 to afford the title compound **371** as a colourless oil (1.78 g, 70%).

$[\alpha]_D^{33}$ = 23.6 ($CHCl_3$, *c* 1.3)

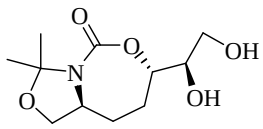
HRMS (+ESI) $[MNa]^+$ $C_{17}H_{29}NO_5Na$ requires 350.1938. Found 350.1927 (3.0 ppm error).

IR (neat, cm^{-1}) ν_{max} 1980, 2937, 2874, 1717, 1693, 1479, 1455, 1389, 1313, 1261, 1202, 1176, 1089, 1046, 986, 947, 853, 807, 769.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.94 (1H, dt, *J* 7.1, 15.6 Hz, C*H*=CHCO$_2$Et), 5.83 (1H, d, *J* 15.6 Hz, CH=C*H*CO$_2$Et), 4.16 (2H, q, *J* 7.0 Hz, CO$_2$C*H*$_2$CH$_3$), 3.97-3.88 (1H, m, C*H*H'O), 3.84-3.68 (2H, m, C*H* and CH*H*'O), 2.28-2.10 (2H, m, C*H*$_2$), 1.81-1.62 (2H, m, C*H*$_2$), 1.62-1.40 (15H, m, C*H*$_3$ x 2 and O(C*H*$_3$)$_3$), 1.27 (3H, t, *J* 7.0 Hz, CO$_2$CH$_2$C*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 166.8 (*C*O), 152.1 (*C*O), 148.4 and 148.2 (CH=CHCO$_2$Et), 122.3 and 122.0 (CH=CHCO$_2$Et), 94.2 and 93.7 (*C*), 80.6 and 80.1 (*C*), 67.1 and 67.0 (*C*H$_2$), 60.6 (CO$_2$*C*H$_2$CH$_3$), 57.5 and 56.9 (*C*H), 32.3 and 31.7 (*C*H$_2$), 29.2 (*C*H$_2$), 28.8 (*C*H$_3$ x 3), 28.0 (*C*H$_3$), 27.1 (*C*H$_3$), 24.8 (*C*H$_3$), 23.5 (*C*H$_3$), 14.6 (CO$_2$CH$_2$*C*H$_3$).

(2*R*,3*S*,6*S*)-6-(1,2-Dihydroxy-ethyl)-3,3-dimethyl-tetrahydro-2,5-dioxa-3a-aza-azulen-4-one



372

Following general **procedure 5**, epoxy-acetal **355** (133 mg, 0.44 mmol) under an atmosphere of nitrogen was reacted with a 2 M solution of $AlMe_3$ (0.66 mL, 1.33 mmol) in dry CH_2Cl_2 (2 mL) for 24 h at -20 ^oC. The residue was purified by flash column chromatography eluting with dichloromethane: methanol/ 1:20 to afford the title compound **372** as a colourless oil (40 mg, 37%).

$[\alpha]_D^{25}$ = -13.5 ($CHCl_3$, *c* 0.9).

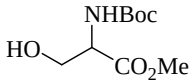
HRMS (+ESI) $[MNa]^+$ $C_{11}H_{19}NO_5Na$ requires 268.1155. Found 268.1152 (1.4 ppm error).

IR (neat, cm^{-1}) ν_{max} 3381, 2982, 2934, 3884, 1660 (C=O), 1409, 1377, 1367, 1323, 1292, 1253, 1238, 1208, 1157, 1080, 1055, 1039, 997, 834, 748.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 4.49-4.40 (1H, m, C*H*OCO), 4.08-3.95 (2H, m, C*H*H'O and C*H*N), 3.84-3.69 (3H, m, CH*H*'O, C*H*OH, C*H*H'OH), 3.59 (1H, dd, *J* 7.8, 7.5 Hz, CH*H*'OH), 2.08-1.74 (4H, m, CH_2 x 2), 1.60 (3H, s, CH_3), 1.53 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 152.7 (*C*O), 96.0 (*C*), 78.7 (*C*HOH), 73.2 (*C*HOCO), 68.8 (*C*H_2O), 62.7 (*C*H_2OH), 55.8 (*C*HN), 26.4 (*C*H_2), 25.5 (*C*H_2), 24.6 (*C*H_3), 24.4 (*C*H_3).

(+/-)-2-*tert*-Butoxycarbonylamino-3-hydroxy-propionic acid methyl ester



387

To a solution of D,L-serine methyl ester hydrochloride **386** (5.0 g, 32.14 mmol) in CH_2Cl_2 under an atmosphere of nitrogen was added triethylamine (9.0 mL, 64.28 mmol) followed by di-*tert*-butyl dicarbonate (7.72 g, 35.35 mmol) and the reaction mixture was stirred for 3 days at RT. The reaction mixture was washed with a 1 M solution of hydrochloric acid (30 mL), followed by a saturated solution of sodium hydrogen carbonate (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **387** as a colourless oil (5.74 g, 82%). Spectroscopic data in agreement with the literature values.[168]

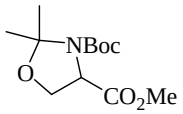
HRMS (+ESI) $[MNa]^+$ $C_9H_{17}O_5NNa$ requires 242.0999. Found 242.0996 (1.0 ppm error).

IR (neat, cm^{-1}) ν_{max} 3397, 2979, 2886, 1739, 1716, 1705, 1516, 1455, 1439, 1393, 1368, 1349, 1288, 1249, 1215, 1165, 1062, 1029, 979, 921, 874, 852, 780, 760.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 5.60 (1H, d, *J* 7.2 Hz, N*H*), 4.38-4.27 (1H, brs, C*H*), 3,91 (1H, dd, *J* 11.0, 2.4 Hz, C*H*H'OH), 3.81 (1H, dd, *J* 11.0, 3.6 Hz, CH*H*'), 3.72 (3H, s, CO_2CH_3), 3.27 (1H, brs, O*H*), 1.40 (9H, s, CH_3 x 3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 171.9 (*C*O), 156.2 (*C*O), 80.6 (*C*), 63.6 (CH_2), 56.1 (*C*H), 52.9 (CO_2CH_3), 28.6 (CH_3 x 3).

(+/-)-2,2-Dimethyl-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester



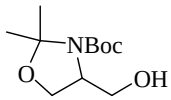
388

Following general **procedure 4**, a solution of amino alcohol **387** (4.76 g, 21.73 mmol) in toluene (40 mL), 2,2-dimethoxypropane (5.35 mL, 43.47 mmol) and *p*-toluenesulfonic acid (380.mg, 2.0 mmol) under an atmosphere of nitrogen was heated under reflux for 2 h. The residue was purified by flash column chromatography eluting with petroleum ether:ethyl acetate/ 2:1 to afford the title compound **388** as a colourless oil (3.6 g, 68%). Spectroscopic data in agreement with the literature values.[168]

HRMS (+ESI) $[MNa]^+$ $C_{12}H_{21}O_5NNa$ requires 282.1311. Found 282.1308 (1.2 ppm error).

IR (neat, cm^{-1}) ν_{max} 2980, 2932, 2882, 1759, 1744, 1707, 1533, 1479, 1453, 1438, 1391, 1288, 1267, 1250, 1205, 1174, 1094, 1063, 1055, 1001, 946, 870, 848, 770, 659, 638.

(+/-)-4-Hydroxymethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester



389

Following general **procedure 7**, a solution of ester **388** (1.0 g, 3.86 mmol) in EtOH (5 mL) under an atmosphere of nitrogen was treated by sodium borohydride (292 mg, 7.72 mmol) and the reaction mixture was stirred at RT for 12 h. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 2:1 to afford the title compound **389** as a white solid (733 mg, 82%). Spectroscopic data in agreement with the literature values.[168]

m.p.: 39-40 ^oC.

HRMS (+ESI) $[MNa]^+$ $C_{11}H_{21}O_4NNa$ requires 254.1363. Found 254.1363 (0 ppm error).

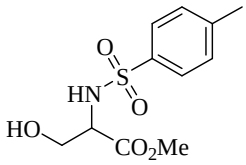
IR (nujol, cm^{-1}) ν_{max} 3460, 1696, 1668, 1456, 1401, 1296, 1251, 1199, 1171, 1105, 1073, 1050, 1020, 857, 843, 767.

The title compound **389** was obtained as a mixture of rotamers (M and m). The following was observed:

^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.00-3.20 (5H, m, C*H*$_2$OH, C*H*$_2$O, C*H*), 1.49 and 1.44 (15H, s x 2, C*H*$_3$ x 5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 154.3 (*C*O, M and m), 94.4 (*C*, M and m), 81.4 (*C*, M), 80.4 (C, m), 65.6 (*C*H$_2$OH and *C*H$_2$O, M), 65.0 (*C*H$_2$OH and *C*H$_2$O, m), 59.7 (*C*H, M), 58.7 (*C*H, m), 28.7 (*C*H$_3$ x 3, M and m), 27.5 (*C*H$_3$, M), 27.0 (*C*H$_3$, m), 14.9 (*C*H$_3$, M), 23.3 (*C*H$_3$, m).

(+/-)-3-Hydroxy-2-(toluene-4-sulfonylamino)-propionic acid methyl ester



390

To a solution of D,L-serine methyl ester hydrochloride **386** (5.0 g, 32.14 mmol) in dry THF (100 mL) under an atmosphere of nitrogen was added triethylamine (9.0 mL, 64.28 mmol) followed by tosylchloride (7.35 g, 38.57 mmol) and the reaction mixture was stirred for 2 days at RT, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **390** as a white solid (6.09 g, 69%). Spectroscopic data in agreement with the literature values.[169]

m.p.: 84-85 ^oC.

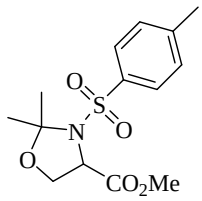
HRMS (+ESI) $[MNa]^+$ $C_{11}H_{15}O_5NNaS$ requires 296.0563. Found 296.0559 (1.4 ppm error).

IR (nujol, cm^{-1}) ν_{max} 3490, 3273, 1747, 1406, 1310, 1288, 1228, 1210, 1161, 1133, 1091, 1067, 1026, 966, 912, 856, 820, 685.

^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.73 (2H, d, *J* 8.1 Hz, *o*-Ar-*H*), 7.27 (2H, d, *J* 8.1 Hz, *m*-Ar-*H*), 6.15 (1H, d, *J* 8.0 Hz, N*H*), 4.11-3.95 (1H, m, C*H*), 3.94-3.78 (2H, m, CH_2), 3.55 (3H, s, CO_2CH_3), 3.31-3.23 (1H, brs, O*H*), 2.39 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 170.8 (*C*O), 144.2 (*C*-Me), 137.0 (*C*-SO2), 130.1 (*o*-Ar-*C*), 127.6 (*m*-Ar-*C*), 64.0 (CH_2), 58.0 (*C*H), 53.2 (CO_2CH_3), 21.9 (CH_3).

(+/-)-2,2-Dimethyl-3-(toluene-4-sulfonyl)-oxazolidine-4-carboxylic acid methyl ester



391

Following general **procedure 4**, a solution of compound **390** (1.0 g, 3.66 mmol) in toluene (5 mL), 2,2-dimethoxypropane (0.90 mL, 7.32 mmol) and pyridinium *p*-toluenesulfonic acid (184 mg, 0.73 mmol) under an atmosphere of nitrogen was heated under reflux for 6 h and stirred at RT for a further 12 h. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 3:1 to afford the title compound **391** as a colourless oil (676 mg, 59%).

m.p.: 85-86 ^oC.

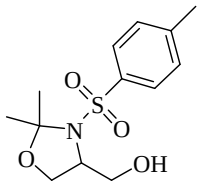
HRMS (+ESI) $[MNa]^+$ $C_{14}H_{19}NO_5NaS$ requires 336.0876. Found 336.0869 (2.2 ppm error).

IR (nujol, cm^{-1}) ν_{max} 1732, 1599, 1496, 1456, 1435, 1367, 1344, 1308, 1283, 1238, 1222, 1161, 1125, 1099, 1081, 1034, 1016, 1002, 949, 938, 855, 824, 802, 666.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.74 (2H, d, *J* 8.1 Hz, *m*-Ar-*H*), 7.27 (2H, d, *J* 8.1 Hz, *o*-Ar-*H*), 4.44-4.38 (1H, m, C*H*), 4.10-4.00 (2H, m, CH_2), 3.59 (3H, s, CO_2CH_3), 2.40 (3H, s, Ar-CH_3), 1.68 (3H, s, CH_3), 1.55 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 171.3 (*C*O), 144.1 (Ar-*C*Me), 138.0 (SO_2C), 129.9 (*m*-Ar-*C*), 128.1 (*o*-Ar-*C*), 99.3 (*C*), 67.6 (CH_2), 60.4 (*C*H), 52.9 (CO_2CH_3), 28.0 (CH_3), 25.9 (CH_3), 21.9 (Ar-CH_3).

(+/-)-[2,2-Dimethyl-3-(toluene-4-sulfonyl)-oxazolidin-4-yl]-methanol



392

Following general **procedure 7**, a solution of ester **391** (575 mg, 1.84 mmol) in EtOH (3 mL) under an atmosphere of nitrogen was treated by sodium borohydride (139 mg, 3.67 mmol) and the reaction mixture was stirred at RT for 15 h. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **392** as a white solid (322 mg, 61%).

m.p.: 57-58 ^oC.

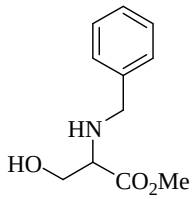
HRMS (+ESI) $[MNa]^+$ $C_{13}H_{19}NO_4NaS$ requires 308.0927. Found 308.0928 (0.2 ppm error).
IR (nujol, cm^{-1}) ν_{max} 3551, 1597, 1461, 1403, 1371, 1349, 1337, 1285, 1251, 1238, 1207, 1146, 1097, 1012, 958, 937, 924, 839, 815, 800, 737, 709, 682, 660.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.20-6.92 (4H, m, Ar-*H*), 3.93 (1H, app. t, *J* 8.1 Hz), 3.78 (1H, dd, *J* 8.1, 5.4 Hz), 3.77 (1H, d, *J* 13.1 Hz), 3.50 (1H, d, *J* 13.1 Hz), 3.43 (1H,

d, *J* 13.1 Hz), (C*H*$_2$O, C*H*O C*H*$_2$OH), 3.22 (3H, s, Ar-C*H*$_3$), 1.19 (3H, s, C*H*$_3$), 1.11 (3H, s, C*H*$_3$).

^{13}C NMR (CDCl$_3$, 75 MHz) δ_C 173.4 (*C*), 139.4 (*C*), 129.2 (Ar-*C* x 2), 128.5 (Ar-*C* x 2), 127.5 (Ar-*C*), 96.7 (*C*), 67.1 (*C*H$_2$O), 64.3 (*C*H), 52.9 (*C*H$_3$), 52.3 (*C*H$_2$OH), 27.0 (*C*H$_3$), 22.7 (*C*H$_3$).

(+/-)-2-Benzylamino-3-hydroxy-propionic acid methyl ester



393

To a solution of D,L-serine methyl ester hydrochloride **386** (1.0 g, 6.43 mmol) in methanol (8 mL) under an atmosphere of nitrogen was added freshly distilled benzaldehyde (750 mg, 7.07 mmol) followed by triethylamine (0.90 mL, 6.43 mmol) and the reaction mixture was stirred for 1 h at RT. The reaction mixture was then cooled to 0 ^{o}C and sodium borohydride was added portionwise over a period of 1 h. The reaction mixture was diluted with a 3 M solution of hydrochloric acid (5 mL) and diethyl ether (20 mL), partitioned between water and diethyl ether, the organic layer discarded and the aqueous layer basified with solid hydrogen carbonate and further extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title compound **393** (1.17 g, 87%) as an oil/solid. The title compound **393** was used for the next step without further purification. Spectroscopic data in agreement with the literature values.[170]

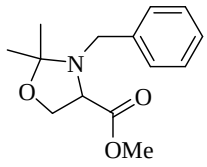
HRMS (+ESI) $[MNa]^+$ $C_{11}H_{15}NO_3Na$ requires 232. 0944. Found 232.0940 (1.8 ppm error).

IR (neat, cm^{-1}) ν_{max} 3323, 3029, 2951, 2864, 1730, 1645, 1603, 1455, 1335, 1201, 1174, 1135, 1055, 1024, 915, 747, 699.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.30-7.18 (5H, m, Ar-*H*), 3.81 (1H, d, *J* 12.9 Hz, C*H*H'Ph), 3.72 (1H, dd, *J* 10.8, 4,5 Hz, CH*H*'OH), 3.68 (3H, s, CO_2CH_3), 3.66 (1H, d, *J* 12.9 Hz, CH*H*'Ph), 3.57 (1H, dd, *J* 10.8, 6.3 Hz, CH*H*'), 3.37 (1H, dd, *J* 6.3, 4.5 Hz, C*H*), 2.41 (1H, brs, O*H*).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 173.9 (*C*O), 139.5 (*C*), 128.9 (Ar-*C* x 2), 128.7 (Ar-*C* x 2), 127.7 (Ar-*C*), 62.9 (CH_2OH), 62.2 (*C*H), 52.6 (CO_2CH_3), 52.4 (CH_2Ph).

(+/-)-3-Benzyl-2,2-dimethyl-oxazolidine-4-carboxylic acid methyl ester



394

Following general **procedure 4**, a solution of compound **393** (7.49 g, 35.8 mmol) in toluene (50 mL), 2,2-dimethoxypropane (5.29 mL, 35.8 mmol) and *p*-toluenesulfonic acid (1.36 g, 7.16 mmol) under an atmosphere of nitrogen was heated under reflux for 3 h. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 10:1 to afford the title compound **394** as a colourless oil (929 mg, 10%). Spectroscopic data in agreement with the literature values.[170]

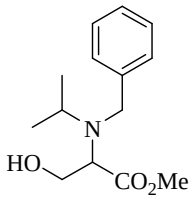
HRMS (+ESI) $[MNa]^+$ $C_{14}H_{19}NO_3Na$ requires 272.1257. Found 272.1253 (1.6 ppm error).

IR (neat, cm^{-1}) ν_{max} 3449, 3086, 3063, 3029, 2951, 2886, 2850, 1737, 1496, 1458, 1435, 1381, 1364, 1328, 1283, 1263, 1199, 1179, 1053, 1027, 995, 938, 912, 863, 844, 822, 748, 700.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.35-7.10 (5H, m, Ar-*H*), 4.09 (1H, dd, *J* 8.4, ,7.5 Hz, CH), 3.95 (1H, dd, *J* 8.4, 5.4 Hz, C*H*H'), 3.93 (1H, d, *J* 13.8 Hz, C*H*H'Ph), 3.67 (1H, d, *J* 13.8 Hz, CH*H*'Ph), 3.60 (1H, dd, *J* 7.5, 5.4 Hz, CH*H*'), 3.82 (3H, s, CO_2CH_3), 1.36 (3H, s, CH_3), 1.27 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 173.4 (*C*O), 139.3 (*C*), 129.4 (Ar-*C* x 2), 129.1 (Ar-*C* x 2), 127.5 (Ar-*C*), 96.7 (*C*), 67.0 (CH_2O), 64.3 (*C*H), 52.9 (CH_2Ph), 52.1 (CO_2CH_3), 27.0 (CH_3), 22.7 (CH_3).

(+/-)-2-(Benzyl-isopropyl-amino)-3-hydroxy-propionic acid methyl ester



396

Following general **procedure 7**, a solution of ester **394** (670 mg, 2.69 mmol) in EtOH (5 mL) under an atmosphere of nitrogen was treated by sodium borohydride (204 mg, 5.38 mmol) and the reaction mixture was stirred at 15 ^{o}C for 4 h. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 5:1 to afford the title compound **396** as a white solid (31 mg, 5%).

HRMS (+ESI) $[MNa]^+$ $C_{14}H_{21}NO_3Na$ requires 274.1414. Found 274.1418 (1.7 ppm error).

IR (neat, cm^{-1}) ν_{max} 3446, 3064, 3029, 2967, 2929, 2850, 2251, 1732, 1495, 1455, 1435, 1393, 1366, 1286, 1236, 1164, 1112, 1075, 1050, 911, 732, 699, 648.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.31-7.15 (5H, m, Ar-*H*), 3.90 (1H, d, *J* 14.4 Hz, C*H*H'Ph), 3.80 (1H, d, *J* 14.4 Hz, CH*H*'Ph), 3.69 (3H, s, CO_2CH_3), 3.69-3.54 (3H, m, C*H*, C*H*H' and CH*H*'), 3.13-3.04 (1H, m, $CH(CH_3)_2$), 1.06 (3H, d, *J* 6.7 Hz, CH_3), 0.99 (3H, d, *J* 6.7 Hz, CH_3), O*H* not observed.

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 173.4 (*C*O), 140.4 (*C*), 129.0 (Ar-*C* x 2), 128.9 (Ar-*C* x 2), 127.5 (Ar-*C*), 60.3 (*C*H), 59.9 (*C*H_2OH), 52.0 (CO_2*C*H_3), 50.6 (*C*H_2Ph), 49.2 (*C*H(CH_3)$_2$), 22.8 (*C*H_3), 18.0 (*C*H_3).

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Part 2

Investigation and Development of a Novel Cascade Reaction

Chapter 1 | INTRODUCTION

In the 1960's, the two independent research groups of Sondheimer and Masamune were working on the chemistry of annulenes (monocyclic polyenes). Interesting observations were made regarding their chemistry, which at the time were not fully understood. These results were only rationalised a decade later, after the publication of Bergman's work on the formation of benzenoid biradical occurring upon thermolysis of suitable constructed enediyne compounds (**Section 1.1**). His work however did not gain full attention by the scientific community and stayed an isolated case of scientific curiosity until the isolation of enediyne antibiotics from bacteria, a class of highly complex natural products with exceptional biological activities (**Section 1.2**). Their mode of action was based upon the discoveries by Bergman and proved to be possible under mild, physiological conditions. These discoveries led to an effervescence of work from scientists of all domains in order to better understand the phenomena surrounding these enediyne antibiotics. From a chemistry point of view, this culminated in the total syntheses of these challenging natural products, as well as synthetic, computational and theoretical studies to understand the driving forces of the thermal Bergman reaction (**Section 1.3**). This led to the design of mimics of these secondary metabolites and also non natural enediynes (pro-drugs) with anticancer properties. More recently, this reaction proved to be feasible under photo irradiation and novel photo-activated enediynes started to emerge (**Section 1.4**). Their further development could find use as agents for the treatment of cancer when used in photodynamic therapy.

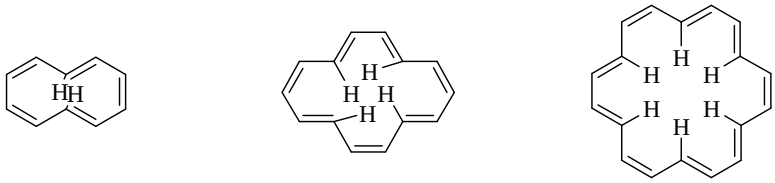
1.1 THE BERGMAN REACTION.

1.1.1 ANNULENE CHEMISTRY.

1.1.1.1 Sondheimer.

Annulene chemistry started to emerge only in the 1960's, although benzene, the [6]-annulene and cyclooctatetraene, the [8]-annulene, whose synthesis was reported in 1911, were well known. As a result, the synthesis of the next compounds of the series was highly desired, with the aromatic annulenes being of particular interest. Based on the "(4n + 2) π-electrons rule", also known as the Hückel's rule, the next aromatic compounds of the series, in accordance to the equations, were the [10]- and [14]-annulenes, **1** and **2**. However, due to proton interactions in these compounds, the planarity requirement for aromaticity cannot be met and [18]-annulene **3** appeared to be the first compound of the series to fulfil this rule.

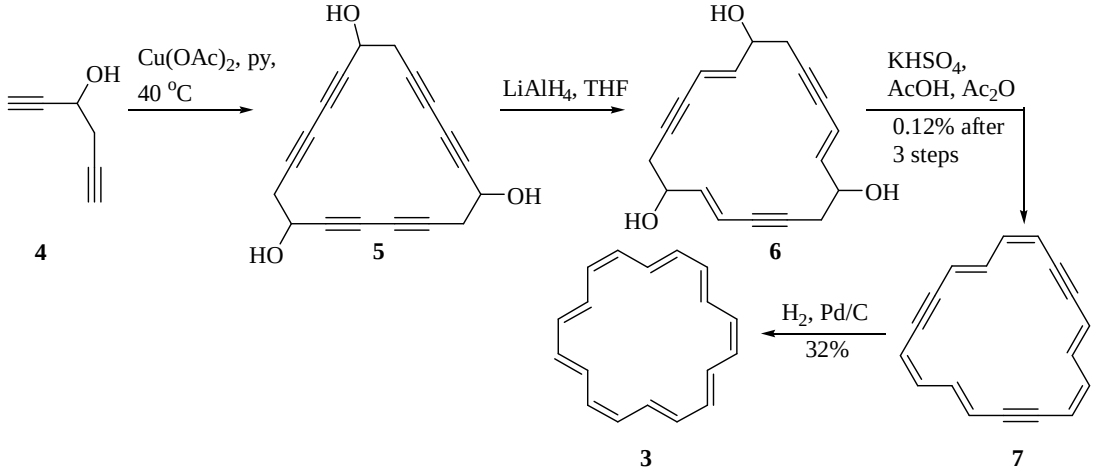
Figure 1. [10], [14] and [18]-Annulenes.



[10]-Annulene **1** [14]-Annulene **2** [18]-Annulene **3**

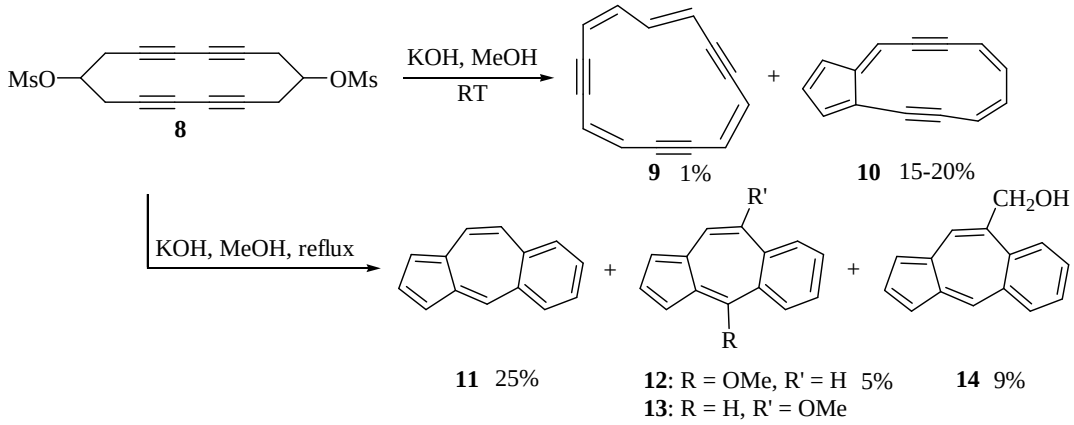
A landmark in annulene chemistry was the synthesis of the [18], [24] and [30]-annulenes by Sondheimer and co-workers in 1962.[1, 2] The synthesis of the [18]-annulene **3** was carried out by oxidative coupling of 1,5-hexadiyn-3-ol **4** with cupric acetate in pyridine, followed by reduction of the propargylic alcohols **5** with lithium aluminium hydride. Dehydration of compound **6** with potassium bisulfate in acetic acid and acetic anhydride and selective hydrogenation of the acetylene bonds of macrocycle **7** using palladium on carbon afforded annulene **3** in 0.04% overall yield (**Scheme 1**).

Scheme 1. [18]-Annulene **3** Synthesis.



This was then followed by work on the [14]-annulene and it was hoped that the synthesis could be achieved by treatment of compound **8** under basic conditions.[3, 4] However, when this compound was reacted with potassium hydroxide in methanol at room temperature, the bicyclic system **10** was the major compound isolated. Under harsher conditions i.e. when the mixture was heated under reflux, the tricyclic compounds **11**, **12** or **13** and **14** were obtained (see **Scheme 2**).

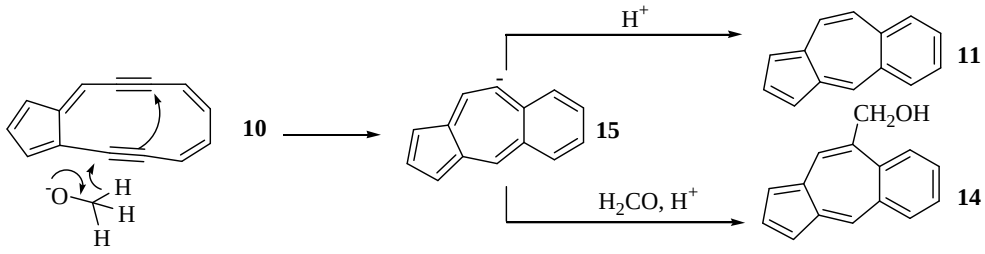
Scheme 2. Towards the Synthesis of [14]-Annulene.



It was postulated that bicyclic system **10** was an intermediate of the reaction and that the formation of these tricyclic compounds occurred by a possible hydrogen transfer from methoxide to the bicyclic system **10**. As a result, anion **15** was generated and was subsequently protonated or reacted with formaldehyde produced *in situ* during the reaction to give the tricyclic systems **11** and **14** (see **Scheme 3**).

In addition, the formation of compounds **12** and **13** was explained by the direct attack of methoxide onto bicyclic system **10**.

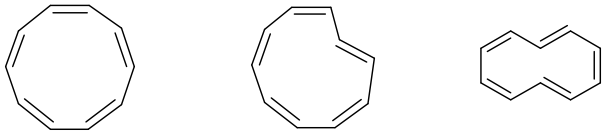
Scheme 3. Proposed Mechanism.



1.1.1.2 Work by Masamune.

The group of Masamune was also interested in annulene chemistry and particularly in the synthesis of the ten-membered ring of the series.[5] [10]-Annulene can exist in three geometrical forms, structures **16-18** (**Figure 2**), which are all very reactive and proved to be difficult to isolate.

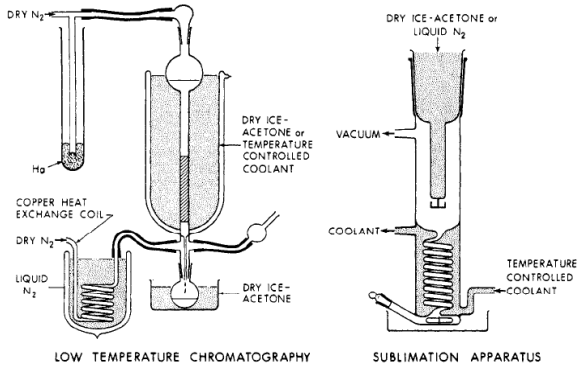
Figure 2. [10]-Annulene.



16 **17** **18**

In order to overcome these issues, the Masamune group reported the use of modified apparatus for the facile purification of unstable compounds at temperatures below -50 ^{o}C. This included sublimation and chromatography apparatus and are represented in **Figure 3**.[6]

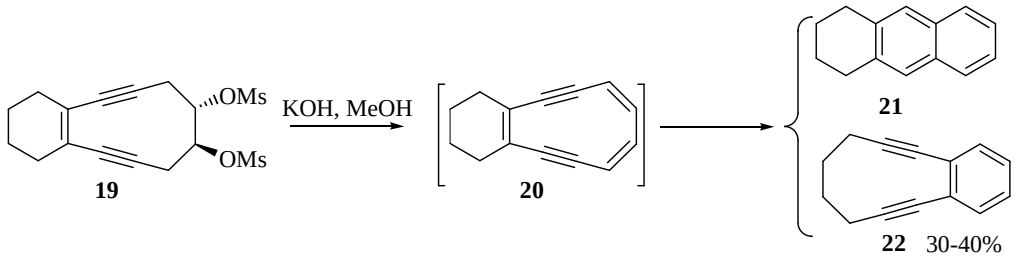
Figure 3. Techniques to Handle Compounds Below -50 ^{o}C.[6]



In an attempted to synthesise 1,5-didehydro[10]-annulene derivatives, enediyne **19** was reacted with potassium hydroxide in methanol. This reaction gave also surprising

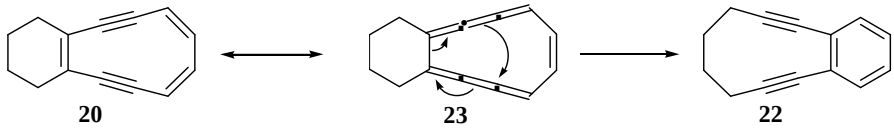
results. Indeed, the tri and bicyclic systems **21** and **22** were isolated, with **22** being obtained in a yield of 30-40% (**Scheme 4**).[7]

Scheme 4. Towards the Synthesis of [10]-Annulene.



It was postulated that intermediate **20** could be in equilibrium with the cumulene species **23**, which could undergo a "Cope-like" reaction to give, after rearrangement, compound **22**. The proposed mechanism of the formation of compound **22** is shown in **Scheme 5**.

Scheme 5. Proposed Mechanism.

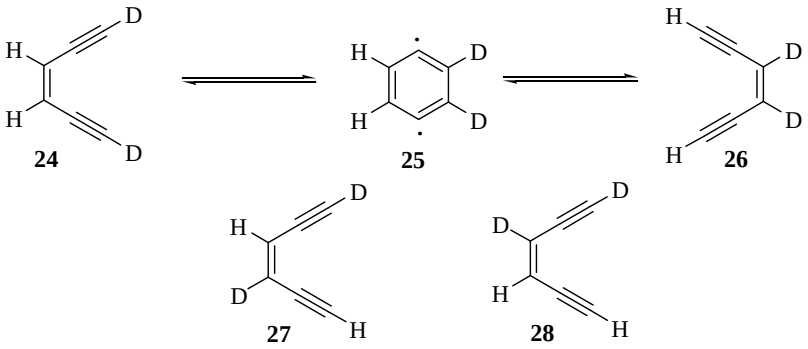


1.1.2 WORK BY BERGMAN.

1.1.2.1 Discovery of the 1,4-Benzenoid Biradical.

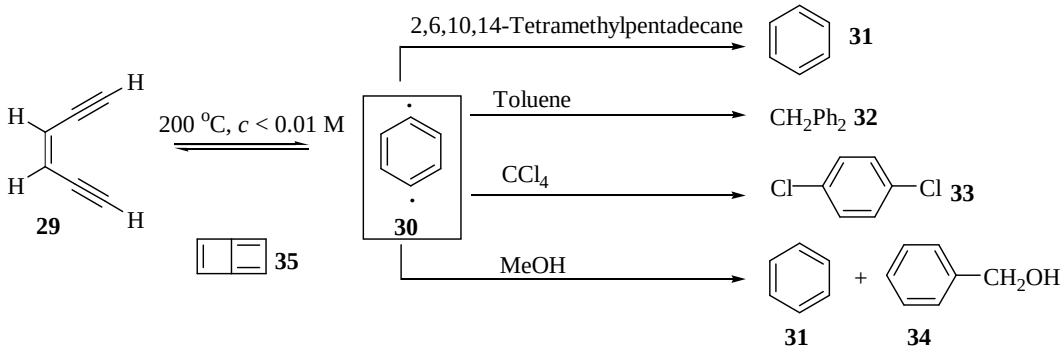
Bergman was interested in reactive 1,4-dehydroaromatics, such as 1,4-dehydrobenzene. He showed that when enediyne **24** was heated at 200 ^{o}C for 5 minutes, it could rapidly convert into enediyne **26**, giving a 1:1 mixture based on NMR analysis (**Scheme 6**).[8] When the crude material was treated under basic conditions, a 1:1 mixture of d_0:d_2 species was obtained by mass spectrometry. This result suggested that the formation of enediynes **27** and **28** did not occur during the course of the reaction. As the result, it was postulated that the reaction occurred through an intermediate with a C_2 axis of symmetry i.e. 1,4-dehydrobenzene **25** or commonly called 1,4-benzenoid biradical.

Scheme 6. The Bergman Reaction.



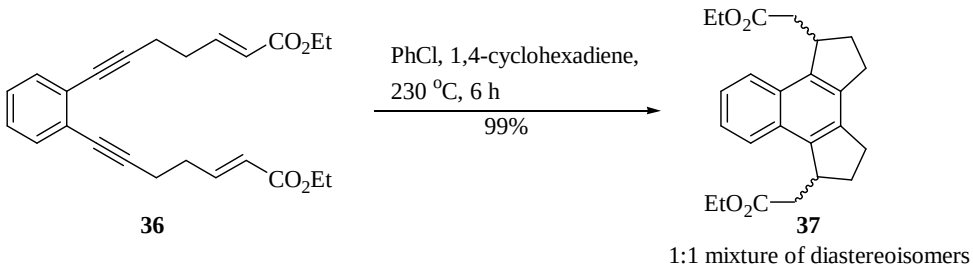
In order to trap the biradical species **25**, this reaction was performed in a range of solvents and usually with a concentration of the starting material lower than 0.01 M to avoid polymerisation.[9] The results obtained were the following (**Scheme 7**): **i**, when enediyne **29** was heated in 2,6,10,14-tetramethylpentadecane at 200 ^{o}C, formation of benzene **31** was observed; **ii**, when the reaction was carried out in toluene, diphenyl methane **32** was the major product obtained; **iii**, under similar conditions and in carbon tetrachloride, the 1,4-dichlorobenzene **33** was isolated; **iv**, finally, when the reaction was performed in methanol, benzene **31** and benzyl alcohol **34** were isolated but not anisole. The latter compound would have been obtained by reaction of methanol with butalene **35**. Therefore, the results obtained were viewed to suggest the formation of the free biradical **30**.

Scheme 7. Trapping the Biradical.



The radical nature of the intermediate was further demonstrated by Grissom and co-workers when the biradical, generated *in situ* from benzodiyne **36** was trapped *via* a double intramolecular 5-*exo* cyclisation onto two *α*,*β*-unsaturated esters (see **Scheme 8**).[10] The biradical intermediate was formed using the Bergman reaction of benzo-diyne **36** in chlorobenzene at 230 ^{o}C and with 1,4-cyclohexadiene as hydrogen atom donor. This tandem reaction could give access to a range of polycylic molecules and was therefore a new methodology for ring annulation.

Scheme 8. Trapping the Biradical.



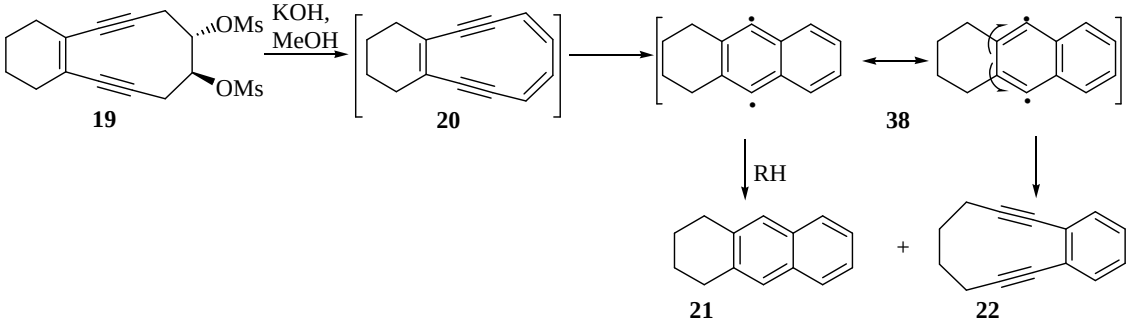
36 **37**

1:1 mixture of diastereoisomers

1.1.2.2 Masamune Revisited.

In view of this discovery, Bergman was able to explain the results obtained by Masamune's research group,[7] when working on the synthesis of ten-membered annulenes (**Section 1.1**). Formation of tricyclic system **21** could be rationalised by the generation of benzenoid biradical **38**, followed by hydrogen abstraction. In addition, the bicyclic system **22** was obtained by the retro-Bergman reaction of the biradical intermediate **38**.

Scheme 9. Masamune's Work Explained by the Bergman Reaction.



19 **20** **38** **21** **22**

In a similar manner, Sondheimer's observations (**Scheme 2**)[3, 4] could also be explained by the formation of a biradical.

1.1.3 CONCLUSION.

The formation of 1,4-dehydrobenzene **30**, a biradical species, can be obtained by the thermal rearrangement of 1,5-diacetylenes, which causes also their isomerisation (**Scheme 6**). This reaction was discovered in 1972 by Bergman, and although did not have any applications at the time, it had later a significant impact on the understanding of the mode of action of the enediyne antibiotics and on the design of exciting anticancer agents.

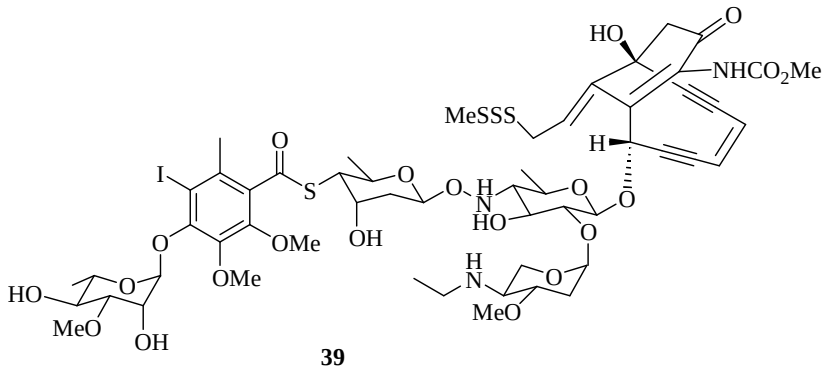
1.2 ENEDIYNE ANTIBIOTICS.

1.2.1 ENEDIYNE ANTIBIOTICS: STRUCTURE, BIOLOGICAL ACTIVITIES, MODE OF ACTION.

The enediynes are a family of secondary metabolites, which comprises for example, calicheamycin γ_1^I **39**, esperamycin, dynemicin, neocarzinostatin and kedarcidin chromophores.

Calicheamycin γ_1^I **39**, isolated and structurally characterised in 1987, has been produced by fermentation of *Micromonospora echinospora* ssp. *Calichensis*, a bacteria isolated from chalky soil. It possesses a highly complex structure, constituted of an enediyne core, a trisulfide moiety and a sugar tail (**Figure 4**).[11, 12]

Figure 4. Structure of Calicheamycin γ_1^I **39**.



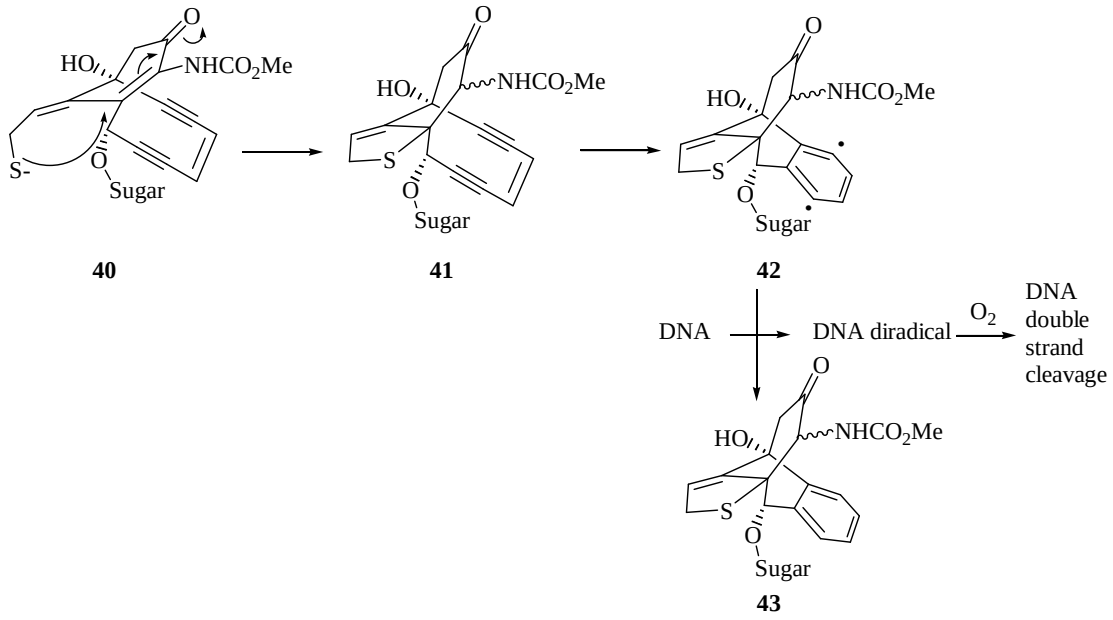
39

It is a highly potent antibacterial agent, which is also active against murine tumors, such as P388 and L1210 leukemias and solid neoplasms, such as colon 26 and B16 melanoma.[13, 14]

The mode of action of these metabolites can be described as follows: upon binding with DNA, the central sulfur of the trisulfide moiety is attacked by a nucleophile to generate a thiol or thiolate anion **40**, which can undergo an intramolecular Michael addition onto the α,β-unsaturated ketone to give compound **41** (**Scheme 10**). This leads to a change in geometry of the molecule (trigonal bridgehead to a tetragonal centre), which brings the two triple bonds closer together. As a result, the molecule can undergo a Bergman cycloaromatisation reaction and generate a highly reactive benzenoid-1,4-biradical **42**, which can then abstract protons from the DNA (**Scheme 10**).[15] As a result, this leads to the cleavage of both DNA strands with specificity for the 5'-TCCT-3' and 5'-TCTC-3' residue sequences and consequently, leads to permanent damage of the genetic

material.[16] Recognition for these specific residue sequences comes from the sugar tail and allows the molecule to bind selectively to the minor groove of DNA through hydrophobic and electrostatic interactions (through hydrogen bonding of the sugar side chain with DNA). This was shown by competition experiments with a minor groove DNA binder, netropsin. When present, in this competition experiment, the cleavage of the DNA strands by calicheamycin γ_1^I **39** was reduced.

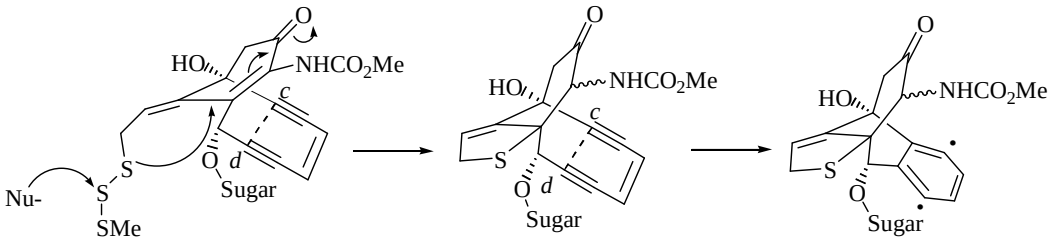
Scheme 10. DNA Cleavage - Proposed Mechanism.



1.2.2 THE DISTANCE THEORY (NICOLAOU).

As described in the previous section (**Section 1.2.1**), the change in geometry of calicheamycin γ_1^I **39** (formation of a sp^3 centre from sp^2 centre) could bring the π system in close proximity and consequently allows the Bergman reaction to take place. Molecular mechanics calculations (MacroModel, MM2) of compounds **39** and **41** showed that the *cd* distance reduced from 3.35 to 3.16 Å and that this distance was sufficient for the molecule to cyclise spontaneously at ambient temperature.[17] Understanding the mechanism that forces enediyne compounds to undergo a cycloaromatisation is essential, and could provide useful information for the design novel enediyne antibiotics.

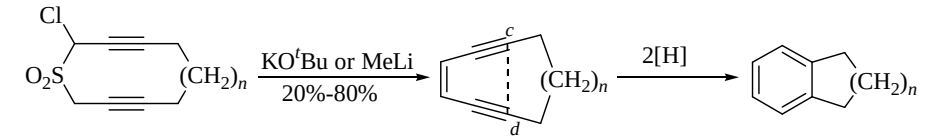
Scheme 11. Calicheamicin: Mode of Action.



39 **41** **42**

In order to study the effect of the ring size (*cd* distance) on the Bergman cyclisation, Nicolaou and co-workers synthesised simple cyclic enediynes **50-56**.[17] Compounds **50-56** were synthesised from the corresponding chlorosulfones **43-49** using the Ramberg-Bäcklung reaction (**Scheme 12**). Only the synthesis of the nine-membered cyclic system (n = 1) failed, and a mixture of compounds containing cyclised products from the Bergman reaction were isolated.

Scheme 12. Synthesis of the Target Enediynes.



n = 2-8 **43-49** **50-56** **57-63**

The calculated *cd* distances (using MM2 program) are summarised in **Table 1**, as well as the observations on the stability of the different compounds. It was possible to check the validity of the MM2 program by comparing the predicted value of the *cd* distance to that of the experimental data for enediyne **51** (*n* = 3) using X-ray crystallography analysis (enediyne **51** was obtained as large colourless plates). The calculated values obtained with MM2 matched the experimental values for the *cd* distance (*cd* distance, MM2 and X-ray, 3.61 Å and 3.661 Å respectively), and also for other geometrical parameters of this compound. This validated the use of the MM2 software in predicting the value of the *cd* distance for the cyclic compounds **50-56**.

Table 1. Calculated *cd* Distance: Effect on the Bergman Cyclisation.[17]

Compound	*n*	Ring Size	*cd* (A)	Stability
50	2	10	3.25	$t_{1/2}$ = 18 h at 25 ^{o}C
51	3	11	3.61	Stable at 25 ^{o}C
52	4	12	3.90	Stable at 25 ^{o}C
53	5	13	4.14	Stable at 25 ^{o}C
54	6	14	4.15	Stable at 25 ^{o}C
55	7	15	4.33	Stable at 25 ^{o}C
56	8	16	4.20	Stable at 25 ^{o}C

The *cd* distance was also calculated using the MM2 program for other compounds, of whose cycloaromatisation reactions were previously studied and published in the literature (**Figure 5**). In view of the results obtained, it was observed that the critical *cd* distance allowing the Bergman cycloaromatisation reaction to take place should be in the range of 3.2-3.31Å (**Table 2**).

Figure 5. *cd* Distance Calculations for Known Compounds.

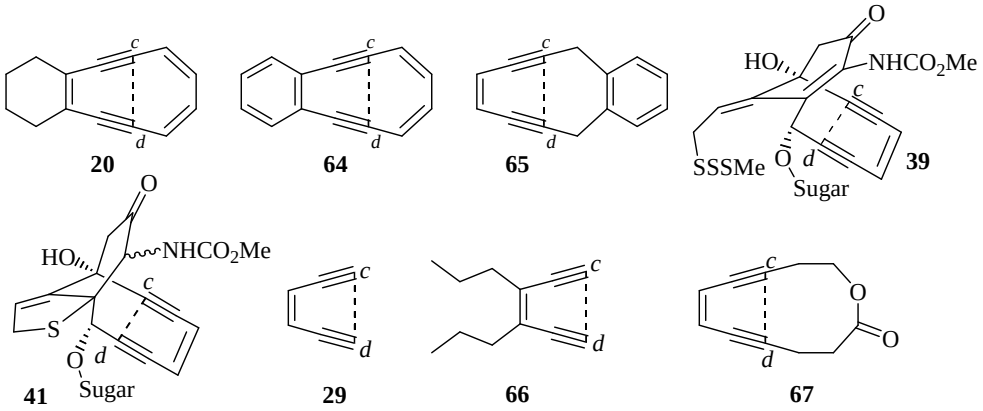


Table 2. *cd* Distance Calculations for Known Compounds.

Compound	Ring Size	*cd* (A)	Stability	References
20	10	2.99	Spontaneous cyclisation	[7]
64	10	3.01	Spontaneous cyclisation	[7]
65	10	3.03	Spontaneous cyclisation	[18]
39	10	3.35	Stable at 25 ^{o}C	[11, 12]
41	10	3.16	Spontaneous cyclisation	[11, 12]
29	-	4.12	Stable at 25 ^{o}C	[8, 9]
66	-	3.94	Stable at 25 ^{o}C	[8, 9]
67	12	3.77	Stable at 25 ^{o}C	[19]

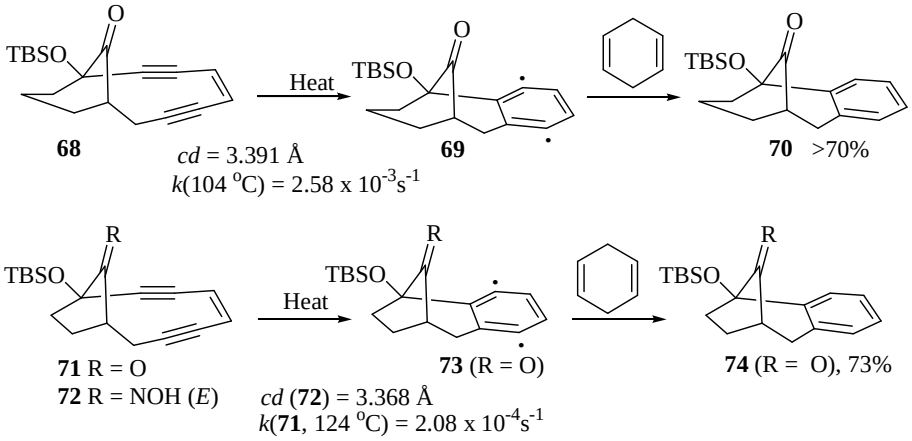
Finally, DFT calculations by Schreiner showed that the *cd* distance allowing spontaneous cycloaromatisation reaction could be extended from 3.4 to 2.9 Å.[20]

1.2.3 STRAIN THEORY (MAGNUS AND SNYDER).

Work by Magnus and Snyder showed that the cycloaromatisation was not always due to a short *cd* distance.[21] Compounds **68**, **71** and **72** were synthesised and X-ray analysis of compounds **68** (trapped in a boat conformation) and (*E*)-oxime **72** showed that the *cd* distance of bicycle[7.2.1]-enediyne **71** was shorter than that of compound **68**. However, although enediyne **71** had the shortest *cd* distance, its cycloaromatisation reaction

proved to be the most difficult (see rate constants on **Scheme 13**). It was then postulated that the Bergman reaction was also controlled by the difference in the strain energy between the transition state and the ground state.

Scheme 13. Rate of Cyclisation of Bicylo[7.3.1] and [7.2.1]-Enediynes.



However, although this theory is correct, the "distance theory" proposed by Nicolaou (see **Section 1.2.2**) gained credibility from the scientific community due to its ease of utilisation.

1.2.4 Applications: Design and Synthesis of Novel Anticancer Enediynes.

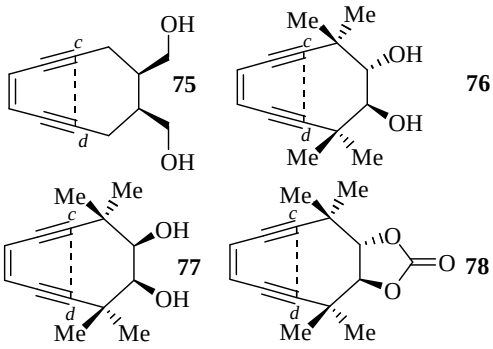
As shown in **Table 1** (**Scheme 12**), enediyne **50** can cyclise at room temperature, but possesses a half life long enough for the molecule to be isolated and handled at ambient temperature. Enediyne **50** was consequently an ideal drug test candidate, which could be also easily modified and lead to the synthesis of novel compounds with DNA cleavage ability. Indeed, modification of its skeleton and introduction of alcohol groups could make the molecules more water soluble (see **Table 3**).[22-25] These compounds could also be further elaborated, by for example attachment of "recognition and delivery systems" and consequently could be used as a novel class of anticancer agents.

Enediyne **75** was one of the first unnatural enediynes, which could significantly cleave phage *Φ*X174 double-stranded super-coiled DNA without any additives. The presence of catalase, superoxide dismutase or EDTA, when enediyne **75** was exposed to the DNA, did not prevent the DNA scission. This gave evidence that the mechanism was

not due to the presence of hydrogen peroxide, superoxide or metals, but due to the direct action of the compound on DNA itself.

Table 3. Novel Unnatural Enediynes.[22, 25]

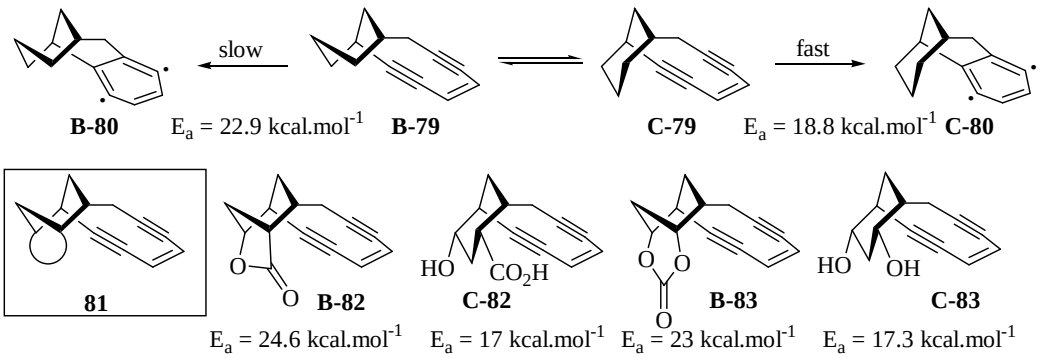
Compound	*n*	Ring Size	*cd* (Å)	Stability
75	-	10	3.20	$t_{1/2}$ = 11.8 h at 37 °C
76	-	10	3.29	$t_{1/2}$ = 4 h at 50 °C
77	-	10	3.34	$t_{1/2}$ = 2 h at 50 °C
78	-	10	3.42	Stable at 25 °C



Enediyne **78** was stable at ambient temperature and also when heated at 100 °C for several hours.[24] To lock the enediyne motifs, in such a way that they can undergo the cycloaromatisation reaction, but only under certain conditions or after activation, is an ingenious approach towards the synthesis and control of highly unstable compounds. The additional strain increases the energy of the transition state more than the energy of the ground state, consequently raising the activation energy towards cyclisation.

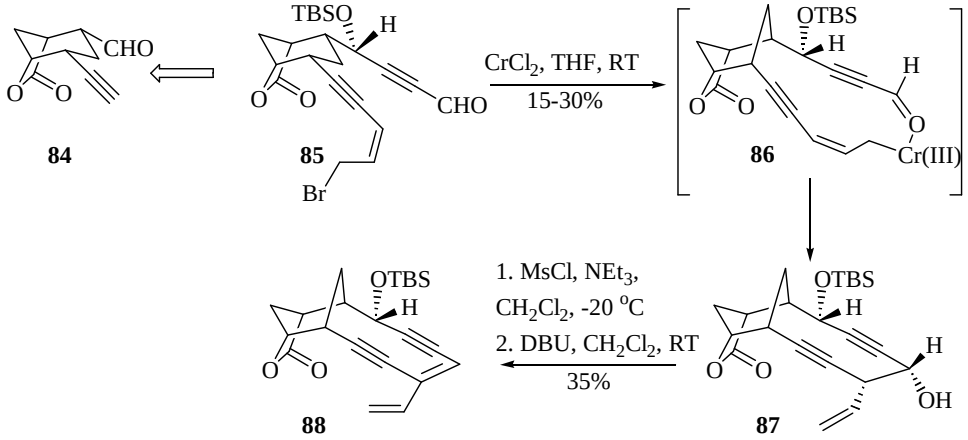
A recent example of conformation control has been reported by Semmelhack and co-workers.[26] DFT calculations showed that enediyne **C-79**, in a chair conformation, would be more reactive towards the cycloaromatisation reaction than enediyne **B-79**, in the boat conformation (**Scheme 14**). Thus, locking the system in a boat conformation (for example molecule **81**) could allow the synthesis of stable compounds, which upon activation i.e. cleavage of the bridge, could flip into a chair conformation and consequently undergo the Bergman reaction (see the activation energy values of **B**/**C**-**82** and **B**/**C**-**83** predicted by DFT calculations).

Scheme 14. Chair *versus* Boat Conformation.



In order to verify this hypothesis, which was based on molecular mechanism analysis, enediyne **88** was synthesised in order to perform further kinetic studes. The key step of the synthesis was the macrocyclisation of intermediate **85** between the aldehyde group and the allyl bromide functionality and was performed using chromium (II) chloride (**Scheme 15**).[26]

Scheme 15. Key Step: Synthesis of Enediyne Locked in a Chair Conformation.



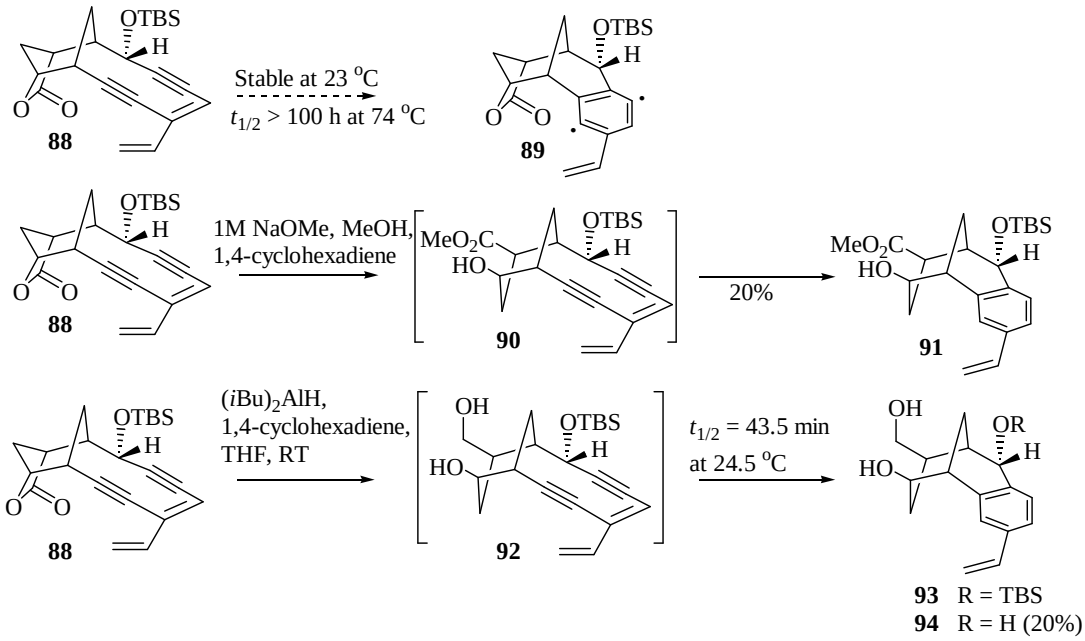
The kinetic studies of enediyne **88** and of the compounds generated from the opening of its bridge are summarised in **Scheme 16**. The following was observed[26]:

- Enediyne **88** proved to be stable at ambient temperature and its half life was greater than 100 h at 74 ^{o}C. It was observed that no product from the cycloaromatisation was obtained.

- Opening of the lactone ring of enediyne **88** with sodium methoxide to give enediyne **90,** led only to the isolation of the cyclised product **91** ($t_{1/2}$ < 2 h at RT).

- The disappearance of the enediyne motif during/after reduction of enediyne **88** using DIBALH in THF was monitored using UV techniques (enediyne unit, λ_{max} 296 nm). It was found that the half life time of enediyne **92** was 43.5 minutes at 24.5 ^{o}C. Reaction on a multi-milligram scale led to the isolation of the desilated compound **94** and was obtained in 20% yield.

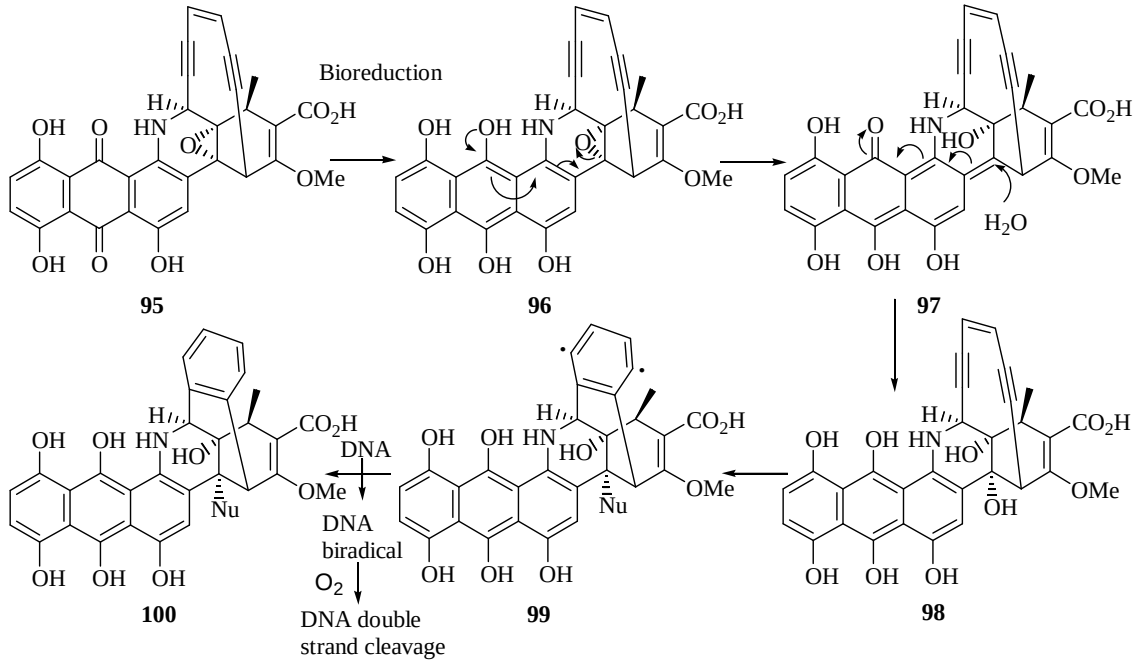
Scheme 16. Half Life Time Study.



Calculation of the free activation energies of compounds **88** (locked) and **92** (opened) using the half life time data provided, were of 29 and 22 kcal.mol^{-1}, respectively. These experimental values differed slightly from the predicted values (see **Scheme 14**), although the difference of energy between the two conformations was correct.[26] As a result, it was proven that the conversion of the system from a boat to a chair conformation upon activation could trigger the cycloaromatisation reaction and consequently, new enediynes could be designed based on these results, to further optimise their reactivity profile.

Dynemycin A **95** belongs to the class of enediyne antibiotic.[27] It contains as calicheamicin γ_1^I **39**, a ten membered enediyne motif, which upon activation (in this case opening of the epoxide group which locks the enediyne core) can undergo the Bergman reaction and form a 1,4-benzenoid biradical **99**. Finally, the biradical produced abstracts protons from the DNA and inflicts permanent damage to genetic material, which leads to the cell death (see **Scheme 17** for the mechanism of its mode of action).

Scheme 17. Mode of Action of Dynemicin A **95**.[25]

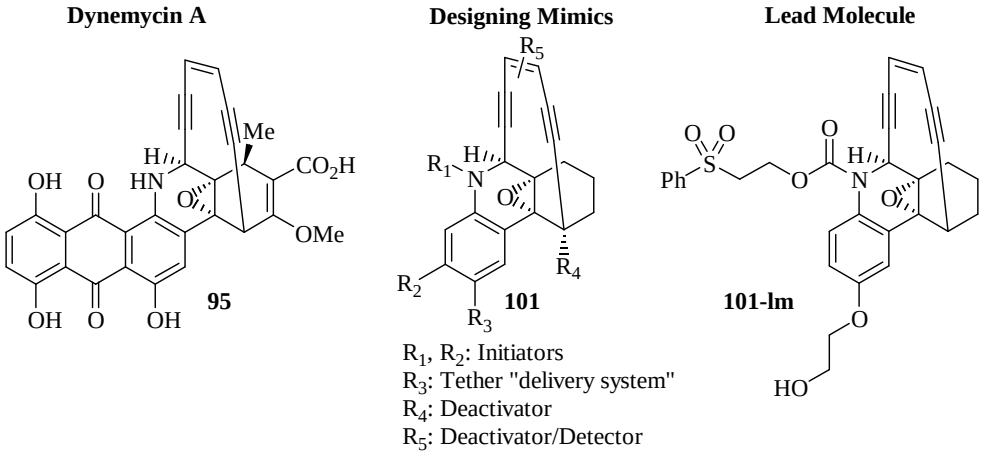


Because of their structural complexities, which make their syntheses extremely challenging, and their high cellular toxicity, these natural products, although having exceptional biological activities, cannot be used in humans without prior modification. Designing mimics of these molecules gives the option of creating molecules with simplified structures, i.e. easier to synthesise and also with improved biological activities, i.e. less toxic and therefore compatible with their use in humans.

For example, mimics of dynemicin A **95** could retain its enediyne core, as well as the epoxide group, which serves to maintain the stability of the molecule, prior to eliciting its biological activity (**Figure 6**). Protection of the nitrogen with an electron withdrawing group, easily removable under mild chemical or physiological conditions, could ensure the stability of the enediyne core although its deprotection could act as the "triggering device" and initiate the Bergman cycloaromatisation reaction (see compound **101** in **Figure 6**). Similarly, substituents R_2 on the aromatic ring could be used as a strategic position to activate the enediyne motif. R_3 Groups on the aromatic ring occupied a neutral position and could be linked to another molecule, which could mimic, for instance, the role of the sugar chair in calicheamicin **39** and serve to bind the molecule to the DNA or RNA. Finally the R_4 and R_5 groups could be used as deactivator groups. Indeed, R_4, as an electron withdrawing group could destabilise the

opening of the epoxide (formation of a carbocation in the α-position) and R_5, as benzene or naphthalene, could adjust the reactivity of the 1,4-benzenoid biradical.[27]

Figure 6. Dynemicin A **95** and Design Enediynes.



In view of these considerations, different mimic molecules were synthesised and biologically tested against leukaemia cell lines.[27] Compound **101-lm**, with a sulfone ethylene carbamate group on the nitrogen was one of the most potent compounds and was consequently further evaluated against a range of tumor cell lines. Of particular interest, it should be noted that enediyne **101-lm** was active against the T cell leukaemia TCAF-DAX, a multiple drug resistant cell line. The results are summarised in **Table 4**.

Table 4. Cytotoxicities of Enediyne **101-lm** Against Tumor Cell Lines.[27]

Cell Type	Cell Line	IC_{50} [M]	Cell Type	Cell Line	IC_{50} [M]
Melanoma	SK-Mel-28	3.1×10^{-6}	Lung carcinoma	H-522	9.8×10^{-8}
Melanoma	M-14	1.6×10^{-6}	Lung carcinoma	UCLA P-3	9.8×10^{-8}
Melanoma	M-21	1.6×10^{-6}	Pancreatic carcinoma	Capan-1	3.1×10^{-9}
Colon carcinoma	HT-29	1.6×10^{-6}	T cell leukemia	TCAF	1.1×10^{-9}
Ovarian carcinoma	Ovcar-3	7.8×10^{-7}	T cell leukemia	TCAF-DAX	1.7×10^{-9}
Ovarian carcinoma	Ovcar-4	7.8×10^{-7}	Myeloma	RPMI-8226	7.7×10^{-9}
Astrocytoma	U-87 UG	7.8×10^{-7}	Mouse leukemia	P-388	4.6×10^{-9}
Glioblastoma	U-251 MG	3.9×10^{-7}	Mouse leukemia	L-1210	1.3×10^{-9}
Breast carcinoma	MCF-7	7.8×10^{-7}	Promyeocytic leukemia	HL-60	3.6×10^{-11}
Lung carcinoma	H-322	3.9×10^{-7}	T cell leukemia	Molt-4	2.0×10^{-14}
Lung carcinoma	H-358	2.0×10^{-7}			

Enediyne **101-lm** showed also a less toxicity towards normal cell lines. The results are shown in **Table 5**.

Table 5. Cytotoxicities of Enediyne **LM-101** Against Normal Cell Line.[27]

Cell Type	Cell Line	IC_{50} [M]
Bone marrow	HNBM	5.0×10^{-5}
Human mammary epithelial cell	HMEC	6.3×10^{-6}
Normal human dermal fibroblast	NHDF	5.0×10^{-6}
Chinese hamster ovary	CHO	3.1×10^{-6}

1.2.5 CONCLUSION.

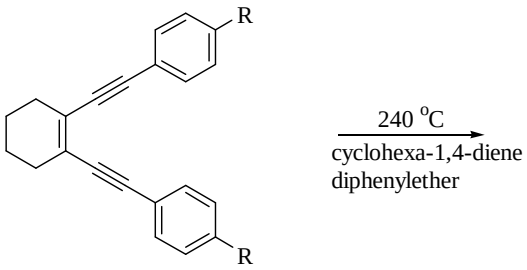
Although the Bergman cycloaromatisation reaction (**Section 1.2.1**), discovered in the 1970's, did not generate wide interest among the scientific community, a tremendous amount of work has been dedicated over the last two decades in order to understand the mechanism, and the driving forces behind this interesting reaction. The renewed interest in this reaction was due to the discovery of the enediyne antibiotics, such as calicheamicin **39** and dynemicin A **95**, a new class of highly potent antitumor agents with a mode of action based on the Bergman reaction feasible at ambient temperature. Work on these challenging natural products led Nicolaou to propose the "distance theory" in order to understand their reactivity (**Section 1.2.2**). Shortly after, Magnus and Snyder showed that the critical factor involved in the Bergman reaction was the difference of strain energies between the ground and transition states (**Section 1.2.3**). As result, unnatural enediynes, as well as mimics of these natural products, were synthesised with removable "locks", which upon activation could damage the DNA by double strand scission (**Section 1.2.4**). This work has led to the emergence of interesting anticancer prodrugs, which have been shown to be highly efficacious in cell based tumors.

1.3 ELECTRONIC EFFECTS ON THE BERGMAN REACTION.[28]

1.3.1 ACTIVATION AT THE ALKYNIC POSITION.

Due to the repulsive π-π interaction between the two triple bonds, the Bergman reaction requires a large activation energy in order to proceed. Introducing suitable substituents at the alkynic, or vinylic positions could lower the activation barrier and consequently permit the reaction to occur under milder reaction conditions. As a result, understanding the electronic effects of the Bergman cycloaromatisation reaction could provide useful information on how to modulate the reactivity of the parent biradical species. This could therefore be used for the design of new biologically active enediynes. Schmittel and Kiau showed that the introduction of an electron-withdrawing substituent at the alkynic positions could reduce the electronic density of the π-bond and consequently lower the energetic barrier of the reaction, which could as a result proceed under slightly milder conditions (**Scheme 18**).[29]

Scheme 18. Substituent Effect at the Alkynic Position.

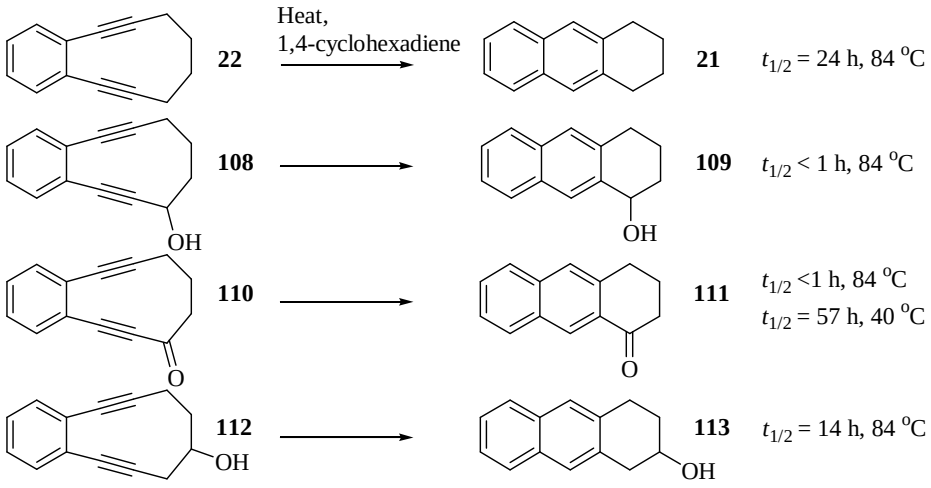


R = OMe **102**
R = H **103**
R = NO_2 **104**

			T(°C) for $t_{1/2}$ = 71 min
R = OMe	**105**	25%	286
R = H	**106**	80%	280
R = NO_2	**107**	15%	250

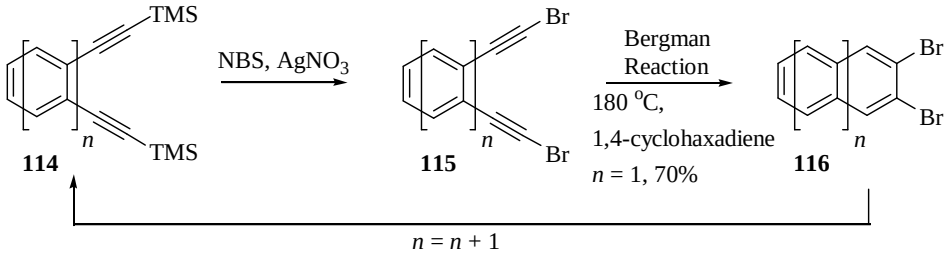
This effect has also been observed in the case of cyclic enediynes (see **Scheme 19**).[30] The presence of the hydroxyl group α to that of the triple bond (enediyne **108**) increased the rate of the cycloaromatisation reaction. The half life time of this compound was also diminished when electron-withdrawing group (ketone in compound **110**) was present. Reduction of the half life time was also observed for enediyne **112**, with an hydroxyl group in the β position.

Scheme 19. Effect of Electron Withdrawing Group on Cyclic Enediynes.



Another example of activation of the Bergman cycloaromatisation reaction with electron-withdrawing groups has been reported by Anthony and co-workers.[31] It was observed that the presence of halogen atoms in the acetylinic positions facilitated the reaction (**Scheme 20**). By using this methodology, it was possible to synthesise acenes **116**, a class of linear fused aromatic hydrocarbons. These polymers can be used as organic conductors and have been investigated within the physical chemistry area.

Scheme 20. Synthesis of Acenes.



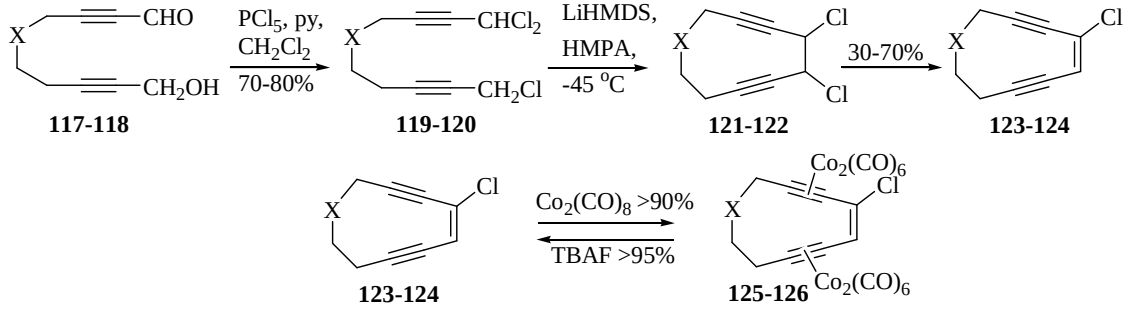
1.3.2 Activation of the Vinylic Position.

1.3.2.1 Vinyl Substitution.

Substitution at the vinyl position can influence greatly the rate of cycloaromatisation. Jones and co-workers studied the Bergman reaction of nine and ten-membered enediynes bearing chlorine substituents.[32] It was hoped that the inductive donor, coupled with the electronegativity of halogen atoms could lead to interesting results. Enediynes **123**, **124** and **129** were synthesised by using an intramolecular carbenoid coupling method (**Scheme 21**). Due to their instability, the compounds were

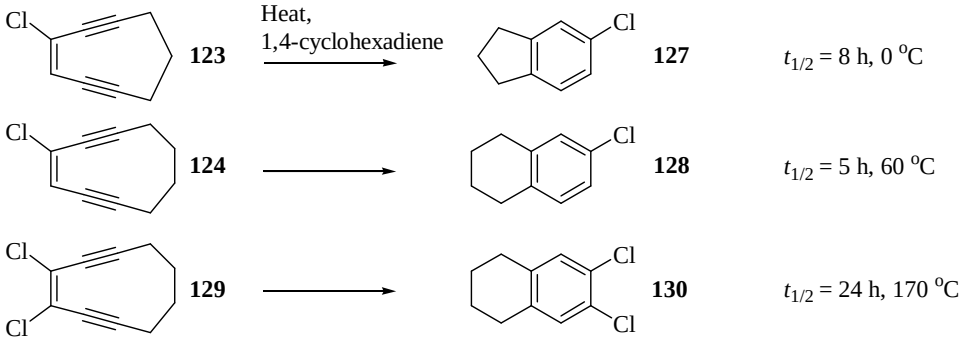
subsequently reacted with dicobalt octacarbonyl in order to mask the triple bonds. The reverse reaction could be achieved using tetrabutylammonium fluoride.

Scheme 21. Synthesis of Enediynes **125-126**.



Substitution of the double bond with chlorine atoms proved to reduce the rate of the Bergman reaction. Cycloaromatisation of nine-membered enediyne **123** had a half life time of 8 h at 0 ^{o}C, although the half life time of the corresponding unsubstituted compound could not be measured due to its rapid reactivity.[17] Similarly, addition of a second chlorine atom increased the stability of enediyne **129** even more. The half life times for these two compounds, **124** and **129**, were 5 h at 60 ^{o}C and 24 h at 170 ^{o}C, respectively (**Scheme 22**).

Scheme 22. Effect of Halogen Substitution on the Bergman Cycloaromatisation Reaction.



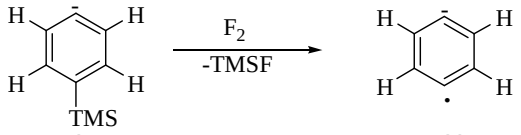
Calculation of the *cd* distance of enediynes **124** and **129** using molecular modeling (PM3) showed no difference of this distance (3.298 Å and 2.297 Å, respectively and 3.293 Å for the unsubstituted ten-membered enediyne). These results demonstrated that the extra stabilisation, obtained by the substitution of the double bond by chlorine atoms, was due to electronic effects and not because of the geometry of these compounds.[31]

Three hypotheses were made in order to explain these results; first, the presence of the halogen atom increased the activation barrier, secondly, the barrier of the retro-reaction (ring opening of the 1,4-benzenoid biradical) is lower and third, the 1,4-benzenoid biradical is more stable to hydrogen abstraction and consequently the reverse reaction is again favoured.

Chen and Logan showed by computational studies that the biradical species, in the triplet state, was a better hydrogen abstractor than the biradical in the singlet state.[33] As a result, increasing the gap between the singlet and triplet state could slow the rate of hydrogen abstraction.

Wenthold *et al*. determined the experimental value of the energy of the singlet-triplet gap by using ultraviolet photoelectron spectroscopy of benzyne anions.[34] The *p*-benzyne **132** was generated in the gas phase reaction of 4-trimethylsilylphenyl anion **131** and molecular fluorine (F_2).

Scheme 23. Preparation of 4-Trimethylsilylphenyl Anion.



131 **132**

It was found that the energy gap between the singlet and triplet states ΔE(ST) was 3.8 kcal.mol^{-1}. Jones and Warner showed using DFT calculations, that the singlet-triplet energy gap decreased in function of the number of halogen atoms (chlorine or fluorine) added at the vinyl positions of hex-3-ene-1,5-diyne.[35] Therefore, substitution of the double bond with halogen atom increases the rate of hydrogen abstraction. Consequently, this could not explain the stability of the chlorinated enediynes **124** and **129**, and consequently the third hypothesis could be eliminated as an increased in ΔE(ST) was required to show the increased stability. On the other hand, the calculations showed that the barrier energy itself increased by substitution of the double bond with halogen atoms. This therefore could explain the increase in stability observed.

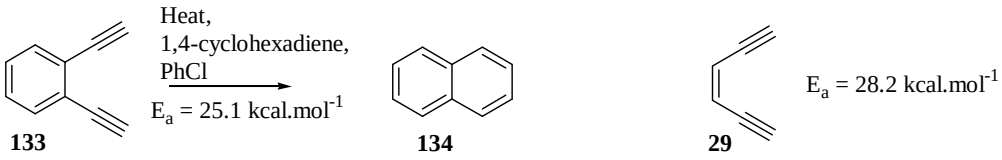
Understanding the important role played of π and σ, donor and acceptor substituents on the rate of cyclisation is essential to be able to efficiently design new enediynes. Further studies were performed and it was observed that σ-donor substituents tended to decrease the cyclisation barrier whereas σ-withdrawing groups raised it. No apparent relationship however, could be drawn with π donor/acceptor groups and for example CHO or OH

groups have no significant effect on the rate of cyclisation, contrary to the fluorine or chlorine substituents. One possible explanation could be the interaction between an in-plane halogen lone pair with the developing radical centre, which is orthogonal to the aromatic π-system. However, work is still ongoing to explain these observations.

1.3.2.2 Annulation.

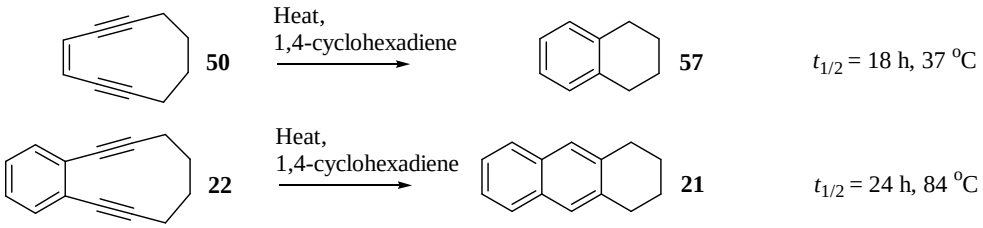
Annulation can be classified as a vinyl type substitution and includes in particular benzannulation and heteroarene fusion. The activation energy for the Bergman reaction of aromatic enediynes was determined experimentally by kinetic studies. It was shown that enediyne **133** had an activation energy of 25.1 kcal.mol^{-1}), which was slightly lower than that of enediyne **29** (E_a = 28.2 kcal.mol^{-1}) and consequently cyclised more rapidly.[36]

Scheme 24. Activation Energy.



However, other examples have been reported to demonstrate a reverse reactivity.[30] For example enediyne **50** had a half life time of 18 h at 37 ^{o}C, although the aromatic version, enediyne **22**, had a half life time of 24 h at 84 ^{o}C (**Scheme 25**).

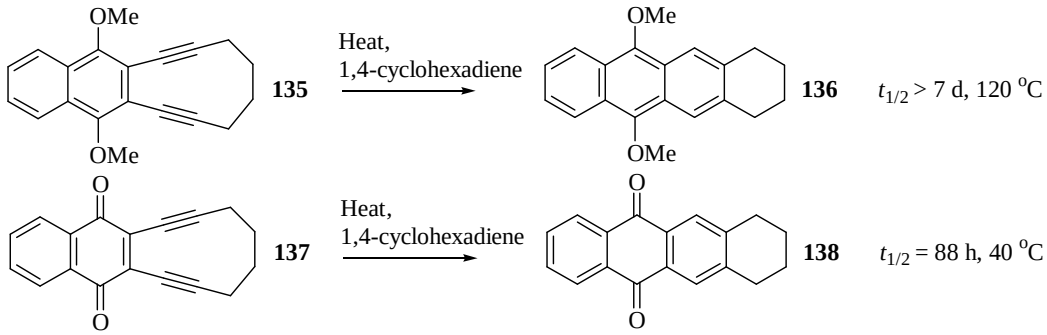
Scheme 25. Reverse Reactivity.



This difference in reactivity has been exploited in the Bergman reaction of quinone and hydroxyquinone type compounds (see **Scheme 26**). Semmelhack and co-workers showed that hydroquinone **135**, was stable towards the cycloaromatisation reaction. On the other hand, quinone **137**, cyclised readily at low temperature. The reactivity of compound **137** was explained by the quinone having "a full double bond character". The conversion of hydroquinone to quinone *via* a redox pathway can be available in

biological systems and could therefore serve as a new triggering system for the Bergman reaction to proceed under physiological conditions.[30]

Scheme 26. Hydroquinone – Quinone: Redox Triggering System.



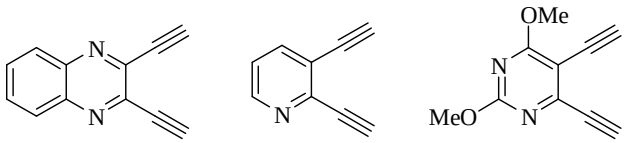
Hirama *et al*. reported that the cycloaromatisation rates of benzannulated enediynes were dependant on the concentration of the hydrogen donor, 1,4-cyclohexadiene.[37] This showed that the hydrogen abstraction step was kinetically more significant in the case of benzannulated systems than in the parent systems, and that the "extent of annulation" of the system directly affected the rate for the limiting step. Hence it is either that the benzo-fusion increases the rate of the retro-Bergman reaction and/or there is an increase in the energy gap between the singlet and triplet states, which resulted in lowering of the rate of hydrogen abstraction.

Alabugin and co-workers showed that substituents on benzannulated enediynes could influence the rate of cycloaromatisation, with the *ortho* substituents having a greater effect than the substituents at the *para* position.[38] Electron withdrawing substituents, such as the nitro group were found to accelerate the rate of cyclisation. This agreed with the theory that electron-withdrawal could decrease the repulsion between the two triple bonds. However, 2,3-diethynyl-1-methoxybenzene, a substituent having an electron donating effect, had also a slight increased in the rate of cyclisation (twice that of 1,2-diethylnylbenzene at 170 °C), but no rationalisation was proposed for these results.

Finally, interesting results have been obtained with heteroarenes enediynes. Russell *et al*. reported the possible cycloaromatisation of a range of enediynes containing nitrogen atoms (compounds **139**-**141** shown in **Figure 7**).[38] It was found that pyrimidine **139** was extremely reactive and had an activation energy of 16.1 kcal.mol^{-1}. The activation energies for pyridine **140** and quinoxaline **141** were of 21.5 and 33.6 kcal.mol^{-1},

respectively. Therefore, these results can be used for the design of novel biological active enediynes, as these molecules can be used as bioisomers

Figure 7. Bergman Cycloaromatisation Reactions of Heteroarene Enediynes.



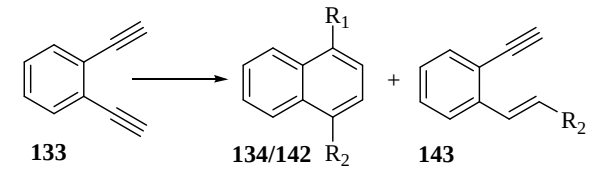
139 **140** **141**

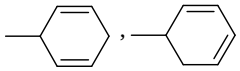
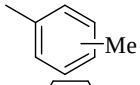
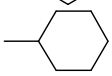
1.3.3 CONCLUSION.

Electronic effects can influence greatly the rate of the Bergman reaction. It was observed that substitution at the terminal alkynic positions had more significant effects than substitution at the vinyl positions. Several studies showed the dependence of the rate of the cyclisation reaction towards the concentration of the hydrogen atom donor, usually 1,4-hexadiene, and as a result, precaution should be made when comparing different rates of cyclisation; this problem can be overcome by using a large excess of the hydrogen atom donor. A second problem is the measurement of the half life time of the reaction. This is usually achieved by monitoring the disappearance of the starting material and it is usually assumed that this occurs only *via* the formation of the benzenoid biradical.

Uckun and co-workers showed that reaction of enediyne **133** with different sources of hydrogen donors, 1,4-hexadiene, tetrahydrofuran, isopropanol, toluene, cyclohexane and 3,4-dihydro-2*H*-pyran led to the isolation of the cyclised products, the cyclised products with the hydrogen atom donor and also occasionally the starting material containing the hydrogen atom donor (**Scheme 27**).[40]

Scheme 27. Reaction of Enediyne **133** with Different Hydrogen Donors.



	R_1	R_2
134	H	H
a	H	
b	H	
c	H	$-C(CH_3)_2OH$
d	H	$-CH_2Ph$
e	H	
f	H	
g	H	

H Atom Donor	**Product**	**Yield (%)**
1,4-Cyclohexadiene	**134**	36
	143a	31
Tetrahydrofuran	**134**	4
	142b	2
	143b	42
Isopropanol	**134**	26
	142c	1
	143c	66
Toluene	**134**	9
	142d	10
	142e	8
	143d	24
Cyclohexane	**134**	10
	142f	5
	143f	18
3,4-Dihydro-2H-pyran	**134**	22
	142g	15
	Adduct-C_2H_2	30
	Adduct C_2H_4	4

The formation of the latter compounds can be explained as follows: the 1,4-benzenoid biradical abstracts a proton from the hydrogen atom donor, generating consequently its radical. The solvent radical can then react with the starting material. The formation of these compounds could therefore result in the measure of a faster apparent rate of cyclisation if the studies are based on the disappearance of the starting material.

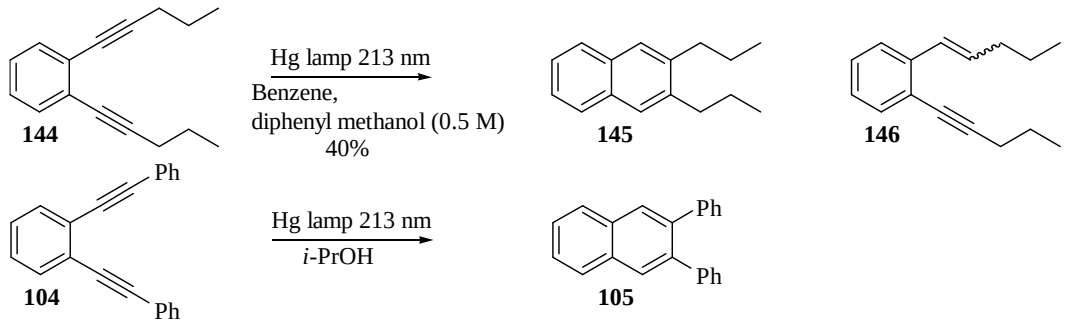
1.4 PHOTO BERGMAN CYCLISATION.

1.4.1 DEVELOPMENT OF NON NATURAL PHOTO-ACTIVATED ENEDIYNES.

Developing stable enediynes, which could generate 1,4-benzenoid biradicals upon photo-irradiation and at ambient temperature only, could be used in photodynamic chemotherapy. This opens consequently the way for the synthesis of novel anticancer drugs, which are able to inflict permanent damage to DNA through sizing of the double helix.

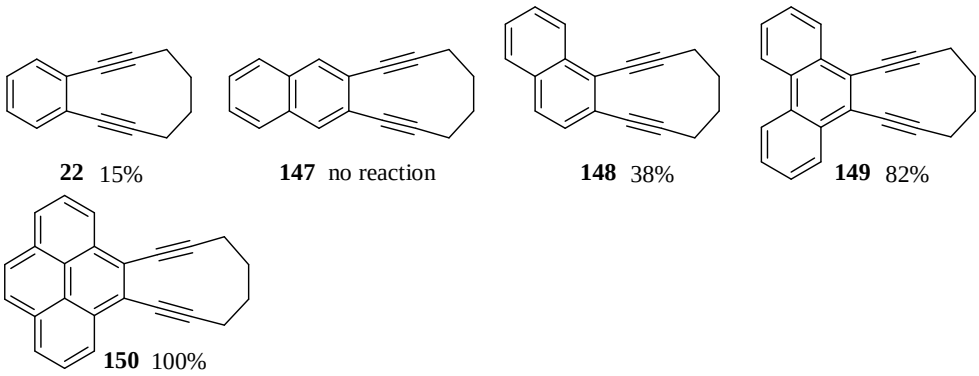
One of the first example of a Bergman cycloaromatisation initiated by photo-irradiation was reported in 1994 by Turro *et al*..[41, 42] When a reaction mixture containing enediyne **144** was irradiated with a medium pressure mercury lamp containing a potassium chromate filter solution (cutting off the wavelengths below 313 nm), in benzene and with diphenyl methanol as hydrogen atom donor, the corresponding cyclised adduct **145** was obtained in 40% yield (**Scheme 28**). In addition, enediyne **104**, when irradiated in 2-propanol gave compound **105**, which was similar to the compound obtained upon thermal Bergman reaction (**Scheme 18**). Reaction of compound **144** in 2-propanol gave the cyclised product **145** as well as the reduced compound 1**46**.

Scheme 28. Photo Bergman Cyclisation of Benzo-Enediynes **144** and **104**.



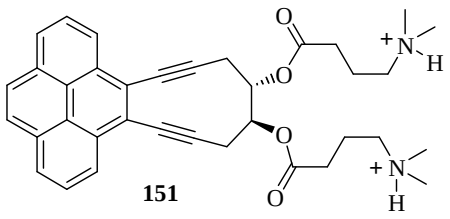
A range of benzoenediynes, compounds **22**, **148**, **149** and **150**, were later reported by Funk and co-workers, to undergo photochemical cycloaromatisation when irradiated (Hanovia 450 W, Et_2O, 18 h) in the presence of 1,4-cyclohexadiene (30 eq.) (**Figure 8**).[43] No reaction was observed for compound **147**. Of particular interest was compound **150**, its cyclisation occurred in quantitative yield when reacted at ambient temperature under sunlight for 3 h in acetonitrile.

Figure 8. Photochemical Cycloaromatisation.



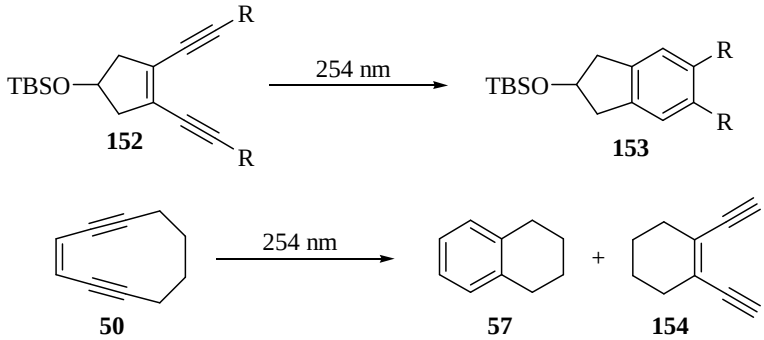
Based on these results, synthesis of water soluble molecules was achieved and it was shown that compound **151** could cleave DNA under photo-irradiation.[43]

Figure 9. Water Soluble Enediyne.



Hirama and co-workers reported the photo cyclisation of non-benzenoid enediynes.[44] Compounds **152a/c** were not reactive towards photo-cyclisation, except for enediyne **152d**, which gave the corresponding cyclised product **153d** in 71%. No reduced products, as previously observed in the reaction of benzenoid enediyne, were observed. In addition, ten-membered enediyne **50** gave the corresponding cyclised product **57**, as well as the product from the retro-Bergman reaction, compound **154**.

Scheme 29. Photo-Cyclisation of Non Benzenoid Enediynes.

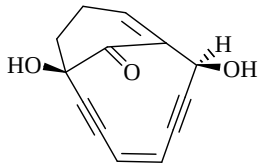


	R	Yield (%)
a	Ph	no reaction
b	TMS	no reaction
c	H	3%
d	Me	71%

	21	154
Hexane	29%	6%
Cyclohexane	26%	20%
Acetonitrile	12%	24%
i-Propanol	3%	-

Enediyne antibibiotics are known to cause double strand DNA cleavage. However, it has been shown that the DNA cleavage was not sufficient to cause the cell death as observed in cells treated with enediynes.[25] This suggests the possible interaction of these molecules with other targets in the cells, hence the study of the effect of enediynes on proteins, which are the most abundant compounds by weight in cells.[45] It has been shown that a model of the core of enediyne antibiotics such as enediyne **155**, could cause extensive protein damage, for instance in proteins of cell membranes, tubulins and histones (**Figure 10**). The presence of thiol to activate the reaction was not necessary and it was postulated that protein nucleophiles or protein thiols themselves could initiate the Bergman reaction.

Figure 10. Core Model of Enediyne Antibiotics.



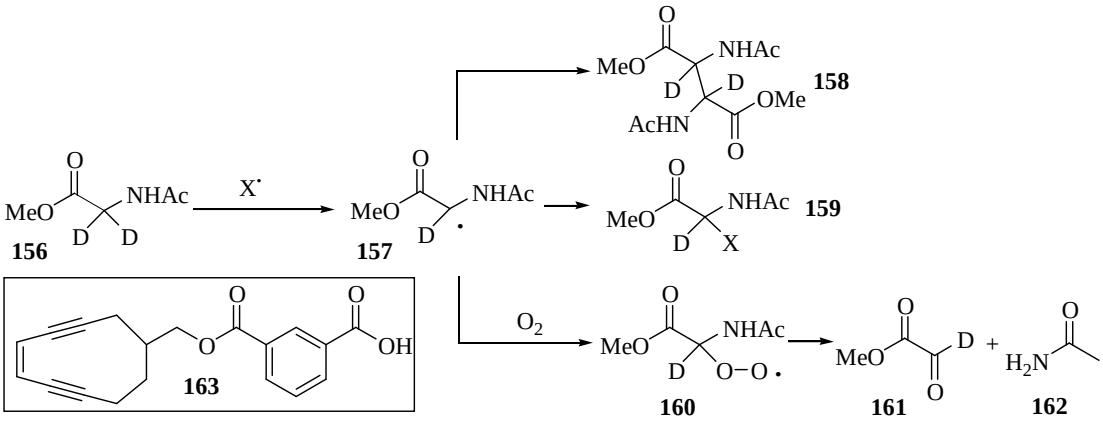
155

In order to understand the mechanism of degradation of proteins, radical reactions on deuteriated amino acids were carried out and it was shown that aryl radicals could abstract deuterium from dideuteroglycine derivatives.[46]

Under aerobic conditions, the radical **157** generated, can react with another stabilised α-centred radical and hence cause dimerisation (**Scheme 30**), cross-linking of proteins, or react with molecular oxygen to give a peroxo-radical **160**, which after rearrangement gives compounds **161** and **162**.[47]

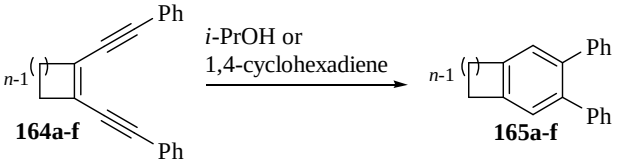
Under anaerobic conditions, radical **157** can also react with the radical source $X^{\cdot}$ to give compound **159**. A range of enediynes activated either thermally or photo-chemically, were reacted with deuteriated glycine **156** and incorporation of deuterium was observed in the corresponding cycloaromatised products. An example of water soluble enediyne, compound **163** used in these experiments is drawn in **Scheme 30**. In addition to the cyclised products, cross linked glycine **158** (under anaerobic conditions), as well as compounds **161** and **162** (when reaction was carried out under aerobic condition), were also isolated.[47]

Scheme 30. Protein Degradation Pathways.



In order to design enediynes aimed at targeting specific proteins, Jones *et al*. studied first the Bergman reaction of a range of enediynes activated upon photo-irradiation.[48] The cycloaromatised products were isolated in low yield, 9-21% (**Table 6**). Contrary to the Bergman thermal reaction, the compounds with the shorter *cd* distance were not the most reactive.

Table 6. Irradiation of a Range of Enediynes.

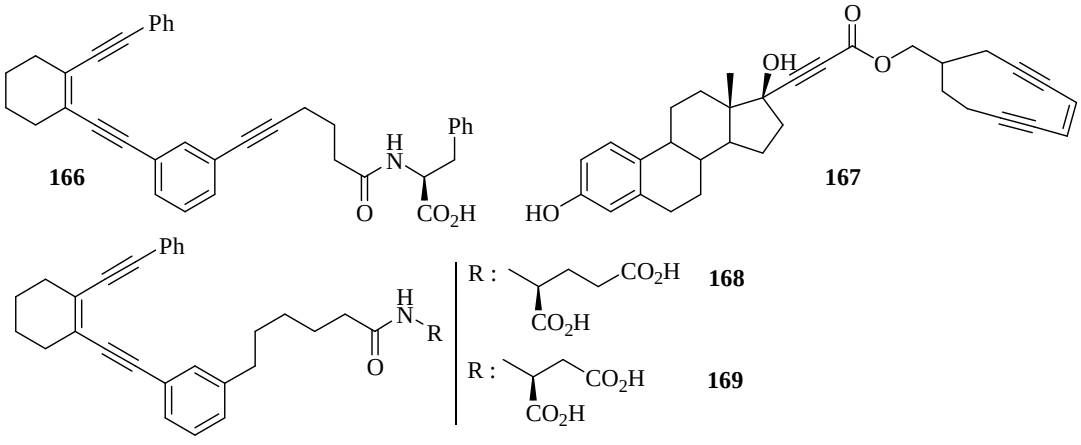


	n	*cd* (Å)	**Yield** (%)[1]
a	2	4.941	0 (0)
b	3	4.284	13 (13)
c	4	4.018	15 (31)
d	4	4.018	21 (22)
e	5	3.947	11 (16)
f	6	3.893	9 (14)

[1] Yield based on recovered starting material

Based on these results, enediynes **166-169** were synthesised and it was shown that they could cause damage to bovine serum albumin, histone and estrogen receptor, respectively (**Figure 11**).[49-51]

Figure 11. Targeting Specific Proteins.



1.4.2 CONCLUSION.

The photo Bergman reaction is another strategy to activate enediynes and could find application in photodynamic therapy, which is currently used to treat cancer.[52] The major advantages are that the reactions can be carried at ambient temperature and below, and that the activation of the drugs can be time controlled and performed by selective exposure to cell permeable photons.

1.5 General Conclusion.

The Bergman cycloaromatisation reaction has permitted us to better understand the mode of action of the enediyne antibiotics, and has led to the design of exciting enediynes, whose inherent reactivity can be triggered thermally and also upon photo-irradiation. This reaction has been over the years a constant source of inspiration for scientists and still continues to give insight into the mode of action or biosynthesis of natural products. For example, it was recently proposed that the biosynthesis of the marine natural products, sporolides A and B, possessing monochlorobenzene cores, occurred *via* a Bergman reaction.[53] The Parsons group also recently developed a novel cyclisation reaction, based on the generation of a biradical intermediate, and which can be used to synthesise a range of natural products, such as for example lactonamycin.[54, 55]

Finally, it should be noted that this discovery has been followed by the development of other reactions, based also on the generation of biradicals. This includes for example, the Myers-Saito[56] and the Schmittel[57] reactions, which involve the reaction of enyne-allenes.

Chapter 2 | RESULTS & DISCUSSION

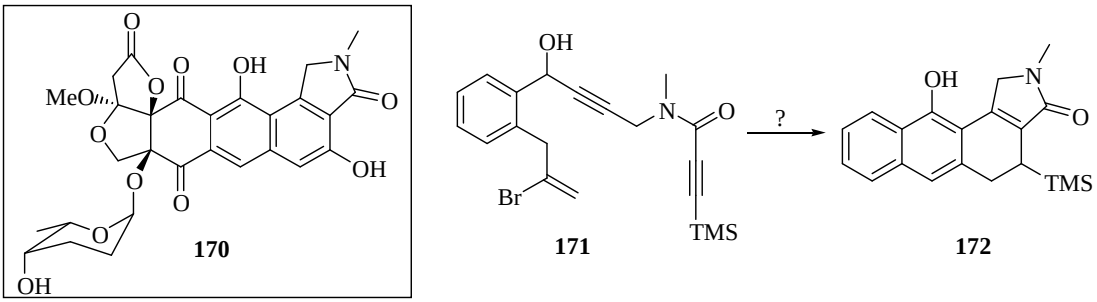
The development of novel strategies provides the synthetic chemists with the means to synthesise interesting chemical structures. In particular, tandem methodologies can give access to molecules with high structural complexities from simple starting materials and achieves this, by carrying out multiple steps in one single synthetic operation. The Parsons group recently developed a novel cyclisation reaction, which, similar to the Bergman reaction described in **Chapter 1**, could generate a biradical species, which could, after being trapped with a suitable alkene, lead to the formation of tricyclic molecules containing heterocyclic cores (see **Section 2.1**). As a result, we wish to further investigate this novel reaction and develop tandem reaction methodology around it. This novel methodology would involve the Bergman type reaction combined with a Diels-Alder reaction to generate pentacyclic molecules, in one synthetic operation from an acyclic precursor. Consequently, **Section 2.2** of this chapter will deal with the synthesis of the different precursors required for this chemistry. The cyclisation reaction will be studied in **Section 2.3** and the subsequent Diels-Alder reaction in **Section 2.4**.

2.1 PREVIOUS WORK AND AIM WITHIN THIS THESIS.

2.1.1 PREVIOUS WORK.

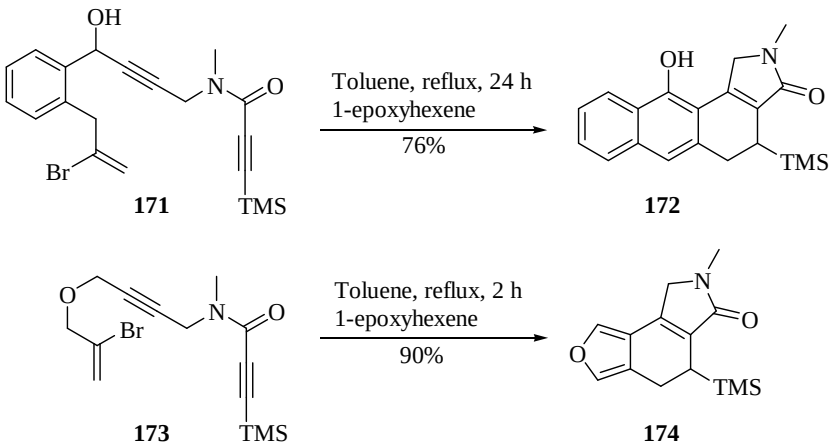
Previous work within the Parsons group toward the total synthesis of lactonamycin **170**, led to the development of a novel reaction for the synthesis of polycyclic heterocyclic rings.[54, 55] One of the key steps in this work was a palladium, or radical mediated cyclisation reaction in order to construct the core of lactonamycin **170**. A model system, endiyne **171**, was built in order to verify the validity of this route. The strategy is shown in **Scheme 31**.[58]

Scheme 31. Lactonamycin **170** and Model System **171**.



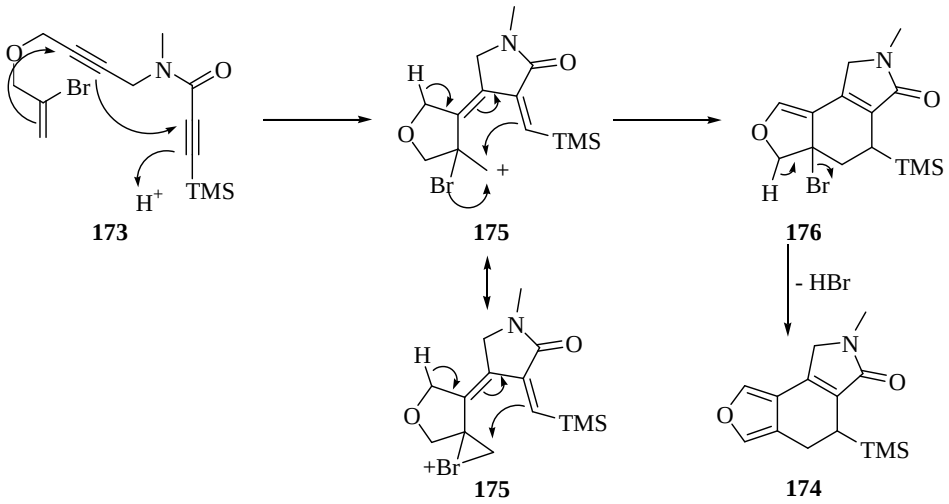
It was however observed that the desired reaction could occur when model system **171** was heated alone under reflux in toluene for 24 h and the desired tetracyclic compound **172** was obtained in 50% yield. Most interestingly, the reaction was performed without any metal catalyst, and in the presence of an acid trap, 1-epoxyhexene, the yield of the reaction was improved to 76% (see **Scheme 32**). In addition, the cyclisation reaction was also successful with other substrates and for example, the formation of furan **174** from enediyne **173** was observed under similar conditions in 90% yield.[54, 55]

Scheme 32. Preliminary Results.



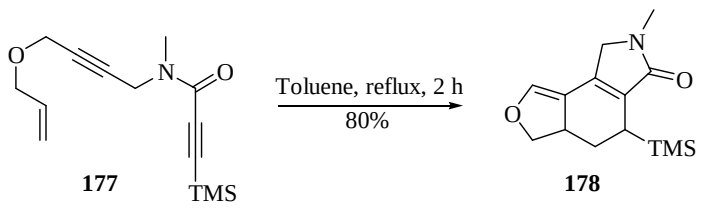
It was first postulated that, due to the possible formation of hydrogen bromide under the reaction conditions, the reaction could be acid catalysed and generate intermediate **175**. The proposed mechanism is shown in **Scheme 33**.[55]

Scheme 33. Acid Catalysed Mechanism.



However, as shown previously in **Scheme 32**, it was observed that the presence of an acid scavenger, 1-epoxyhexene, increased the yield of the reaction. This result consequently indicated that an acid catalysed mechanistic pathway was likely to be disfavoured. In order to verify this hypothesis, the cyclisation reaction of compound **177** was tested (**Scheme 34**). In this particular case, the formation of acid was not possible during the reaction. Therefore if the reaction were acid catalysed then no product would have been obtained. In fact, it was observed that this reaction was possible and that the desired dihydrofuran **178** was afforded in 80% yield when the precursor **177** was heated under reflux in toluene for 2 h (see **Scheme 34**).[54, 55]

Scheme 34. Other Preliminary Result.



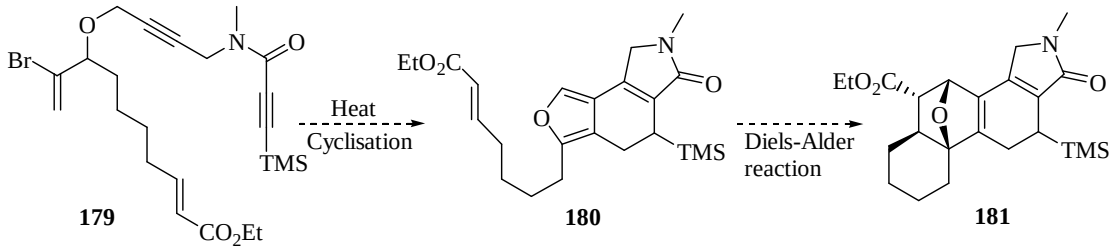
Consequently, this result disfavoured an acid catalysed mechanism for this cyclisation reaction. In order to explain these observations, it was postulated that the reaction was possibly initiated by the formation of a diene biradical, generated from the two triple bonds and that subsequent addition to the remaining double bond was occurring. Work

in order to determine the mechanism of this reaction is still on-going in the Parsons group, but has not been the aim of this thesis. However, the proposed mechanism of the reaction will be discussed later on in **Section 2.3**.

2.1.2 AIM WITHIN THIS THESIS.

As seen previously, this novel methodology gives access to interesting tricyclic ring systems containing both a furan and a lactam moiety. To further expand this novel reaction developed within the Parsons group, we wished to investigate an intramolecular Diels-Alder reaction to the furan ring generated during the initial Bergman like step. If successful, this cascade reaction would give access to a novel methodology for the synthesis of pentacyclic derivatives in one synthetic operation and from an acyclic material. The cascade reaction that we wished to studied is shown in **Scheme 35**. In addition, if this methodology is successful, the possible aromatisation of the central ring system could also be investigated.

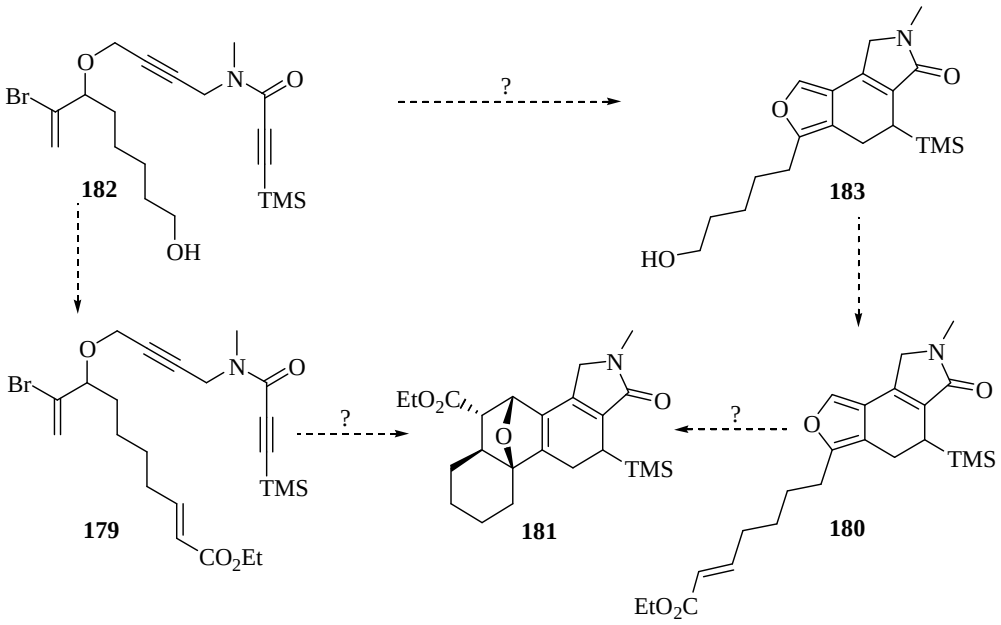
Scheme 35. Aim within this Thesis.



179 **180** **181**

Before attempting the cascade reaction shown in the previous scheme, we decided to look at the feasibility of both synthetic operations. The free alcohol **182** represented an ideal substrate to test the first cyclisation as it was structurally similar to the final precursor **179**. Thus, if this cyclisation reaction was successful, i.e., if the formation of the corresponding tricyclic compound **183** occurred, then the double bond would be constructed by oxidation and olefination of the primary alcohol to give compound **180**. The Diels-Alder reaction would then be tested on this substrate. Finally, the target molecule **179** could be synthesised from compound **182** by again oxidation and olefination of the alcohol group. The strategy that we wished to realise is described in **Scheme 36**.

Scheme 36. Strategy Employed to Test Both Steps Independently.

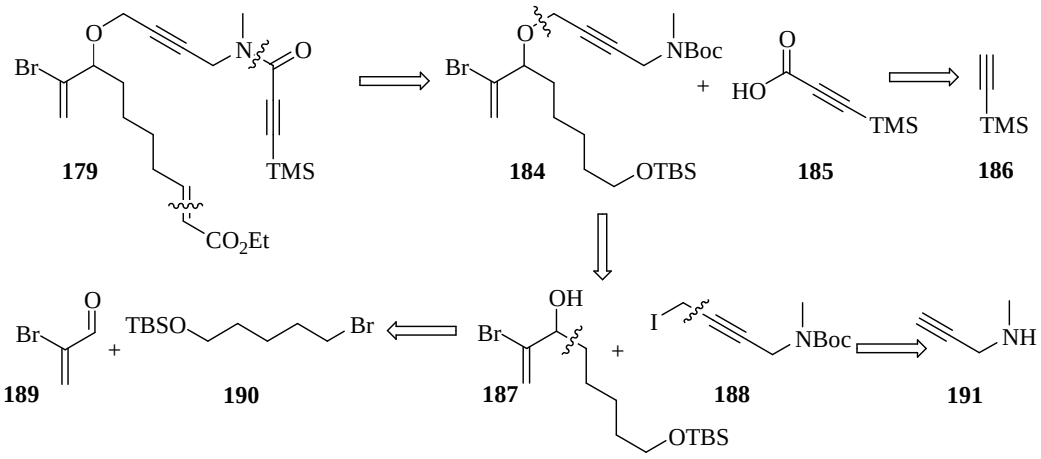


2.2 SYNTHESIS OF KEY PRECURSORS 179 AND 182.

2.2.1 RETROSYNTHETIC ANALYSIS.

Retrosynthetic disconnection of the target precursor **179**, as shown in **Scheme 37**, provides intermediates **184** and **185**. Compound **179** can be easily synthesised by oxidation followed by a Horner-Wadsworth-Emmons reaction[59, 60] of deprotected alcohol **184** and the amide bond could be introduced by reaction of the amine with the corresponding carboxylic acid **185**. Reaction of secondary alcohol **187** and propargyl iodide **188** can provide ether **184**. Alcohol **187** can be synthesised by reaction of *α*-bromoacrolein **189** and the Grignard reagent of bromopentanol silyl ether **190**. Finally, propargyl iodide **188** can be obtained from the commercially available *N*-methylpropargylamine **191** and *α*-bromoacrolein **189** from acrolein.

Scheme 37. Retrosynthetic Analysis.



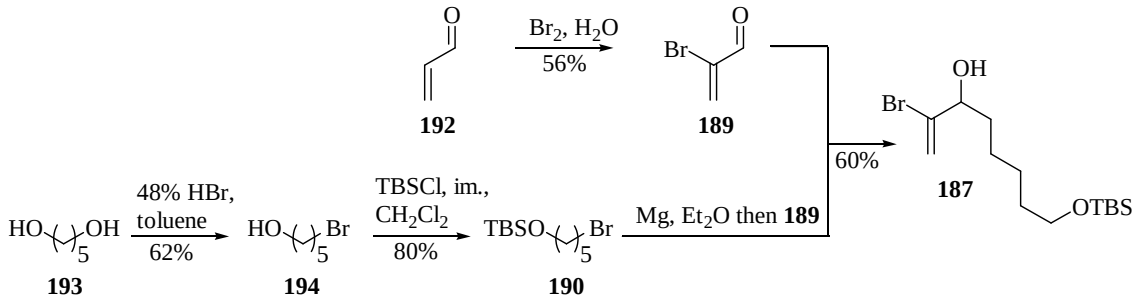
2.2.2 SYNTHESIS OF THE PRECURSORS 179 AND 182.

2.2.2.1 Formation of Key Intermediate, Secondary Alcohol 187.

The synthesis started by the monobromination of pentanediol **193**. This reaction was carried out using 48% aqueous hydrogen bromide in toluene at reflux and bromopentanol **194** was afforded in 62% yield after purification by flash column chromatography in order to remove the dibrominated compound.[61] The primary alcohol was then protected using *tert*-butyldimethylsilyl chloride, imidazole in dichloromethane to give **190** in 80% yield.[62] Reaction of compound **190** with magnesium turnings, or powder, in dry diethyl ether generated the corresponding Grignard reagent, which was subsequently reacted with *α*-bromoacrolein to give secondary alcohol **187** in 60% yield. It should be noted that *α*-bromoacrolein **189** was

synthesised by reaction of acrolein **192** with bromine in water and obtained in 56% yield after purification by steam distillation.[63]

Scheme 38. Formation of Secondary Alcohol **187**.

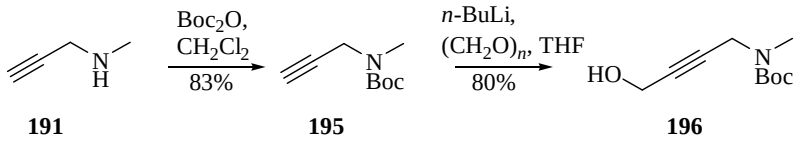


2.2.2.2 Synthesis of Propargyl Iodide 188.

i. Formation of Propargyl Alcohol **196**.

N-Methylpropargylamine **191** was *N*-Boc protected using Boc_2O in dichloromethane to give compound **195** in 83% yield.[55] Deprotonation of the acetylenic proton using a 2.3 M solution of *n*-BuLi in hexanes at -78 °C in dry THF and subsequent reaction with paraformaldehyde afforded propargyl alcohol **196** in 80% (**Scheme 39**).[55]

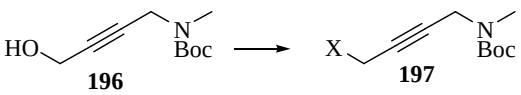
Scheme 39. Synthesis of Propargyl Alcohol **196**.



ii. Formation of Propargyl Iodide **188**.

In order to synthesise ether **185**, transformation of primary alcohol of **196** into a leaving group was required in order to be reacted with secondary alcohol **187**.

Scheme 40. Conversion of the Alcohol Moiety into a Leaving Group.



X = OMs, OTs, Br, I

Reaction of propargyl alcohol **196** with MsCl or TsCl with triethylamine in dichloromethane did not lead to the isolation of the desired products. Attempts to form the corresponding halides (X = Cl or Br) using PCl_3 or PBr_3 with pyridine in ether or THF led only to the decomposition of the starting material.[64] Under milder conditions, using carbon tetrabromide, triphenylphosphine in THF, no reaction was observed and

only the starting material was recovered.[65] Under similar conditions but with the use of a more nucleophilic phosphine, tris(dimethylamino)phosphine, the corresponding propargyl bromide was obtained in 56% yield. Formation of the corresponding propargyl iodide **188** using iodine, triphenylphosphine, imidazole in diethyl ether led to decomposition of the starting material.[66] Finally, propargyl iodide **188** was obtained in 30% yield using methyltriphenoxyphosphonium iodide in DMF[67] and in 60% yield using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), triphenylphosphine, tetrabutyl-ammonium iodide in dichloromethane at RT and for 30 minutes.[68] This method was the most reliable, fast and did not require any work-up. In addition, the product was easily purified by flash column chromatography. The results are summarised in **Table 7**.

Table 7. Transformation of the Primary Alcohol into a Leaving Group.

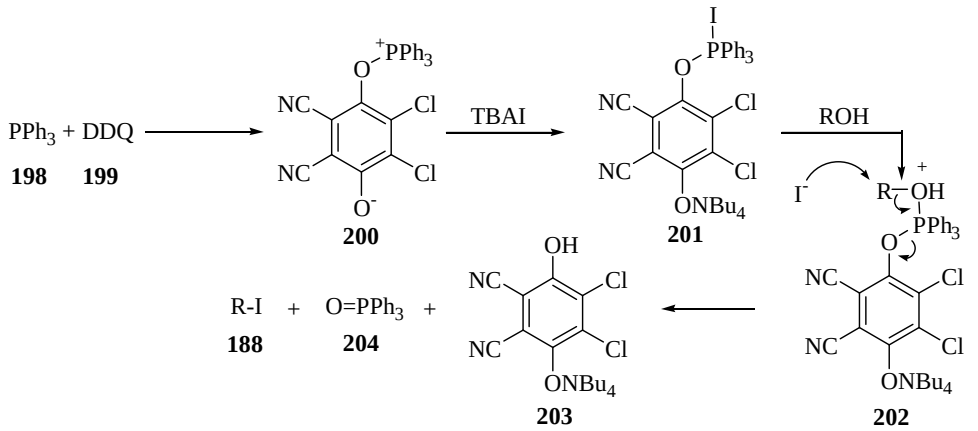
Entry	X	Conditions	Yield
i	OMs	MsCl, Et_3N, CH_2Cl_2	?
ii	OTs	TsCl, Et_3N, CH_2Cl_2	?
iii	Cl	PCl_3, py, Et_2O	Decomposition
iv	Br	PBr_3, py, Et_2O	Decomposition
v		CBr_4, PPh_3, THF/Et_2O	No reaction
vi		CBr_4, HMPT, Et_2O	56%
vii	I	I_2, PPh_3, im., Et_2O	Decomposition
viii		Methyltriphenoxyphosphonium iodide, DMF	30%
ix		DDQ, PPh_3, TBAI, CH_2Cl_2	60%

Discussion.

As seen previously, the best result was obtained when using DDQ, triphenylphosphine and tetrabutylammonium iodide. The order of addition of the different reagents was important and was performed as follows. To a solution of DDQ **199** in dichloromethane was firstly added triphenylphosphine **198**. This generated intermediate **200** as shown in **Scheme 41** Then, tetrabutylammonium iodide was added to the reaction mixture and the corresponding neutral species **201** was formed. Finally, the alcohol, which was added last, displaced the iodide group to give intermediate **202**. The iodide ions could then attack the alcohol group to give the corresponding iodide **188**. Therefore, the driving forces of the reaction are the aromatisation of DDQ, compound **203** and the formation

of stable triphenylphosphine oxide **204**. The proposed mechanism is shown in **Scheme 41**.[68]

Scheme 41. Proposed Mechanism.[68]

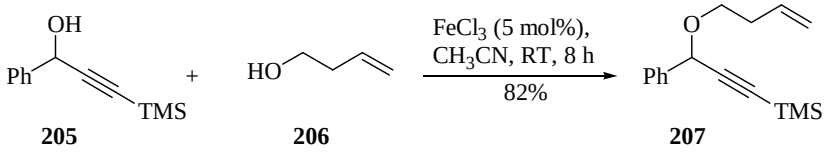


2.2.3 Introducing the Propargylic Motif.

2.2.3.1 Coupling of Propargyl Alcohol 196 with Secondary Alcohol 187.

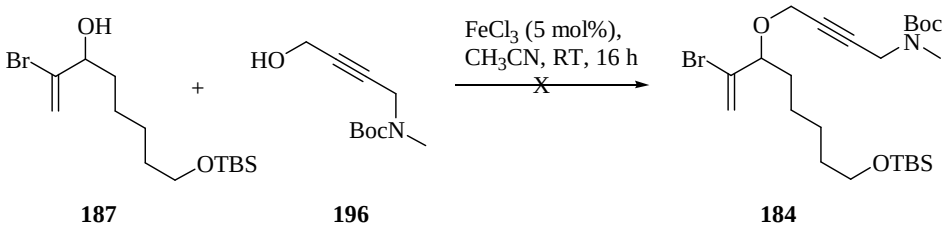
We first decided to investigate the coupling of secondary alcohol **187** with propargyl alcohol **196**. In the literature, we found that Zhang and co-workers recently reported the nucleophilic substitution of propargyl alcohols using a catalytic amount of iron chloride in acetonitrile.[69] A wide range of nucleophiles could be used and included for example alcohols, thiols, amides and allyltrimethylsilane. In additions, in comparison to other catalysts such as cobalt or gold, iron chloride was cheap and required very mild conditions, hence the interest in this reaction. An example is shown in **Scheme 42**.

Scheme 42. Nucleophilic Substitution of Propargyl Alcohol Using Iron (III) Chloride.



Unfortunately, when secondary alcohol **187** and propargyl alcohol **196** were reacted with a catalytic amount of iron (III) chloride in acetonitrile, no desired product **184** was isolated. We observed by TLC analysis, the disappearance of propargyl alcohol **196** and the possible decomposition of secondary alcohol **187**.

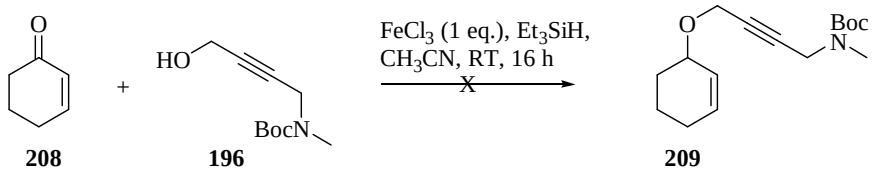
Scheme 43. Reaction of Secondary Alcohol **187** and Propargyl Alcohol **196** with Iron (III) Chloride.



187 **196** **184**

Simultaneously, a similar reaction involving the reaction of a ketone with an alcohol using iron (III) chloride (1 eq.) and triethylsilane in acetonitrile was carried out following the literature procedure.[70] In order to test this methodology, cyclohexenone **208** was used as model system of secondary alcohol **187**. The reaction is described in **Scheme 44**. However, it was unclear if the reaction had worked as no desired product **209** was isolated.

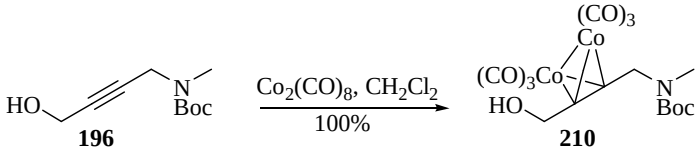
Scheme 44. Reaction of Cyclohexenone **208** and Propargyl Alcohol **196** Using Iron Chloride and Triethylsilane.



208 **196** **209**

The use of dicobalt octacarbonyl was also examined in order to perform the coupling of secondary alcohol **187** and propargyl alcohol **196**. As seen in **Chapter 1**, the cobalt reagent can be used as protecting group of a triple bond (see **Scheme 21**). They are also able to stabilise carbocation α to the previously existing triple bond. This strategy has been widely used in synthesis.[71] After reaction, the triple bond can be regenerated using for example ceric ammonium nitrate.[72] Thus, reaction of propargyl alcohol **196** with dicobalt octacarbonyl in dicholoromethane gave the corresponding product **210** in quantitative yield and as a deep red oil (**Scheme 45**).[72]

Scheme 45. The Nicholas Reaction of Propargyl Alcohol **210**.

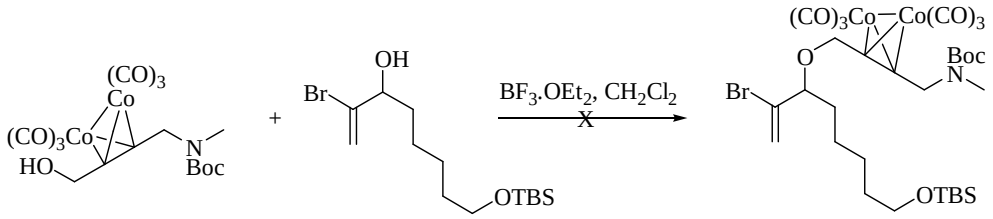


196 **210**

Treatment of compound **210** with boron trifluoride etherate in dichloromethane followed by addition of secondary alcohol **187** did not afford the desired product **211**

and only the cleavage of the TBS group of **187** was observed under these conditions (see **Scheme 46**).[72]

Scheme 46. Reaction of Compound **210** with Secondary Alcohol **187**.



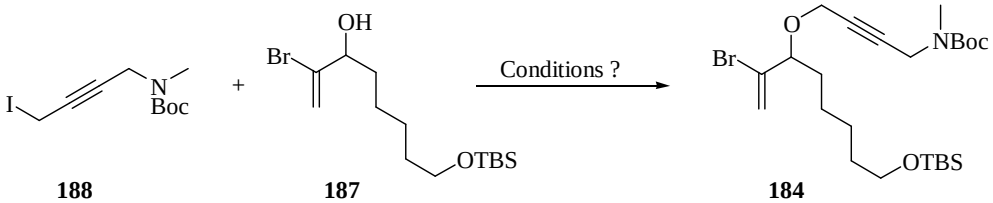
210 **187** **211**

To conclude this section, the use of dicobalt octacarbonyl was an excellent strategy. However, a successful reaction would have required a change of protecting group. For this reason we decided not to proceed and investigate instead the coupling reaction of secondary alcohol **187** with propargyl iodide **188**, which was previously synthesised in **Section 2.2.2.2**.

2.2.3.2 Coupling of Propargyl Iodide 188 with Alcohol 187.

As seen previously, reaction between alcohol **187** and propargyl alcohol **196** was unsuccessful and a more classical approach was investigated in order to form the ether linkage. As a result, different conditions were tested in order to couple alcohol **187** with propargyl iodide **188**.

Scheme 47. Formation of Ether **184**.



188 **187** **184**

Reaction of propargyl iodide **188** with secondary alcohol **187** and sodium hydride in THF led to the desired product **184** in low yield.[73] Using these reagents, different reactions were carried out in order to improve the yield of the reaction. The order of addition of the reagents was investigated and two types of reactions were performed, either the alcohol was first deprotonated with sodium hydride and then iodide **188** was added to the reaction mixture or sodium hydride was directly added to a mixture of alcohol **187** and propargyl iodide **188**. In addition, the time and reaction temperature were investigated but the yield of this reaction stayed still very low and on average

around 15%. The product was difficult to separate from the unreacted starting materials and several flash columns chromatography were necessary to purify it.

Reaction with LDA in THF or silver triflate and potassium carbonate in dichloromethane[74] led to the decomposition of the starting materials and no desired products were isolated. No reaction was observed either when using inorganic bases such as sodium or cesium carbonate in acetonitrile.[75]

Finally, the most successful results were obtained when using sodium hydroxide, tetrabutylammonium hydrogensulfate in dichloromethane and water and the coupling product **184** was isolated in 30% yield.[76] This reaction condition was found when trying to couple secondary alcohol **187** with propargyl bromide (see following **Section 2.2.3.3**). This reaction was further improved and it was found that reaction under neat conditions at RT for 3 days gave the desired product **184** in 65% yield. All the reaction conditions are summarised in **Table 8**.

Table 8. Formation of Ether **184**.

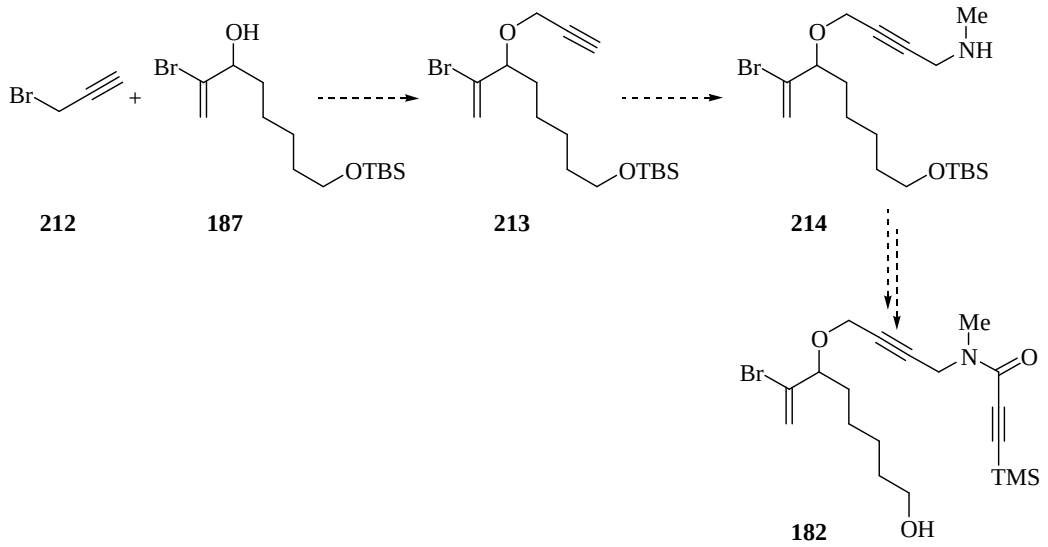
Entry	Conditions	Yield and Observations
i	NaH, THF, reflux	15%
ii	LDA, THF	Decomposition of **187**
iii	AgOTf, K_2CO_3, CH_2Cl_2	Decomposition of **188**
iv	K_2CO_3 or $CsCO_3$, CH_3CN	No reaction
v	50% NaOH, TBA(HSO_4), CH_2Cl_2	30%
vi	50% NaOH, TBA(HSO_4), neat	65%

2.2.3.3 Alternative Route.

Because of the difficulties encountered to generate the propargyl iodide **188**, we decided to investigate an alternative route for the synthesis of ether **184**. Coupling of alcohol **187** with propargyl bromide **212** (which is commercially available) and then introduction the amine moiety using a Mannich reaction[77] were investigated. As can be seen in **Scheme 48**, this route has several advantages. It shortens the number of steps in the synthesis and avoids the formation of propargyl iodide **188**, which requires three steps to be synthesised and the use of expensive reagents (such as *N*-methylpropargylamine **191** and DDQ **198**). In addition, there would be also no need to

remove the Boc group and amine **214** could be after a TBS deprotection, directly reacted with the corresponding acid chloride to give the first target molecule **182** (see **Scheme 48**).

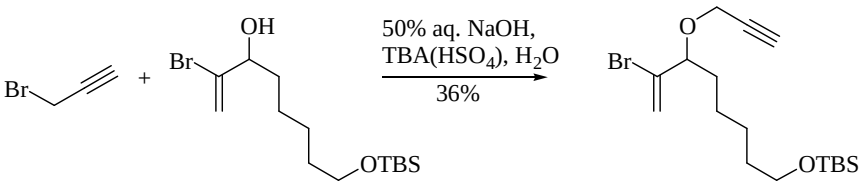
Scheme 48. New Route: Etherification, Mannich Reaction and Amide Formation.



212 **187** **213** **214** **182**

Different reaction conditions were tested in order to perform the coupling reaction between secondary alcohol **187** and propargyl bromide **212**. Thus, reaction with sodium hydride in THF at reflux for 16 h gave ether **213** in 31%.[73] The use of phase transfer catalysts was also examined. Consequently, reaction of alcohol **187** with propargyl bromide **212**, 50% aqueous sodium hydroxide, tetrabutylammonium iodide in water afforded the corresponding product **214** in only 9% yield.[76] However, when reacted with tetrabutylammonium hydrogensulfate, the desired compound **214** was obtained in 36% yield (**Scheme 49**).[76]

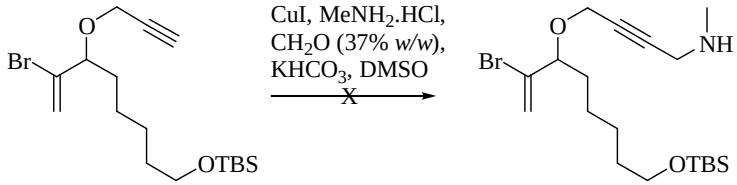
Scheme 49. Reaction of Alcohol **187** with Propargyl Bromide **212**.



212 **187** **213**

Reaction of ether **213** with methyl amine hydrochloride, potassium hydrogencarbonate, aqueous formaldehyde (37% *w/w*) and copper iodide in DMSO was attempted several times, but no desired product **214** was isolated after purification by flash column chromatography.[77] The reaction is described in **Scheme 50**.

Scheme 50. Mannich Reaction.



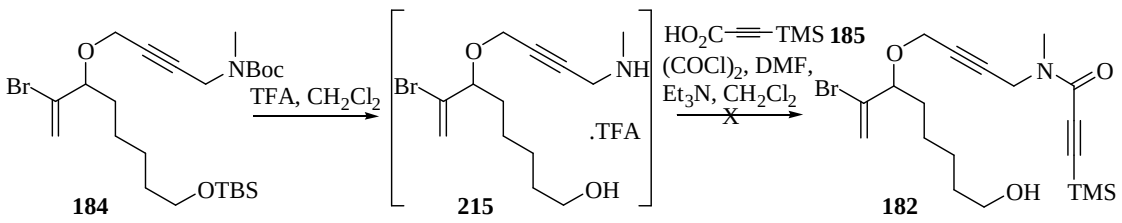
213 **214**

It should be noted that the amine moiety could have been introduced by reductive amination. However, this required four additional steps (formation of propargyl alcohol, oxidation to the aldehyde, reaction with methylamine and reduction to give the corresponding amine) and use of relatively strong conditions (strong bases such as *n*-BuLi), which could not have been employed due to the relative sensitivity of the molecule. Therefore, this route was abandoned and the previous one was scaled-up in order to supply more material for the subsequent steps.

2.2.4 FORMATION OF KEY PRECURSOR 182.

In order to achieve the synthesis of precursor **182**, the TBS and Boc groups were required to be removed. It was hoped that cleavage of both protecting groups could be achieved simultaneously by using TFA in dichloromethane. Following work carried out within the Parsons group,[54, 55] after reaction with TFA, the free amine could then have been reacted without any purification with a suitable acid chloride in the presence of triethylamine to afford the first key precursor **182**. Unfortunately, after reaction of compound **184** with TFA in dichloromethane for 18 h, followed by evaporation under reduced pressure and subsequent reaction of the crude material with triethylamine and the acid chloride of compound **185**, no desired product was obtained. The acid chloride was generated *in situ* by reaction of trimethylsilanylpropynoic acid **185**, oxalyl chloride in dichloromethane and with a drop a DMF.[54, 55] A large excess of triethylamine was added to the crude amine **215** before addition to the acid chloride thus formed. Because this reaction was unsuccessful, it was therefore decided to proceed stepwise in order to synthesise amide **182**.

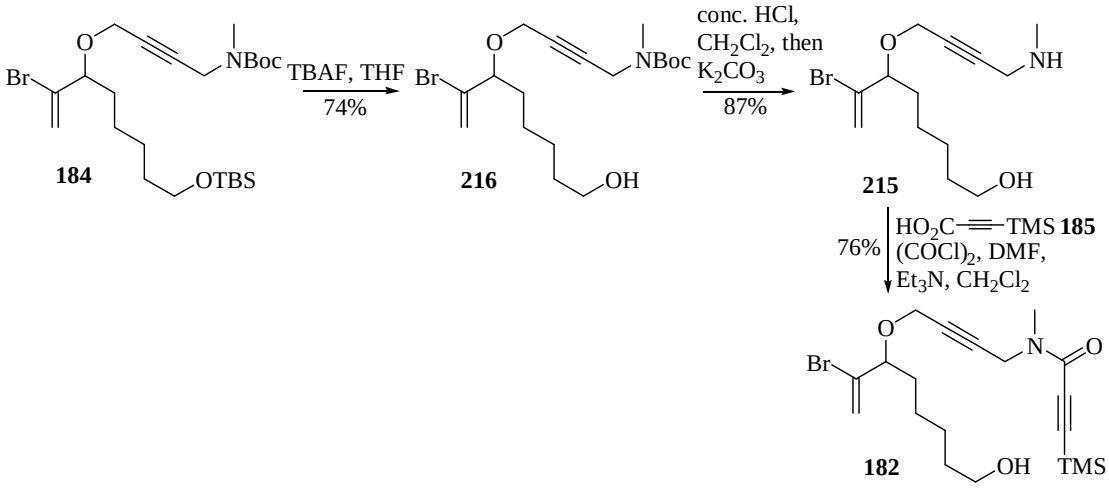
Scheme 51. TFA Deprotection Followed by Amide Formation.



184 **215** **182**

Consequently, deprotection of the silyl group was achieved with TBAF in THF and the free alcohol **216** was afforded in 74% yield. Removal of the Boc group was carried out using concentrated hydrogen chloride (5 equivalents) in dichloromethane to afford amine **215** in 87% yield, after reaction with potassium carbonate and purification by flash column chromatography. Removal of the Boc group could also be achieved using a 2 M solution of hydrochloric acid in diethyl ether and the amine **215** was obtained in similar yield. Finally, reaction with the corresponding acid chloride formed *in situ* by reaction of carboxylic acid **185** with oxalyl chloride and a catalytic amount of DMF in dichloromethane afforded the desired product **182** in 76% yield.[54, 55]

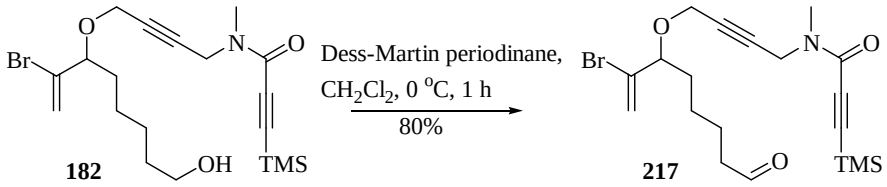
Scheme 52. Formation of Precursor **182**.



2.2.5 Formation of Final Precursor 179.

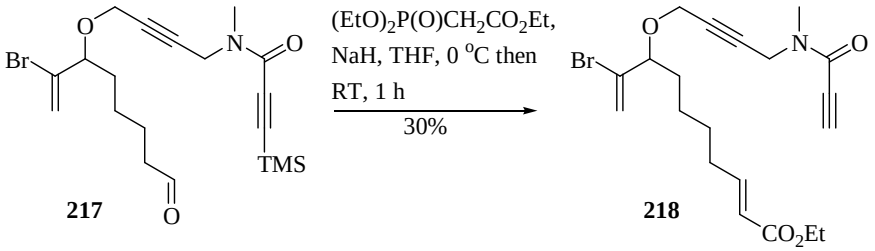
In order to synthesise the final precursor, the *α,β*-unsaturated ester group had to be built up from the free alcohol **182**. This transformation could be achieved by oxidation of the alcohol moiety to the corresponding aldehyde, followed by reaction with a phosphorus ylid using the Wittig reaction.[60] As a result, oxidation of alcohol **182** under the Parikh-Doering conditions[78] (SO_3.py, DMSO, Et_3N, CH_2Cl_2) did not afford the corresponding aldehyde **217** and only the starting material **182** was recovered. Aldehyde **217** was obtained using the Dess-Martin periodinane in dichloromethane and in 80% yield (**Scheme 53**).[79]

Scheme 53. Oxidation of Alcohol **182**.



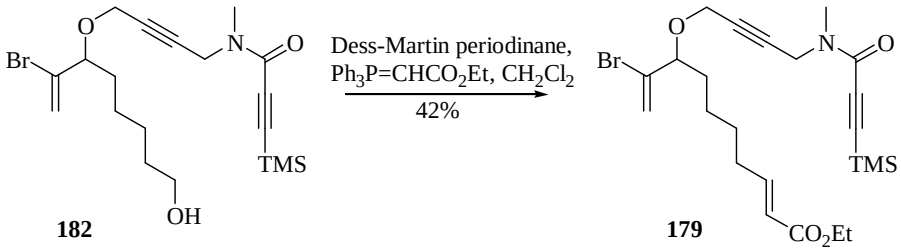
Olefination of aldehyde **217** was carried out using triethyl phosphonoacetate and sodium hydride in THF.[59, 60] However, we observed the loss of the TMS group during the reaction and compound **218** isolated in 30% yield (**Scheme 54**).

Scheme 54. Olefination and Loss of the TMS Group.



Finally, due to the lack of material, the final precursor was obtained using a one pot procedure and by reaction of alcohol **182** with the Dess-Martin periodinane and the corresponding phosphorus ylid in dichloromethane.[80] The final intermediate **179** was obtained in 42% yield.

Scheme 55. Synthesis of the Final Precursor **179**.

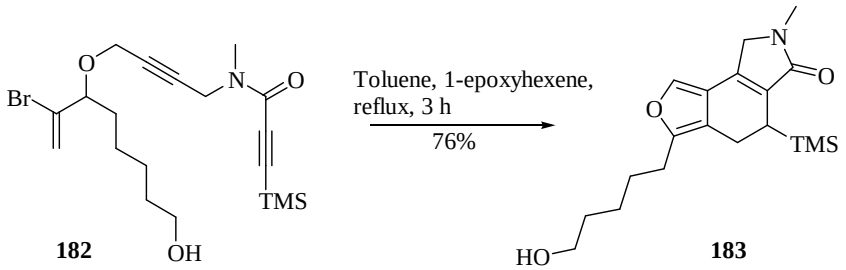


2.3 RESULTS: CYCLISATION REACTIONS.

2.3.1 PRELIMINARY RESULTS.

Having both precursors in hand, compounds **179** and **182**, we decided to investigate the cyclisation reaction using the conditions developed previous within the Parsons group.[54, 55] Thus, reaction of precursor **182** with 1-epoxyhexene (10 equivalents) at reflux in toluene for 3 h afforded the corresponding furan **183** in 53% yield on a 50 mg scale. On a larger scale (230 mg), the yield of the reaction was slightly improved and compound **183** was isolated in 76% yield.

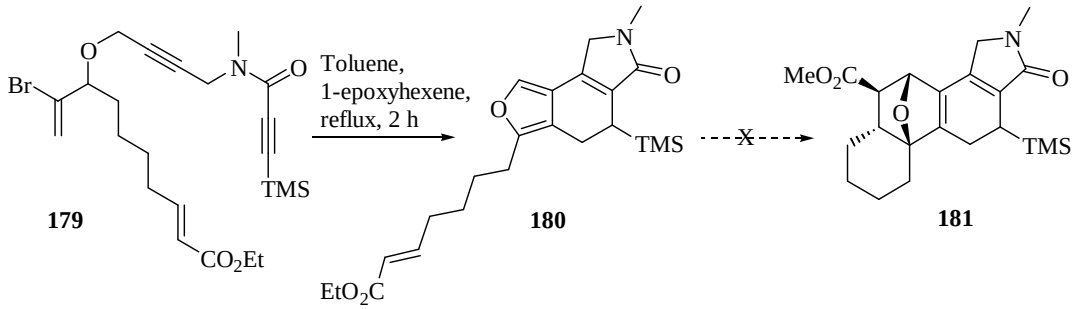
Scheme 56. Cyclisation of Compound **182**.



182 **183**

Compound **179** was reacted under similar condition on a 15 mg scale. ^{1}H NMR spectrum of the crude material showed the presence of a furan peak at 7.24 ppm and hence the formation of furan **180**. However, no Diels-Alder product **181** was observed, and due to the small scale of the reaction, no purification was carried out.

Scheme 57. Cyclisation of Target Precursor **179**.



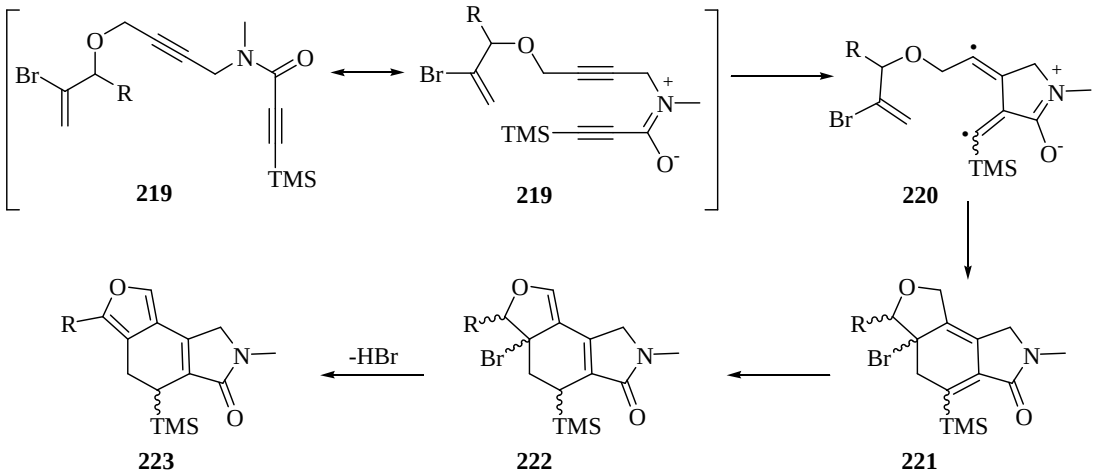
179 **180** **181**

2.3.2 DISCUSSION.

We were delighted to observe the cyclisation of both substrates **179** and **182**. As mentioned in **Section 2.1**, the reaction was carried out in the presence of a large excess of an acid trap, 1-epoxyhexene. It was postulated that because of the amide resonance (compound **219**), the two triple bonds of the substrates were closer in space and that consequently a diene biradical **220** similar to the Bergman reaction was formed (see

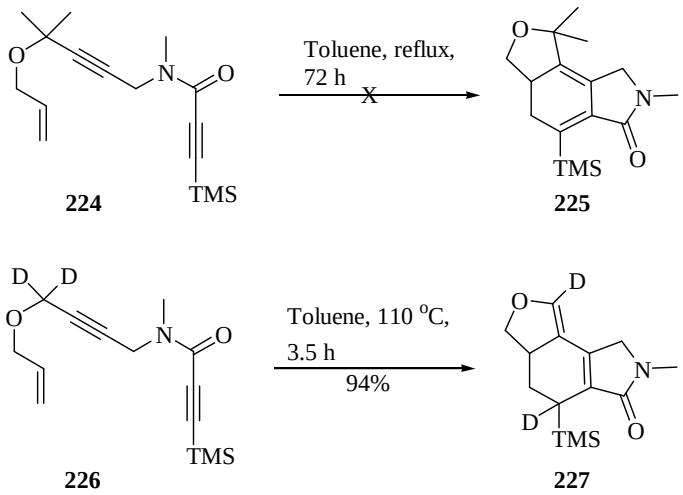
Scheme 58).[55] After addition to the remaining double bond (compound **221**), rearrangement (compound **222**) and loss of hydrogen bromide, the corresponding furan **223** was formed.

Scheme 58. Proposed Mechanism.



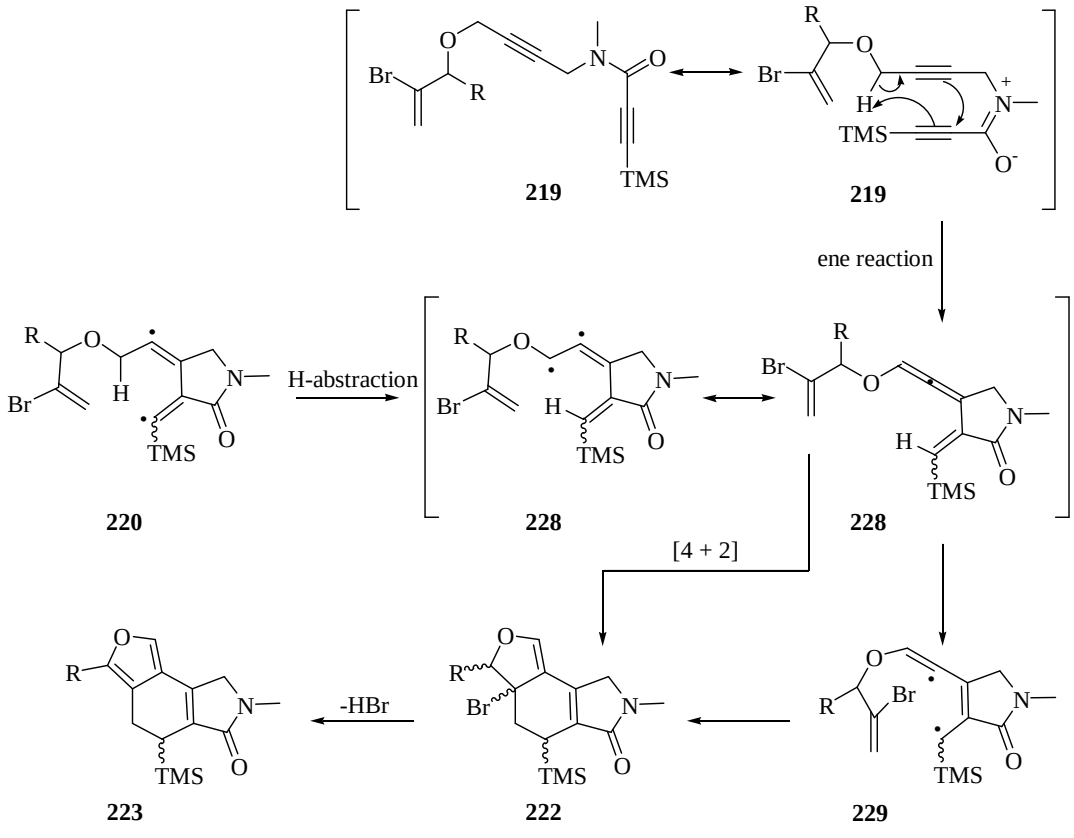
The mechanism of this reaction was refined when two experiments shown in **Scheme 59** were carried out. First, the dimethylated enediyne **224** was heated under reflux in toluene for 72 h and no reaction *i.e.* formation of tetrahydrofuran **225** was observed.[81] No by-products were isolated also and only the starting material **224** was recovered in quantitative yield. Secondly, reaction of the deuteriated species **226** in boiling toluene afforded the cyclised product **227** in 94%. NMR analysis showed loss of a proton in the α-position to the TMS group.[81]

Scheme 59. Further Mechanistic Results.



As a result, the first experiment showed that at least one hydrogen atom should be present on the carbon between the oxygen atom and the triple bond for the reaction to proceed. This result, combined with the deuteriated study, showed that a 1,5-hydrogen abstraction is a possibility and that an allene intermediate **228** was possibly generated during the reaction (**Scheme 60**).[81] This intermediate **228** could then collapse to generate a biradical species with a double bond in the lactam ring, intermediate **229**. Finally, addition of the radicals to the remaining double bond formed the tetracyclic molecule **222**, which after elimination of hydrobromic acid gave the corresponding furan ring **223**. Alternatively, the allene intermediate **228** can undergo a [4 +2] reaction to give compound **222**. In addition allene **228** could also be formed *via* an ene reaction from enediyne **219**. The proposed mechanism of this reaction is described in **Scheme 60**. Further mechanistic studies are on-going in the Parsons group in order to elucidate the reaction pathway.

Scheme 60. Proposed Mechanism.[81]

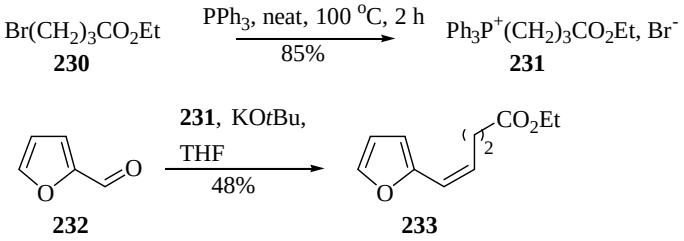


2.4 STUDIES ON THE INTRAMOLECULAR DIELS-ALDER REACTION OF FURAN DERIVATIVES.

2.4.1 Synthesis of a Furan Model.

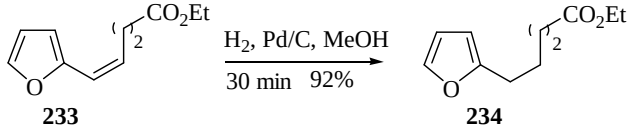
In order to further investigate the intramolecular Diels-Alder reaction of furans, we decided to synthesise a simple model system, which could allow us to test different reaction conditions. We started the synthesis of this model system with the commercially available furaldehyde **232**. Olefination of the aldehyde group was achieved using phosphonium salt **231**, potassium *tert*-butoxide in THF and compound **233** was obtained as the *cis*-isomer in 48% yield. Phosphonium salt **231**, was obtained by reaction of triphenylphosphine with ethyl 4-bromobutyrate **230**, neat at 100 ^{o}C for 2 h and in 85% yield after recrystallisation from ethanol and diethyl ether (**Scheme 61**).[82] This reaction was also carried out in benzene, however, contrary to the literature procedure, no precipitation was observed.[83]

Scheme 61. Olefination of Furaldehyde **232**.



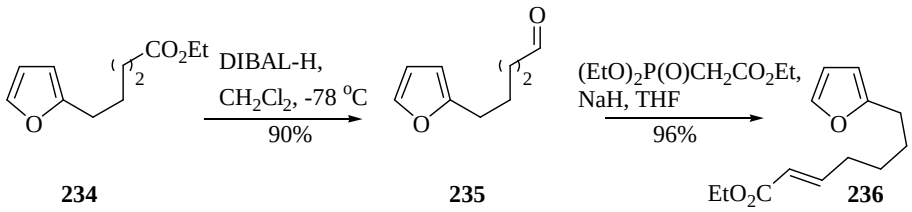
Hydrogenation of the double bond was carried out using palladium on carbon in methanol and under a balloon of hydrogen.[83] The reaction was difficult to monitor as product **234** and starting material **233** had both the same R_f by TLC. They were also both UV active and had a very similar colour when revealed with the vanillin dip (deep blue) and as result, if the reaction was left too long we observed the hydrogenation of the double bond, as well as the hydrogenation of the furan ring. However, by dipping the TLC plates in a silver nitrate solution and after activation in an oven at 110 ^{o}C for 30 minutes, the product and starting material had a slightly different R_f using these TLC plates. The monitoring of the reaction was consequently possible and compound **234** was obtained in 92% yield.

Scheme 62. Hydrogenation of Compound **233**.



Finally, the ester group was reduced to the corresponding aldehyde **235** using DIBAL-H in dichloromethane at -78 ^{o}C. Olefination was carried out using a Horner-Wadsworth-Emmons reaction using triethyl phosphonoacetate, sodium hydride in THF and the *trans*-isomer **236** was obtained in 96% yield.[59]

Scheme 63. DIBAL-H Reduction and Olefination.



234 **235** **236**

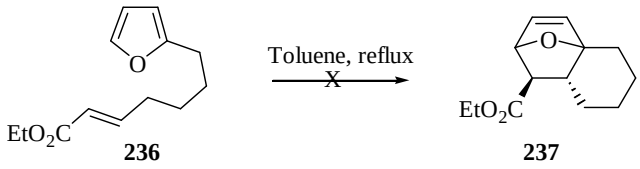
2.4.2 DIELS-ALDER REACTION OF MODEL SYSTEM 236.

Having model system **236** in hand, we decided to investigate different reaction conditions in order to test the intramolecular Diels-Alder reaction of this substrate.[84] The different methods used are described in the following sections.

2.4.2.1 Use of Additives.

Furan model **236** was firstly heated under reflux in toluene for several hours but no reaction was observed when monitored by TLC (**Scheme 64**).

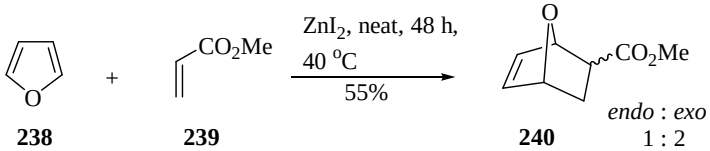
Scheme 64. Furan **236** Heated Under Reflux in Toluene.



236 **237**

Furans, due to their aromaticity, are poor dienes in Diels-Alder reactions and this could explain the lack of reaction of furan **236**. As a result, the use of additives and in particular Lewis acid was investigated in order to perform this reaction. Zinc iodide was reported by Brion to accelerate the Diels-Alder reaction of furan with electron deficient dienophiles.[85] For instance, the reaction between furan **238** and methyl acrylate **239** is described in **Scheme 65**.

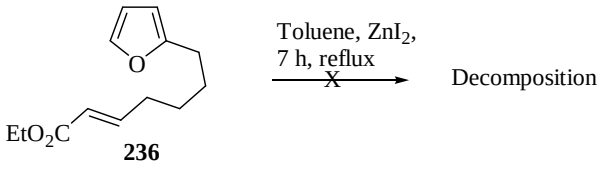
Scheme 65. Diels-Alder Reaction Catalysed by Zinc Iodide.



238 **239** **240** *endo* : *exo* 1 : 2

Because the conditions used to perform the intramolecular Diels-Alder reaction had to be compatible with the conditions developed for the first cyclisation (previous part), we decided to carry out the reaction in toluene as solvent and not in neat conditions as described in the example above. As a result, furan **236** was heated under reflux in toluene and in the presence of zinc iodide. Zinc iodide was before use dried in a vacuum oven and subjected to sublimation.[86] Unfortunately, extensive decomposition was observed by TLC analysis.

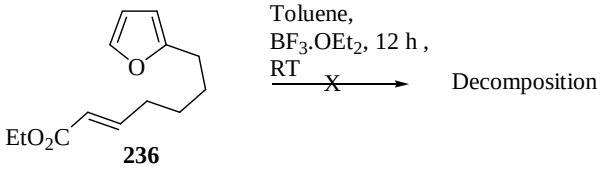
Scheme 66. Reaction of Furan **236** in Toluene and in the Presence of Zinc Iodide.



236

Similarly, reaction of furan **236** was carried out in the presence of boron trifluoride etherate in toluene at RT. Only decomposition of the starting material was observed (**Scheme 67**).[84]

Scheme 67. Reaction with Boron Trifluoride Etherate.



236

2.4.2.2 Use of Microwave Technology.

Because decomposition was observed when furan **236** was heated under reflux in toluene with zinc iodide, we then investigated the use of microwave technology. In comparison to conventional heating methods, such as for instance using a bath or heating jacket, heating using microwave irradiations offers several advantages. Conventional heating is slow and a gradient of temperature can develop within the reaction vessel. This can lead to local overheating, which plays a role in the decomposition of the products, substrates and reagents. Heating with microwave irradiation on the other hand, does not heat the wall of the reaction vessel, but only the solvent and reagents contained within the reaction flask.[87] As the result, the temperature increases quickly, is uniform within the vessel and consequently, less decomposition occurs. Microwave irradiations have been shown to speed up the reaction and this by either modifying the pre exponential factor A, which represents the

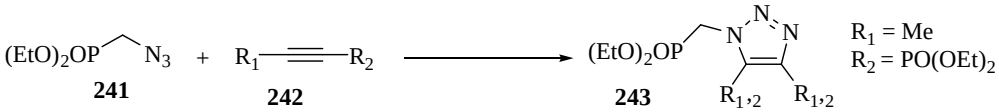
probability of molecular impact, or by affecting the free energy of activation and consequently the exponential factor in the Arrehenius law (**Eq. 1**).[88]

Equation 1. The Arrhenius Law.

$$k = A \exp\left(-\frac{\Delta G}{RT}\right)$$

Specific microwave effects can be expected when the polarity of the transition state is increased from the ground state.[88] This is for example the case of 1,3-dipolar cycloaddition. For example, azidomethyldiehtylphosphonate **241** could be reacted with acetylene **242** to give triazole **243** under solvent free conditions. The use of microwave increased significantly the yield of the reaction and the cyclo-adduct **243** was obtained in 73% yield, instead of 5% yield under conventional heating.[89]

Scheme 68. 1,3-Dipolar Cycloaddition.



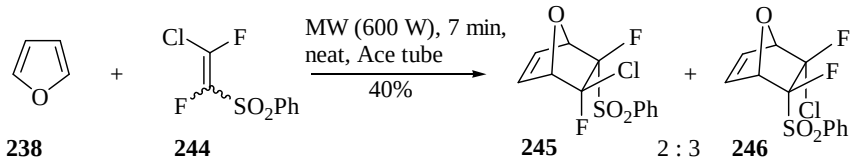
241 **242** **243**

	Time	T	Yield
Heat	20 min	90 °C	5%
Mw	20 min	90 °C	73%

However, specific microwave effects are not expected for isopolar transition state reaction.[88] This is for example the case of the Diels-Alder, Cope or ene reactions, where no partial charges are formed during the reaction path. Nevertheless, several groups have reported the microwave activation of Diels-Alder reactions using furans derivatives and this, with or without any catalysts.

For instance, Rao and co-workers reported the Diels-Alder cycloaddition of furan with 1,2-difluoro-1-chlorovinylphenylsulfone **244** under microwave irradiation.[90] The desired products were obtained as a mixture 2:3 mixture of compounds **245** and **246** and in 40% yield (**Scheme 69**). It should be noted that under conventional heating, i.e. under reflux in chlorobenzene for 3 days, no reaction was observed.

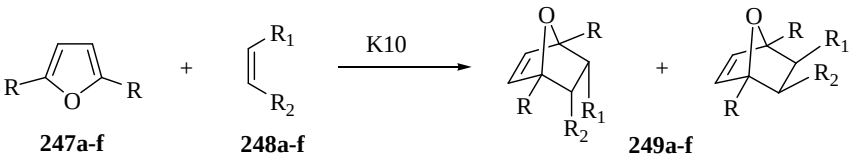
Scheme 69. Reaction of Furan **238** with Alkene **244** under Microwave Irradiation.



238 **244** **245** 2 : 3 **246**

The Diels-Alder reaction of furans with a range of alkenes, activated by microwave irradiation and in the presence of Montmorillonnite K10 clay, was also reported by the group of Cintas.[91] The results are summarised in **Table 9** and it was shown that the use of microwave to perform the reaction, reduced the time of the reaction.

Table 9. Diels-Alder Reaction Catalysed by Montmorillonite K10 Clay.

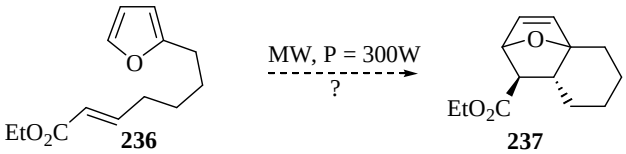


247a-f **248a-f** **249a-f**

	R	R_1	R_2	Conditions	Time	Yield	*Endo*:*Exo*
a	H	-CO-NPh-CO-		0 ^{o}C	24 h	85 %	1.3:1
b	H	-CO-NPh-CO-		MW, 150 W	15 min	90%	1.5:1
c	H	-CO-O-CO-		0 ^{o}C	3 h	36%	1:3
d	H	-CO-O-CO-		MW, 150 W	2 min	16%	1:3
e	Me	-CO-NPh-CO-		0 ^{o}C	90 min	77%	2.3:1
f	Me	-CO-NPh-CO-		MW, 300 W	10 min	100%	2.3:1

As a result, a range of reaction conditions using a CEM discovery microwave oven were tested. The power was set up to 300 W and the use of different solvents and temperatures was investigated.

Scheme 70. Reaction of Furan **236** under Microwave Irradiation.



236 **237**

The results are summarised in **Table 10**. When furan **236** was heated under reflux in dichloromethane or toluene only, no reaction was observed. When furan **236** was heated at 130 ^{o}C in toluene for 30 minutes and in the presence of zinc iodide, only the starting material and decomposed compounds from the starting material and/or products were observed.

Table 10. Reactions Carried Out Using Microwave Technology (P =300 W)

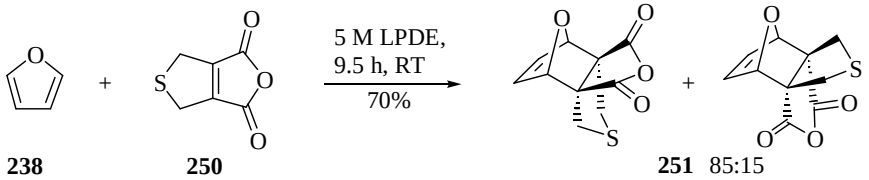
Entry	Conditions	Temperature	Time	Observations
i	CH_2Cl_2	70 ^{o}C	20 minutes	SM
ii	CH_2Cl_2	120 ^{o}C	20 minutes	SM
iii	Toluene	130 ^{o}C	30 minutes	SM
iv	Toluene, ZnI_2	130 ^{o}C	30 minutes	SM + decomposition

No improvement was observed with the use of microwave irradiation in the optimisation of the intramolecular Diels-Alder reaction for the synthesis of cyclised product **237** from furan **236**. In the case of furan derivatives, high temperatures can lead to cycloreversion of the product back to the corresponding starting materials.[92] That is why other methods, which did not involve any heating, were investigated and are described in the following two sections.

2.4.2.3 Lithium Perchlorate in Diethyl Ether.

The use of lithium perchlorate (LPDE) in diethyl ether has been reported to promote a wide range of reactions, such as for example pericyclic reactions, nucleophilic additions and substitutions and Mannich type reactions.[93] In particular, Diels-Alder reactions can be performed under very mild conditions. For example, furan **238**, when reacted with dienophile **250** in a 5 M solution of lithium perchlorate in diethyl ether at RT and under atmospheric pressure, gave a 85:15 mixture of cycloadduct **251** (see **Scheme 71**).[94] It should be noted that this reaction had been previously reported by Dauben, when reacted in dichloromethane at RT under a pressure of 15 Kbar for 6 h.[95] As described previously, a similar ratio of product **251** was obtained.

Scheme 71. Diels-Alder Reaction Performed in LPDE.



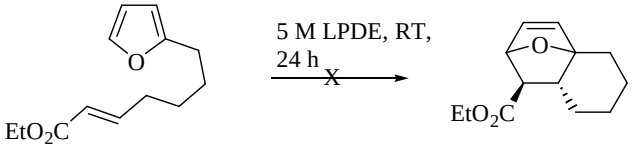
238 **250** **251** 85:15

The rate enhancement observed in many cases when use of this unusual solvent was reported by numerous groups. Its mode of action was however more difficult to explain, and led to a significant debate in the 1990's. Grico[94] and Kumar[96] attributed its properties because of an increase of the internal pressure within the solvent, although Forman,[97] Righetti[98] and Kabalka[99] explained the activation effect by the action of the lithium cation as Lewis acid.

In order to find suitable reaction conditions to perform the intramolecular Diels-Alder reaction of furan **236**, we decided to probe this methodology. As a result, precursor **236** was treated by a 5 M solution of lithium perchlorate in diethyl ether, at RT and at

ambient pressure for 24 h and the reaction was monitored by TLC. Unfortunately, no product formation was observed.

Scheme 72. Reaction of Furan **236** in LPDE.

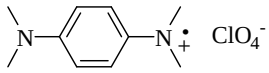


236 **237**

2.4.2.4 Radical Cation.

Finally, the use of a commercially available radical cation to perform the Diels-Alder reaction of furan **236** was investigated.[99] This is one of the first examples of stable radical cations, compound **252**, which was isolated by Wurster at the end of the nineteen's century.[100] Its structure is shown in **Figure 12**.

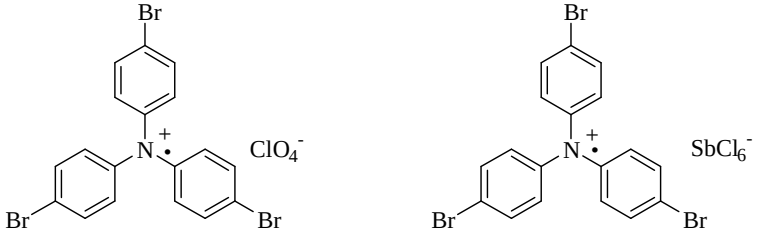
Figure 12. Wurster's Salt.



252

Over the years, a range of radical cations, triarylammonium salts, which are air stable were synthesised by Weitz and Schwechten in 1926 then by Walter in 1954 and usually as the corresponding salts.[101] Ledwith and co-workers reported the synthesis of *tris*(*p*-bromophenyl)aminium hexachloroantimonate **253** and perchlorate **254**. The use of the radical cation hexachloroantimonate **253** was reported to be thermally more stable than the corresponding perchlorate radical cation **254**. Compound **253** was in addition commercially available and was consequently chosen as initiator for the Diels-Alder reaction.

Figure 13. *tris*(*p*-Bromophenyl)Aminium Hexachloroantimonate **253** and Perchlorate **254**.

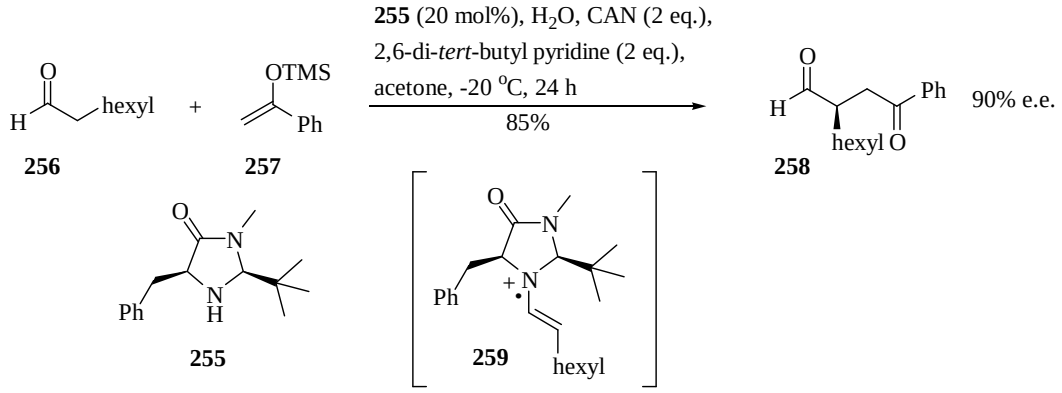


253 **254**

It should be noted that, more recently, MacMillan developed a novel strategy for enantioselective organocatalysis based on singly occupied molecular orbital activation (SOMO activation).

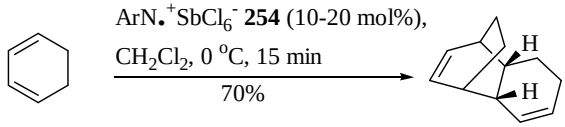
For example, the enantioselective α-enolation of aldehydes was possible. The mode of action can be described as the following. A chiral amine catalyst (for example **255**) reacts with an aldehyde (**256**) to generate the enamine catalyst, which upon one electron oxidation gives the putative radical cation catalyst **259**. The SOMO catalyst **259** can then react with a wide range of nucleophiles, such as for example enolsilane **257**. An example is described in **Scheme 73**.[102]

Scheme 73. Enantioselective *α*-Enolation of Aldehyde.



Radical cations, such as radical cation **254** shown in **Scheme 74**, have been reported to promote Diels-Alder reactions and have found applications especially when using neutral or electron rich dienophiles. The removal of one electron generates highly reactive electron deficient cation radicals, which can then react very rapidly with the dienes. For example, the Diels-Alder dimerisation of 1,3-cyclohexadiene **260** was achieved using a catalytic amount of *tris*(*p*-bromophenyl)aminium hexachloroantimonate **254** in dichloromethane at 0 °C and for 15 minutes. The product **261** was obtained in 70% and as 5:1 ratio of the *endo*:*exo* cycloadducts (see **Scheme 74**). Under thermal condition, at 200 °C for 20 h, 1,3-cyclohexadiene **260** furnished product **261** in 30% yield and as a 4:1 ratio between the *endo*:*exo* isomers.[103] Diels-Alder reactions initiated by electron transfer are fast, can be performed at temperature as low as -78 °C and have a similar preference towards the formation of the *endo*-product.[103]

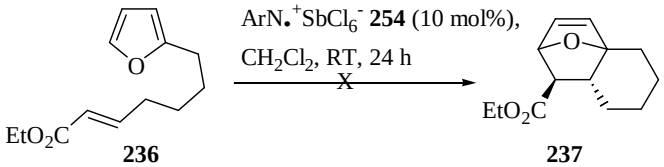
Scheme 74. Diels-Alder Dimerisation of 1,3-Cyclohexadiene **260**.



260 **261** 5:1 *endo*:*exo*

As a result, we decided to investigate the reaction of furan **236** when reacted with a catalytic amount of *tris*(*p*-bromophenyl)aminium hexachloroantimonate **254** (10 mol%) in dry dichloromethane and at RT. Before carrying out the reaction, the solvent was degassed by performing three cycles of "freeze-pump-thaw", and was kept under argon in a Schlenk tube. The reaction was also performed as a 0.01 M solution of the substrate to avoid polymerisation. Unfortunately, under these conditions, no reaction was observed after several hours and only the starting material was recovered (**Scheme 75**).

Scheme 75. Reaction of Furan **236** with Radical Cation **254**.



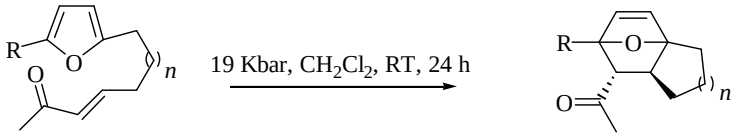
236 **237**

2.4.3 Preliminary Conclusion and Future Work.

The intramolecular Diels-Alder reaction of the furan model **236** was difficult and currently no conditions have been found to perform this reaction. Due to lack of time, no other conditions have been carried out, but a couple of other conditions could be tried. In particular, the use of other Lewis acids, such as dichloromethylaluminium could be investigated. The use of high pressure technology could also be explored.

Harwood and co-workers reported the intramolecular cyclisation of furans under a pressure of 19 Kbar.[104] The results obtained are described in **Table 11**. To avoid cycloreversion, the cycloadducts were hydrogenated using palladium and under an hydrogen atmosphere of 200 psi.[104]

Table 11. Intramolecular Diels-Alder Reaction of Furan Derivatives **262a-c** Under High Pressure.



262a-c **263a-c**

			SM : *exo* : *endo*, (%)*
n = 2	R = H	**a**	15 : 70 : 15
n = 2	R = Me	**c**	0 : 95 : 5
n = 3	R = H	**b**	50 : 30 : 20

*Ratio determined by NMR analysis immediately after depressurisation

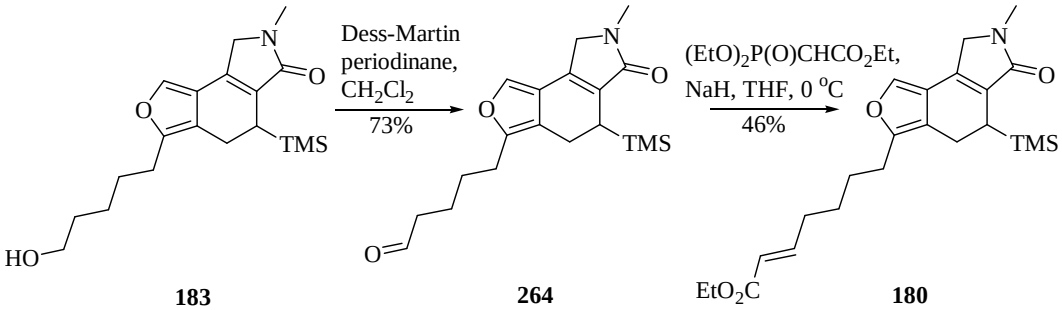
This result provides exciting evidence that this strategy could play out.

2.4.4 TESTING THE DIELS–ALDER REACTION ON THE REAL SYSTEM.

2.4.4.1 Synthesis of Precursor 180.

As seen in the previous part, the first cyclisation reaction was possible and the Diels-Alder proved to be more difficult than expected. In order to study this reaction, we decided to synthesise furan **180** and, as a result, to test independently this reaction. Consequently, oxidation of alcohol **183** was carried out using the Dess-Martin periodinane and aldehyde **264** was obtained in 73% yield.[79] Finally, reaction of aldehyde **264** with triethyl phosphonoacetate and sodium hydride in THF gave the desired compound **183** in 46% yield.[59]

Scheme 76. Synthesis of Furan **180**.



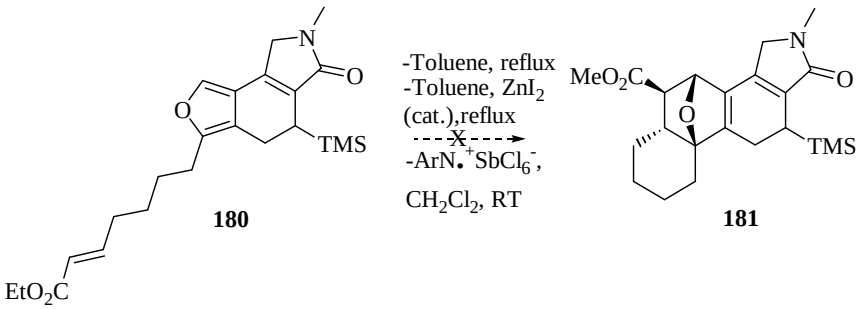
183 **264** **180**

2.4.4.2 Results.

The synthesis of furan **180** and the Diels-Alder study of the model system **236** were carried out simultaneously. As a result, similar experiments were performed with both substrates. Furan **180** was heated under reflux in toluene for several hours and with or without a Lewis acid, zinc iodide, but unfortunately, no desired product was obtained.

In addition, reaction of furan **180** with a catalytic amount of *tris*(*p*-bromophenyl)aminium hexachloroantimonate **254** (10 mol%) in dry and degassed dichloromethane at RT did not give any product either.

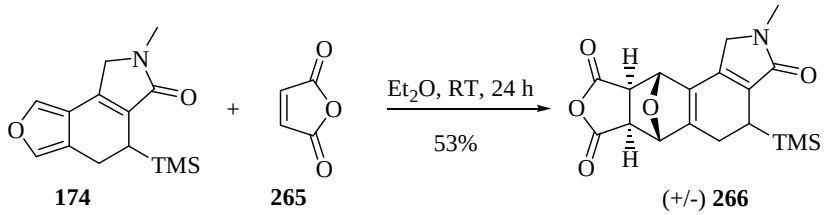
Scheme 77. Testing the Diels-Alder Reaction on Furan **180**.



2.4.4.3 Conclusion.

As expected, the intramolecular Diels-Alder reaction of the real system **180** using the reaction conditions tested on the model system **236** was also unsuccessful. It was previously shown in the Parsons group that the intermolecular Diels-Alder reaction of a similar system, compound **174** with maleic anhydride **265** was however possible, when reacted in diethyl ether at RT for 24 h. The desired cycloadduct **266** was afforded in 53% yield (**Scheme 78**).[55] However, reaction of compound **174** with 1,4-benzoquinone under a range of conditions, which varied the temperature and also under microwave irradiation failed to yield any product.[81]

Scheme 78. Intermolecular Diels-Alder Reaction of a Similar System.



Consequently, these results demonstrate the difficulty of the inter and intramolecular Diels-Alder reactions of these furan derivatives. As mentioned in **Section 2.4.3**, a range of other reaction conditions could also be tried to perform these reaction. In the case of the intramolecular reaction, the electronics of the alkene could also be modified to generate a more reactive substrate. This could be achieved by changing the current ester group to for example a more electron-withdrawing group such as ketone or Meldrum's ester.

Chapter 3 | CONCLUSION & FUTURE WORK

The development of a route for the synthesis of target molecule **179** and furan **180** has been developed and their syntheses successfully achieved. The metal free cyclisation developed within the Parsons group was successful on compound **182** and when heated under reflux in toluene in the presence of an acid trap, the corresponding furan **183** was obtained in good yield (76%). Target molecule **179** also cyclised under the reaction conditions to give the corresponding furan **180**, but no products from the subsequent Diels-Alder reaction were isolated. This result was confirmed by the synthesis of the corresponding cyclised product **180** *via* an alternative route.

The Diels-Alder reactions on model furan **236** and target precursor **180** have not been successful yet, and further work on the model system **236** will be required in order to perform this reaction.

The use of Lewis acids and especially organoaluminium based reagents could be examined. As seen in **Section 2.4.3**, high pressure chemistry could also be investigated as the reaction was successful on similar furan systems. Modification of the substrate **236** could also be studied. For instance, the ester group on the double bond could be replaced by more electron-withdrawing groups, such as ketone or Meldrum's ester. In addition, introduction of a saturation in the chain (especially with a *cis*-geometry) could give access to a more rigid molecule and consequently favour the Diels-Alder reaction.

Chapter 4 | EXPERIMENTAL

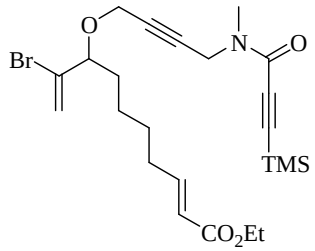
Except where specified, all reagents were purchased from commercial sources and were used without further purification. When necessary, diethyl ether and THF were distilled from sodium/benzophenone immediately before use and dichloromethane from calcium hydride. Petroleum ether refers to the fraction with boiling range 40-60 ^{o}C.

Reaction were monitored by tlc, using Merck glass backed tlc plates pre-coated with a 250 μm layer of 60 F$_{254}$ silica gel containing a fluorescent indicator and visualised with ultraviolet light at 254 nm and/or $KMnO_4$ or vanillin dips. Flash column chromatography was carried out using Merck Kiesel gel 60 silica gel, 35-70 μm, using the eluent specified.

Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

Infra-red (IR) spectra were recorded on a Perkin Elmer 1710 Fourier transform spectrometer with NaCl plates. Optical rotations were recorded using a Perkin Elmer 241 polarimeter with a 1 cm-path length cell. The solution concentrations are given in g.100mL^{-1} and optical rotations of a mixture of diastereoisomers were not recorded. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Brüker Advance AC-300 at 300 MHz and 75 MHz respectively or a Varian-500 at 500 MHz and 125 MHz respectively. Chemical shifts are quoted in ppm, using residual solvent peaks as internal standards (δ_H 7.26 for $CDCl_3$ and δ_C 77.0 for $CDCl_3$). Full proton and carbon assignment has been made when possible, however where signal identity is ambiguous no assignment is offered. Mass spectra were recorded on a Fison VG autospec mass spectrometer (low resolution EI) or on a Bruker Daltonics APEX III (ESI).

9-Bromo-8-{4-[methyl-(3-trimethylsilanyl-propynoyl)-amino]-but-2-ynyloxy}-deca-2,9-dienoic acid ethyl ester

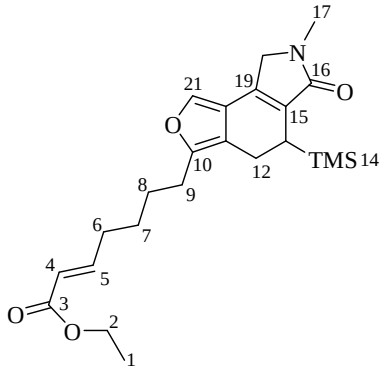


179

To a solution of alcohol **182** (50 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) under an atmosphere of nitrogen was added the Dess-Martin periodinane (59 mg, 0.14 mmol) and (carbethoxymethylene) triphenylphosphorane (49 mg, 0.14 mmol). The resulting reaction mixture was stirred for 10 h at RT, concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with methanol/: dichloromethane/ 1:30 to afford the title compound **179** as a pale yellow oil (24 mg, 42%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.96 (1H, dt, *J* 15.8, 7.5 Hz, C*H*=CHCO$_2$Et), 5.91 (1H, app. s, C*H*H'=CBr), 5.82 (1H, d, *J* 15.8 Hz, CH=C*H*CO$_2$Et), 5.70 (1H, app. s, CH*H*'=CBr), 4.45 (1H, app. s, C*H*H'N), 4.28 (1H, app. s, CH*H*'N), 4.26-3.95 (4H, m, ≡C*H*$_2$O, OC*H*$_2$CH$_3$), 3.90 (1H, t, *J* 6.6 Hz, C*H*), 3.27 and 3.02 (3H, s x 2, C*H*$_3$N), 2.29-2.13 (2H, m, C*H*$_2$), 1.69-1.32 (6H, m, C*H*$_2$ x 3), 1.30 (3H, t, J 7.1 Hz, OCH$_2$C*H*$_3$), 0.26 (9H, s, Si(C*H*$_3$)$_3$).

(7-Methyl-6-oxo-5-trimethylsilanyl-5,6,7,8-tetrahydro-4H-2-oxa-7-aza-as-indacen-3-yl)-hept-2-enoic acid ethyl ester



180

To a suspension of sodium hydride (60% in mineral oil) (10 mg, 0.26 mmol) in dry THF was added triethylphosphonacetate (59 mg, 0.26 mmol) and the mixture was stirred at 0 ^{o}C for 30 minutes. A solution of aldehyde **264** (83 mg, 0.24 mmol) in dry THF (1 mL) was added and the reaction mixture stirred for a further 1 h at RT. The reaction mixture was partitioned between ether and water. The aqueous layer was further extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with MeOH: CH_2Cl_2/ 1:30 to afford the title compound **180** as a yellow oil (49 mg, 46%).

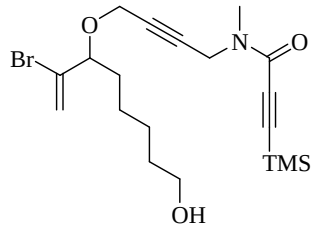
HRMS (+ESI) $[MNa]^+$ $C_{23}H_{33}NO_4NaSi$ requires 438.2071. Found 438.2100 (6.6 ppm error).

IR (neat, cm^{-1}) ν_{max} 2984, 2924, 1736 (CO), 1678, 1446, 1421, 1394, 1264, 1249, 1208, 1167, 1112, 1049, 1022, 967, 841, 778, 744.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.24 (1H, s, H-21), 6.94 (1H, dt, *J* 15.6, 7.0 Hz, H-5), 5.81 (1H, d, *J* 15.6 Hz, H-4), 4.19 (2H, q, *J* 7.2 Hz, H-2), 4.17 (1H, d, *J* 17.9 Hz, H-18), 3.96 (1H, d, *J* 17.9 Hz, H-18'), 3.08 (3H, s, H-17), 2.78-2.72 (2H, s, H-12), 2.65-2.51 (2H, m, H-9), 2.38-2.32 (1H, m, H-13), 2.22 (2H, dt, *J* 13.9, 7.2 Hz, H-6), 1.71-1.59 (2H, m, H-8), 1.56-1.46 (2H, m, H-7), 1.28 (3H, t, *J* 7.2 Hz, H-1), -0.08 (9H, s, H-14).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 165.0 (C-3), 149.7 (C-10), 148.6 (C-5), 136.2 (C-19), 134.4 (C-15), 133.6 (C-21), 121.6 (C-4), 119.6 (C-20), 115.2 (C-11), 61.2 (C-2), 51.8 (C-18), 31.8 (C-6), 29.3 (C-17), 27.6 (C-8), 27.5 (C-7), 26.0 (C-9), 22.5 (C-13), 19.8 (C-12), 14.2 (C-1), -2.3 (C-14).

3-Trimethylsilanyl-propynoic acid {4-[2-bromo-1-(5-hydroxy-pentyl)-allyloxy]-but-2-ynyl}-methyl-amide



182

To a solution of carboxylic acid **185** (81 mg, 0.57 mmol) in dry CH_2Cl_2 (1 mL) under an atmosphere of nitrogen was added oxalyl chloride (72 mg, 0.57 mmol) and one drop of DMF. The reaction mixture was stirred for 1 h at RT and then added dropwise to a solution of amine **215** (158 mg, 0.52 mmol) and Et_3N (0.30 mL, 2.08 mmol) in CH_2Cl_2 (1 mL). The resulting solution was stirred for 15 h at RT, diluted with CH_2Cl_2 (10 mL), washed with a 5% aqueous solution of hydrochloric acid (10 mL) and then with a saturated solution of potassium carbonate (2 x 10 mL). The organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with MeOH: CH_2Cl_2/ 1:20 to afford the title compound **182** as a pale yellow oil (168 mg, 76%).

HRMS (+ESI) $[MNa]^+$ $C_{19}H_{30}O_3NNaSiBr$ requires 450.1071. Found 450.1063 (1.6 ppm error).

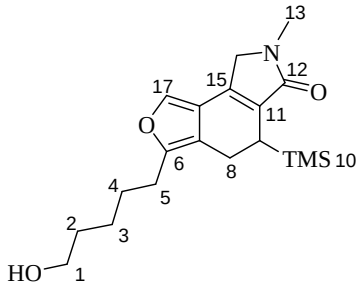
IR (neat, cm^{-1}) ν_{max} 3457 (br), 2929, 2864, 1623 (CO), 1480, 1446, 1396, 1346, 1251, 1241, 1123, 1059, 999, 844, 761, 734.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.87 (1H, d, *J* 4.2 Hz, C*H*H'=C), 5.67 (1H, d, *J* 4.2 Hz, CH*H*'=C), 4.42 (1H, s, ≡C*H*H'N), 4.25 (1H, s, ≡CH*H*'N), 4.22 (1H, dd, *J* 15.6, 10.8

Hz, OC*H*H'≡), 4.01 (1H, dd, *J* 15.6, 15.0 Hz, OCH*H*'≡), 3.91 (1H, dt, *J* 14.1, 6.6 Hz, C*H*), 3.66-3.59 (2H, m, CH_2OH), 3.24 and 2.99 (3H, s x 2, NCH_3), 1.73-1.59 (2H, m, CH_2), 1.59-1.50 (2H, m, CH_2), 1.44-1.30 (4H, m, CH_2 x 2), 0.23 (9H, s, Si(CH_3)$_3$), (O*H* was not observed).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 153.6 and 153.5 (*C*O), 134.2 and 134.1 (*C*), 119.7 and 119.6 (*C*H_2=C), 98.2 and 98.1 (*C*≡CTMS), 95.5 and 95.3 (C≡*C*TMS), 82.0 and 81.5 (*C*H), 80.5 and 80.3 (OCH$_2$C≡*C*CH$_2$N), 80.1 and 79.8 (OCH$_2$*C*≡CCH$_2$N), 62.7 and 62.6 (*C*H$_2$OH), 55.8 and 55.7 (O*C*H$_2$C≡), 40.9 and 35.6 (*C*H$_2$N), 35.5 and 31.6 (N*C*H$_3$), 33.7 and 33.6 (*C*H$_2$), 32.6 and 32.5 (*C*H$_2$), 25.5 and 25.4 (*C*H$_2$), 24.9 and 24.8 (*C*H$_2$), -0.71 and -0.72 (Si(*C*H$_3$)$_3$).

3-(4-Hydroxy-butyl)-7-methyl-5-trimethylsilanyl-4,5,5a,7,8,8a-hexahydro-2-oxa-7-aza-as-indacen-6-one



183

To a solution of **182** (232 mg, 0.55 mmol) in dry toluene was added 1,2-epoxihexene (548 mg, 5.47 mmol) and the reaction mixture heated under reflux for 2.5 h under an atmosphere of nitrogen. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with MeOH: CH_2Cl_2/ 1:30 to afford the title compound **183** as a pale yellow oil (145 mg, 76%).

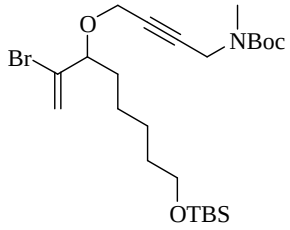
HRMS (+ESI) $[MNa]^+$ $C_{19}H_{29}O_3NNaSi$ requires 370.1809. Found 370.1823 (3.9 ppm error).

IR (neat, cm^{-1}) ν_{max} 3377, 2931, 2860, 1665, 1622, 1447, 1423, 1397, 1278, 1248, 1130, 1112, 1066, 915, 909, 840, 728, 693, 645.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.22 (1H, s, H-17), 4.17 (1H, d, *J* 18.2 Hz, H-14), 3.95 (1H, d, *J* 18.2 Hz, H-14'), 3.63 (2H, t, *J* 6.6 Hz, H-1), 3.06 (3H, s, H-13), 2.74 (2H, s, H-8), 2.62-2.51 (2H, m, H-5), 2.36-2.30 (1H, m, H-9), 1.70-1.62 (2H, m, H-4), 1.62-1.54 (2H, m, H-2), 1.44-1.54 (2H, m, H-3), -0.09 (9H, s, H-10), (O*H* not observed).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 171.2 (C-12), 150.0 (C-6), 136.4 (C-15), 134.3 (C-11), 133.6 (C-17), 119.5 (C-16), 115.0 (C-7), 62.7 (C-1), 51.8 (C-14), 32.4 (C-2), 29.3 (C-13), 27.9 (C-4), 26.2 (C-5), 25.4 (C-3), 22.4 (C-9), 19.7 (C-8), -2.3 (C-10).

(4-{2-Bromo-1-[5-(*tert*-butyl-dimethyl-silanyloxy)-pentyl]-allyloxy}-but-2-ynyl)-methyl-carbamic acid *tert*-butyl ester



184

To propargyl iodide **188** (2.0 g, 5.93 mmol) was added a solution of alcohol **187** (1.83 g, 5.93 mmol) in CH_2Cl_2 (2 mL) followed by an aqueous solution of sodium hydroxide (950 mg, 23.72 mmol in 7 mL of H_2O) and tetrabutylammonium hydrogensulfate (2.01 g, 5.93 mmol). The reaction mixture was stirred at RT for 3 days, diluted with CH_2Cl_2 (5 mL), partitioned between water and CH_2Cl_2 and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 20:1 to afford the title compound **184** as a colourless oil (910 mg, 30%).

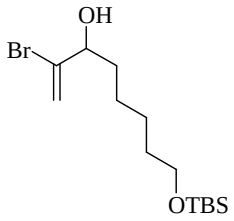
HRMS (+ESI) $[MNa]^+$ $C_{24}H_{44}NO_4NaSiBr$ requires 540.2115. Found 540.2128 (2.4 ppm error).

IR (neat, cm^{-1}) ν_{max} 2930, 2858, 1704 (CO), 1623, 1472, 1462, 1418, 1391, 1367, 1347, 1249, 1225, 1172, 1151, 1099, 1075, 1007, 875, 836, 775.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.89 (1H, s, C=C*H*H'), 5.68 (1H, s, C=CH*H'*), 4.23 (1H, d, *J* 13.3 Hz, OC*H*H'C=C), 4.08 (2H, brs, C=CCH_2N), 4.00 (1H, d, *J* 13.3 Hz, OCH*H'*C=C), 3.92 (1H, t, *J* 6.6 Hz, C*H*O), 3.59 (2H, t, *J* 6.6 Hz, CH_2OTBS), 2.90 (3H, s, NCH_3), 1.70-1.05 (8H, m, CH_2 x 4), 1.46 (9H, s, OC(CH_3)$_3$), 0.88 (9H, s, SiC(CH_3)$_3$), 0.04 (6H, s, Si(CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 134.7 (*C*), 120.2 (C=*C*H_2), 82.2 (*C*), 82.1 (*C*H), 80.5 (*C*), 79.3 (*C*), 63.5 (*C*H_2OTBS), 56.2 (=C*C*H_2O), 34.1 (*C*H_2), 33.9 (N*C*H_3), 28.8 (OC(*C*H_3)$_3$), 26.4 (SiC(*C*H_3)$_3$), 26.0 (*C*H_2), 25.4 (*C*H_2), 23.0 (*C*H_2), 18.7 (*C*Si), -4.9 (Si (*C*H_3)$_2$), (*C*O and =C*C*H_2N not observed).

2-Bromo-8-(*tert*-butyl-dimethyl-silanyloxy)-oct-1-en-3-ol



187

A solution of bromoalcohol **190** (11.61 g, 40.30 mmol) in dry diethyl ether (35 mL) was slowly added to magnesium powder using a dropping funnel over a period of 5 h and the reaction mixture was heated to maintain a gentle reflux for 5 h. The reaction mixture was heated for a further 45 minutes, the solution cooled to 0 ^{o}C and a solution of bromoacrolein **189** (7.24 g, 53.69 mmol) in diethyl ether (5 mL) slowly added *via* cannula. The resulting mixture was stirred for 30 minutes at 0 ^{o}C, warmed to RT and stirred for a further 12 h. The reaction mixture was quenched with water (20 mL) and 10% aqueous hydrochloric acid until the excess of magnesium powder disappeared. The reaction mixture was partitioned between water and ether and the aqueous layer was further extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 7:1 to afford the title compound **187** (7.67g, 60%) as a colourless oil.

HRMS (+ESI) $[MNa]^+$ $C_{14}H_{29}O_2NaSiBr$ requires 361.0998. Found 361.0994 (1.2 ppm error).

IR (neat, cm^{-1}) ν_{max} 3400, 2930, 2858, 1626, 1472, 1463, 1388, 1361, 1255, 1100, 1047, 1006, 896, 835, 814, 776.

^1H NMR (300 MHz, $CDCl_3$) δ_H 5.86 (1H, brs, C=C*H*H'), 5.55 (1H, d, *J* 1.8 Hz, C=CH*H'*), 4.08 (1H, t, *J* 6.3 Hz, C*H*OH), 3.60 (2H, t, *J* 6.3 Hz, CH_2OTBS), 1.80-1.20 (8H, m, CH_2 x 4), 0.89 (9H, s, C(CH_3)$_3$), 0.04 (6H, s, OSi(CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 137.4 (*C*), 117.4 (C=*C*H_2), 76.4 (*C*H), 63.5 (*C*H_2OTBS), 35.7 (*C*H_2), 33.1 (*C*H_2), 26.3 (C(*C*H_3)$_3$), 25.9 (*C*H_2), 25.4 (*C*H_2), 18.8 (*C*), -4.9 (Si(*C*H_3)$_3$).

(4-Iodo-but-2-ynyl)-methyl-carbamic acid *tert*-butyl ester

188

To a solution of DDQ (250 mg, 1.10 mmol) in CH_2Cl_2 (2 mL) under an atmosphere of nitrogen was added portionwise triphenylphosphine (289 mg, 1.10 mmol) followed by tetrabutylammonium iodide (406 mg, 1.10 mmol) and propargyl alcohol **196** (200 mg, 1.0 mmol). The reaction mixture was stirred for 45 minutes at RT. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 7:1 to afford the title product **188** as a colourless oil (202 mg, 60%).

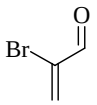
HRMS (+ESI) $[MNa]^+$ $C_{10}H_{16}NO_2NaI$ requires 332.0118. Found 332.0115 (1.0 ppm error).

IR (neat, cm^{-1}) ν_{max} 3004, 2976, 2930, 1693, 1480, 1454, 1419, 1391, 1366, 1248, 1230, 1167, 1145, 1048, 1030, 953, 874, 770, 666.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.00 (2H, s, CH_2N), 3.62 (2H, s, CH_2I), 2.83 (3H, s, CH_3N), 1.37 (9H, s, CH_3 x 3).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 81.3 (*C*), 80.6 (*C*), 33.9 (N*C*H_3), 28.8 (*C*H_3 x 3), *C*H_2 x 2 not observed.

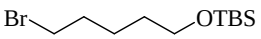
2-Bromo-propenal



189

Prepared following the literature procedure.[63] Spectroscopic data in agreement with the literature values.[63]

(5-Bromo-pentyloxy)-*tert*-butyl-dimethyl-silane



190

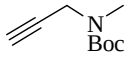
To a solution of *tert*-butyldimethylsilyl chloride (4.76 g, 31.59 mmol) and imidazole (2.15 g, 31.59 mmol) in CH_2Cl_2 (40 mL) was added a solution of bromopentanol **194** (4.79 g, 28.72 mmol) in CH_2Cl_2 (10 mL) at 0 ^{o}C under an atmosphere of nitrogen. The reaction mixture was stirred for 1.5 h at 0 ^{o}C, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 30:1 to afford the title compound **190** (6.96 g, 86%) as a colourless oil.

IR (neat, cm^{-1}) ν_{max} 3437, 2945, 2930, 2894, 2858, 1472, 1460, 1388, 1255, 1104, 835, 775, 666.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.61 (2H, t, *J* 6.0 Hz, C*H*$_2$OTBS), 3.41 (2H, t, *J* 6.6 Hz, C*H*$_2$Br), 1.92-1.82 (2H, m, BrC$_2$H$_4$C*H*$_2$C$_2$H$_4$OTBS), 1.58-1.44 (4H, m, BrCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$OTBS), 0.89 (9H, s, C*H*$_3$ x 3), 0.04 (6H, s, C*H*$_3$ x 2).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 63.2 (*C*H$_2$OTBS), 34.2 (*C*H$_2$), 33.0 (*C*H$_2$), 32.3 (*C*H$_2$), 26.4 (*C*H$_3$ x 3), 25.0 (*C*H$_2$), 18.7 (*C*), -4.9 (*C*H$_3$ x 2).

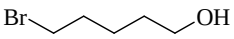
Methyl-prop-2-ynyl-carbamic acid *tert*-butyl ester



191

Prepared following the literature procedure.[55] Spectroscopic data in agreement with the literature values.[55]

5-Bromo-pentan-1-ol



194

Prepared following the literature procedure.[61] Spectroscopic data in agreement with the literature values.[61]

(4-Hydroxy-but-2-ynyl)-methyl-carbamic acid *tert*-butyl ester

196

To a cooled solution of amine **191** (4.0 g, 23.67 mmol) in dry THF (40 mL) under an atmosphere of nitrogen, was added a 2.3 M solution of *n*-BuLi in hexanes (11.32 mL, 26.04 mmol) at -78 ^{o}C. The resulting mixture was stirred at this temperature for 1 h. Paraformaldehyde (1.42 g, 47.34 mmol) was added in one portion to the reaction

mixture and stirred for a further 5 h. The reaction mixture was then allowed to warm to RT. Water (40 mL) was added and the mixture was partitioned between water and THF. The organic layer was removed and the aqueous layer was further extracted with diethyl ether (4 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated reduced pressure. The residue was purified by flash column chromatography, eluting with petroleum ether: ethyl acetate/ 2:1 to afford the title compound **196** as a colourless oil (3.69 g, 78%). Spectroscopic data in agreement with the literature values.[55]

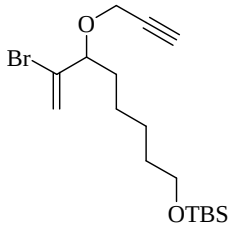
HRMS (+ESI) $[MNa]^+$ $C_{10}H_{17}O_3Na$ requires 222.1101. Found 222.1100 (0.1 ppm errror).

IR (neat, cm^{-1}) ν_{max} 3410, 2978, 2933, 2870, 1693, 1483, 1453, 1422, 1398, 1368, 1349, 1252, 1230, 1149, 1125, 1048, 1023, 955, 871, 771, 666.

^1H NMR (300 MHz, $CDCl_3$) δ_H 4.28 (2H, s, CH_2O), 4.05 (2H, s, CH_2N), 2.86 (3H, s, CH_3N), 1.47 (9H, s, CH_3 x 3).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 155.2 (*C*O), 82.0 (*C*), 81.1 (*C*), 80.2 (*C*), 50.9 (*C*H_2OH), 37.9 (*C*H_2N), 33.5 (N*C*H_3), 28.8 (*C*H_3 x 3).

(7-Bromo-6-prop-2-ynyloxy-oct-7-enyloxy)-*tert*-butyl-dimethyl-silane



213

To alcohol **187** (1.5 g, 4.45 mmol) was added propargyl bromide (80%, 0.79 mL, 8.90 mmol), tetrabutylammonium hydrogensulfate (757 mg, 2.23 mmol), a 4.5 M solution of sodium hydroxide (4 mL, 17.8 mmol) and the reaction mixture stirred for 20 h at RT. The reaction mixture was diluted with dichloromethane (20 mL) and the reaction

mixture partitioned between water and dichloromethane. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 20:1 to afford the title compound **213** as a colourless oil (645 mg, 36%).

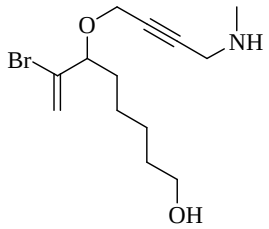
HRMS (+ESI) $[MNa]^+$ $C_{17}H_{31}O_2NaSiBr$ requires 397.1169. Found 397.1176 (1.7 ppm error).

IR (neat, cm^{-1}) ν_{max}.3310, 2930, 2897, 2858, 1623, 1472, 1463, 1444, 1388, 1361, 1256, 1099, 1006, 902, 836, 813, 776, 666, 628.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.91 (1H, s, C=C*H*H'), 5.69 (1H, s, C=CH*H'*), 4.23 (1H, d, *J* 15.9 Hz, OC*H*H'C≡CH), 4.05-5.90 (2H, m, C*H* and OCH*H'*C≡CH), 3.59 (2H, t, *J* 6.6 Hz, CH_2OTBS), 2.42 (1H, brs, C≡C*H*), 1.74-1.58 (2H, m, CH_2), 1,58-1.43 (2H, m, CH_2), 1.43-1.22 (4H, m, CH_2), 0.88 (9H, s, SiC(CH_3)$_3$), 0.04 (6H, s, Si(CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 134.5 (*C*), 120.3 (C=*C*H_2), 81.9 (*C*H), 79.7 (C≡*C*H), 75.0 (*C*), 63.5 (*C*H_2OTBS), 55.8 (O*C*H_2≡), 34.1 (*C*H_2), 33.1 (*C*H_2), 26.4 (SiC(*C*H_3)$_3$), 26.0 (*C*H_2), 25.3 (*C*H_2), 18.8 (*C*Si), -4.9 (Si(*C*H_3)$_2$).

7-Bromo-6-(4-methylamino-but-2-ynyloxy)-oct-7-en-1-ol



215

To a solution of alcohol **216** (233 mg, 0.58 mmol) in CH_2Cl_2 (3 mL) under an atmosphere of nitrogen was added concentrated hydrochloric acid (32%, 0.30 mL, 2.89 mmol) and the reaction mixture was stirred at RT for 20 h. Potassium carbonate (500

mg) was added and the reaction mixture was stirred for a further 30 minutes at RT. The mixture was filtered and concentrated reduced pressure. The residue was purified by flash column chromatography eluting with MeOH: CH_2Cl_2/ 1:10 to afford the title compound **215** as a colourless oil (152 mg, 87%).

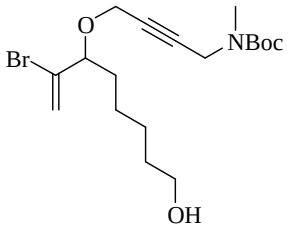
HRMS (+ESI) $[M]^+$ $C_{13}H_{22}NO_2Br$ requires 304.0907. Found 304.0906 (0.3 ppm error).

IR (neat, cm^{-1}) ν_{max} 3391, 3313, 2935, 2859, 1623, 1447, 1335, 1121, 1071, 903.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.90 (1H, s, C=C*H*H'), 5.67 (1H, s, C=CH*H'*), 4.25 (1H, d, *J* 15.6 Hz, OC*H*H'C≡), 4.00 (1H, d, *J* 15.6 Hz, OCH*H'*C≡), 3.97 (1H, t, *J* 6.6 Hz, C*H*), 3.62 (2H, t, *J* 6.2 Hz, CH_2OH), 3.46 (2H, brs, ≡CCH_2N), 2.60-2.20 (5H, m, NCH_3, O*H*, N*H*), 1.68-1.61 (2H, m, CH_2), 1.61-1.48 (2H, m, CH_2), 1.48-1.25 (4H, m, CH_2 x 2).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 134.7 (*C*), 120.1 (C=*C*H_2), 83.0 (*C*), 81.5 (*C*H), 80.1 (*C*), 63.0 (*C*H_2OH), 56.2 (O*C*H_2C≡), 56.2 (≡C*C*H_2N), 35.3 (N*C*H_3), 34.0 (*C*H_2), 33.0 (*C*H_2), 25.7 (*C*H_2), 25.1 (*C*H_2).

{4-[2-Bromo-1-(5-hydroxy-pentyl)-allyloxy]-but-2-ynyl}-methyl-carbamic acid *tert*-butyl ester



216

To a solution of **184** (303 mg, 0.58 mmol) in dry THF (1 mL) was added tetrabutylammonium fluoride trihydrate (202 mg, 0.64 mmol) in one portion. The reaction was stirred at RT for 20 h, diluted with diethyl ether (10 mL) and water (10 mL), partitioned between water and diethyl ether and the aqueous layer was further extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed

with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 1:1 to afford the title compound **216** as a colourless oil (174 mg, 74%).

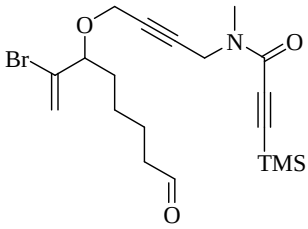
HRMS (+ESI) $[MNa]^+$ $C_{18}H_{30}NO_4NaBr$ requires 426.1250. Found 426.1253 (0.6 ppm error).

IR (neat, cm^{-1}) ν_{max} 3461, 2977, 2934, 2861, 1739, 1695, 1623, 1481, 1455, 1420, 1392, 1368, 1348, 1248, 1173, 1152, 1124, 1075, 1049, 903, 873, 771.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.88 (1H, s, C=C*H*H'), 5.66 (1H, d, *J* 1.2 Hz, C=CH*H'*), 4.23 (1H, d, *J* 15.6 Hz, OC*H*H'≡), 4.06 (2H, brs, ≡CH_2N), 4.00 (1H, d, *J* 15.6 Hz, OCH*H'*≡), 3.97-3.91 (1H, m, C*H*), 3.62 (2H, t, *J* 6.5 Hz, CH_2OH), 2.89 (3H, s, NCH_3), 1.86 (1H, brs, OH), 1.70-1.20 (8H, m, CH_2 x 4), 1.44 (9H, s, C(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 155.7 (*C*O), 134.6 (*C*), 120.1 (C=*C*H_2), 82.4 (*C*), 81.6 (*C*H), 80.6 (*C*), 79.3 (*C*), 63.1 (*C*H_2OH), 56.2 (O*C*H_2C≡), 38.4 (≡C*C*H_2N), 34.0 (*C*H_2), 33.0 (*C*H_2), 29.4 (OC(*C*H_3)$_3$), 25.2 (*C*H_2), 23.0 (*C*H_2), (N*C*H_3 was not observed).

3-Trimethylsilanyl-propynoic acid {4-[2-bromo-1-(5-oxo-pentyl)-allyloxy]-but-2-ynyl}-methyl-amide



217

To a solution of alcohol **182** (50 mg, 0.12 mmol) in dry dichloromethane (1 mL) was added the Dess-Martin periodinane (56 mg, 0.13 mmol) and the mixture was stirred at 0 ^oC for 1h. Saturated solutions of sodium thiosulfate (0.25 mL) and potassium carbonate (0.25 mL) were added and the mixture was then partitioned between ether and water. The aqueous layer was further extracted with diethyl ether (3 x 5 mL) and the combined

organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with MeOH: CH_2Cl_2/ 1:50 to afford the title compound **217** as a yellow oil (40 mg, 80%).

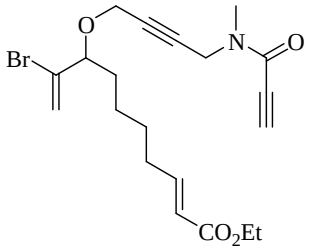
HRMS (+ESI) $[MNa]^+$ $C_{19}H_{28}O_3NNaSiBr$ requires 450.0900. Found 450.0907 (1.5 ppm error).

IR (neat, cm^{-1}) ν_{max} 2924, 2847, 1722 (CHO), 1633 (CO), 1478, 1439, 1395, 1344, 1251, 1233, 1122, 1073, 844, 761, 732.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.77 (1H, m, C*H*O), 5.90 (1H, brs, C*H*H'=C), 5.69 (1H, dd, *J* 4.9, 1.7 Hz, CH*H*'=), 4.44 (1H, app. s, ≡C*H*H'N), 4.27 (1H, app. s, ≡CH*H*'N), 4.23 (1H, ddt, *J* 13.0, 11.2, 1.9 Hz, OC*H*H'≡), 4.02 (1H, tt, *J* 15.7, 1.9 Hz, OCH*H*'≡), 3.92 (1H, dt, *J* 9.5, 6.6 Hz, C*H*), 3.26 and 3.01 (3H, s x 2, NCH_3), 2.45 (2H, t, *J* 7.0 Hz, CH_2), 1.73-1.63 (4H, m, CH_2 x 2), 1.49-1.35 (2H, m, CH_2), 0.25 (9H, s, Si(CH_3)$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 202.3 and 202.2 (*C*HO), 153.5 and 153.4 (*C*O), 133.9 and 133.8 (*C*), 119.8 and 119.7 (*C*H_2=C), 98.1 (*C*≡CTMS), 95.6 and 95.3 (C≡*C*TMS), 81.9 and 81.5 (*C*H), 80.4 (OCH_2C≡*C*CH_2N), 80.2 and 79.6 (OCH_2*C*≡CCH_2N), 55.8 and 55.7 (O*C*H_2≡), 43.7 (*C*H_2CHO), 40.9 and 35.6 (*C*H_2N), 35.5 and 31.6 (N*C*H_3), 33.5 and 33.4 (*C*H_2), 24.7 and 24.6 (*C*H_2), 21.7 and 21.6 (*C*H_2), -0.70 and -0.72 (Si(*C*H_3)$_3$).

9-Bromo-8-[4-(methyl-propynoyl-amino)-but-2-ynyloxy]-deca-2,9-dienoic acid ethyl ester



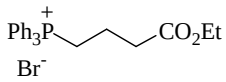
218

To a suspension of sodium hydride (60% in mineral oil, 4 mg, 0.096 mmol) in dry THF (0.2 mL) under an atmosphere of nitrogen was added at 0 ^oC triethylphosphonoacetate

(22 mg, 0.096 mmol) and the reaction mixture was stirred for 10 minutes at this temperature. A solution of aldehyde **217** (34 mg, 0.080 mmol) in dry THF (1 mL) was added and the reaction mixture stirred at 15 ^{o}C for a further 1 h. The reaction mixture was diluted with water (3 mL), partitioned between water and dichloromethane and the aqueous layer was further extracted with dichloromethane (3 x 3 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with methanol: dichloromethane/ 1:30 to afford the title compound **218** as a pale yellow oil (10 mg, 30%).

HRMS (+ESI) $[MNa]^+$ $C_{20}H_{26}NO_4NaBr$ requires 446.0937. Found 446.0961 (5.3 ppm error).

(4-Carbethoxybutyl)triphenylphosphonium bromide



231

Ethyl 4-bromobutyrate (16 mL, 111.80 mmol) was added to triphenylphosphine (25.5 g, 97.22 mmol) and the mixture was heated neat at 100 ^{o}C for 3 h. The title compound **231** was recrystallised from ethanol: diethyl ether and isolated as a white solid (37.96 g, 85%). Spectroscopic data in agreement with the literature values.[82]

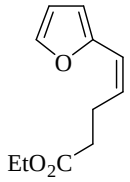
HRMS (+ESI) $[M]^+$ $C_{24}H_{26}O_2PBr$ requires 377.1670. Found 377.1661 (0.3 ppm error).

IR (neat, cm^{-1}) ν_{max} 3707, 3697, 3681, 3663, 2974, 2945, 2865, 2844, 1719 (C=O), 1438, 1371, 1320, 1213, 1200, 1140, 1112, 1054, 1033, 1216, 744, 723, 690.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.87 (2H x 3, dd, *J* 12.6, 7.8 Hz, *o*-Ar-*H* x 3), 7.77 (1H x 3, dd, *J* 7.8, 6.7 Hz, *p*-Ar-*H* x 3), 7.68 (2H x 3, ddd, *J* 7.8, 7.8, 3.2 Hz, *m*-Ar-*H* x 3), 4.08 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.07-4.01 (2H, m, $Ph_3P^+CH_2$), 2.87 (2H, t, *J* 6.5 Hz, CH_2CO_2Et), 1.94-1.87 (2H, m, $P^+CH_2CH_2CH_2CO_2Et$), 1.21 (3H, t, *J* 7.2 Hz, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 171.3 (*C*O), 134.9 (J_{CP} 3.0 Hz, Ar*C*), 133.7 (J_{CP} 10.0 Hz, Ar*C*), 130.4 (J_{CP} 12.0 Hz, Ar*C*), 118.3 (J_{CP} 85.5 Hz, *C*), 60.6 (O*C*H_2CH$_3$), 33.2 (J_{CP} 18.1 Hz, *C*H_2), 21.8 (J_{CP} 50.9 Hz, P*C*H_2), 18.1 (J_{CP} 2.8 Hz, *C*H_2), 14.1 (OCH$_2$*C*H$_3$).

5-Furan-2-yl-pent-4-enoic acid ethyl ester



233

To a suspension of the phosphonium salt **231** (30.0 g, 65.64 mmol) in dry THF (200 mL), was added in one portion potassium *tert*-butoxide (8.47 g, 75.49 mmol) at 0 ^oC and the reaction mixture stirred for 2 h at this temperature. Furaldehyde was added and the reaction mixture stirred at RT for a further 14 h. The reaction mixture was partitioned between water (100 mL) and diethyl ether. The aqueous solution was further extracted with diethyl ether (3 x 150 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting white solid was washed with petroleum ether (40 mL) and the extract was evaporated to give to yellow oil, which was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 50:1 to afford the title compound **233** as a pale yellow oil (5.49 g, 48%). Spectroscopic data in agreement with the literature values.[83]

HRMS (+ESI) $[MNa]^+$ $C_{11}H_{14}O_3Na$ requires 217.0841. Found 217.0837 (1.4 ppm error).

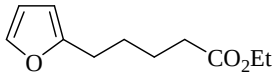
IR (neat, cm^{-1}) ν_{max} 2982, 1730 (C=O), 1372, 1350, 1254, 1215, 1175, 1151, 1054, 1013, 923, 808, 730.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.37 (1H, brs, OC*H*), 6.37 (1H, m, OCH=C*H*CH=C), 6.26 (1H, d, *J* 3.1 Hz, OCH=CHC*H*=C), 6.20 (1H, d, *J* 11.8 Hz, CC*H*=CHCH$_2$), 5.51 (1H, dt, *J* 11.8, 7.4 Hz, CCH=C*H*CH$_2$), 4.13 (2H, q, *J* 7.3 Hz, OC*H*$_2$CH$_3$), 2.78 (2H, dt,

J 7.4, 7.2 Hz, CH=CHC*H*$_2$), 2.47 (2H, t, *J* 7.2 Hz, C*H*$_2$CO$_2$Et), 1.24 (3H, t, *J* 7.3 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR (CDCl$_3$, 125 MHz) δ_C 173.0 (*C*O), 152.9 (*C*), 141.5 (OC*H*=CH), 128.2 (CCH=*C*HCH$_2$), 118.3 (C*C*H=CHCH$_2$), 111.0 (OCH=*C*H), 109.4 (OCH=CH*C*H=C), 60.3 (O*C*H$_2$CH$_3$), 34.1 (*C*H$_2$CO$_2$Et), 24.7 (CH=CH*C*H$_2$), 14.2 (OCH$_2$*C*H$_3$).

5-Furan-2-yl-pentanoic acid ethyl ester



234

As per standard method of hydrogenation, 5-furan-2-yl-pent-4-enoic acid ethyl ester **233** (2 g, 10.3 mmol) was treated with 5% palladium on carbon (200 mg) in methanol under a balloon of hydrogen for 30 minutes at RT. The solution was filtered through Celite® and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with dichloromethane: hexanes/ 1:1 then 100% dichloromethane to afford the title compound **234** as a colourless oil (1.86 g, 92%). Spectroscopic data in agreement with the literature values.[83]

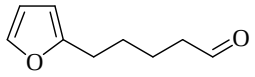
HRMS (+ESI) [MNa]$^+$ $C_{11}H_{16}O_3Na$ requires 219.0997. Found 219.0994 (1.4 ppm error).

IR (neat, cm^{-1}) ν_{max} 3681, 2974, 2938, 2366, 2844, 1732 (C=O), 1461, 1456, 1373, 1241, 1177, 1148, 1055, 1033, 1007, 727.

^{1}H NMR (CDCl$_3$, 500 MHz) δ_H 7.28 (1H, brs, OC*H*=CH), 6.26 (1H, m, C*H*), 5.98 (1H, m, C*H*), 4.12 (2H, dq, *J* 7.2, 2.2 Hz, OC*H*$_2$CH$_3$), 2.71-2.60 (2H, m, CC*H*$_2$), 2.35-2.28 (2H, m, C*H*$_2$CO$_2$Et), 1.75-1.62 (4H, m, CCH$_2$C*H*$_2$C*H*$_2$CH$_2$CO$_2$Et), 1.25 (3H, dt, *J* 7.2, 2.2 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 173.4 (*C*O), 155.8 (*C*), 140.7 (O*C*H=CH), 110.0 (OCH=*C*H), 104.8 (OCH=CH*C*H=C), 60.2 (O*C*$H_2$$CH_3$), 34.0 (*C*$H_2$$CO_2$Et), 27.6 (*C*$H_2$), 27.5 (*C*$H_2$), 27.4 (*C*$H_2$), 14.2 (O$CH_2$*C*$H_3$).

5-Furan-2-yl-pentanal



235

To a solution of 5-furan-2-yl-pentanoic acid ethyl ester **234** (1.86 g, 9.49 mmol) in CH_2Cl_2 (20 mL) was added a 1 M solution of di*iso*butyl aluminium hydride in dichloromethane (9.49 mL, 9.49 mmol) over a 30 minutes period at -78 ^oC. A saturated solution of potassium sodium tartrate (20 mL) was added and the reaction mixture stirred for 3 days at RT. The solution was then partitioned between water and dichloromethane and the aqueous layer was further extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 20:1 to afford the title compound **235** as a pale yellow oil (1.29 g, 90%).

HRMS (+ESI): -

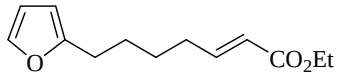
LRMS (EI) [M+] calc. $C_9H_{12}O_2$. Found 152, 53 (30%), 81 (100), 95 (32).

IR (neat, cm^{-1}) ν_{max} 2937, 1721 (CHO), 1596, 1507, 1391, 1146, 1007, 923, 801, 729.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 9.76 (1H, t, *J* 1.5 Hz, C*H*O), 7.29 (1H, m, OC*H*=CH), 6.27 (1H, m, OCH=C*H*), 5.98 (OCH=CHC*H*C), 2.69-2.61 (2H, m, CCH_2), 2.49-2.41 (2H, m, CH_2CHO), 1.72-1.66 (4H, m, $CCH_2C$$H_2$$CH_2$$CH_2$CHO).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 202.2 (*C*O), 155.5 (*C*), 140.8 (O*C*H), 110.0 (OCH=*C*H), 105.0 (OCH=CH*C*HC), 43.5 (*C*H_2CHO), 27.6 (C*C*H_2), 27.5 (CCH_2*C*H_2), 21.5 ($C(CH_2)_2$*C*$H_2$$CH_2$CHO).

7-Furan-2-yl-hept-2-enoic acid ethyl ester



236

To a suspension of sodium hydride (60% in mineral oil, 305 mg, 7.63 mmol) in dry THF (10 mL) was added triethyl phosphonoacetate (1.71 g, 7.63 mmol) at 0 ^{o}C and the resulting solution was stirred for 1 h at this temperature. A solution of 5-furan-2-yl-pentanal **235** (1.06 g, 6.94 mmol) was added to the resulting mixture, stirred for a further 15 minutes at 0 ^{o}C. The mixture was partitioned between water and diethyl ether and the aqueous layer was further extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether: ethyl acetate/ 20:1 to afford the title compound **236** as a pale yellow oil (1.28 g, 96%).

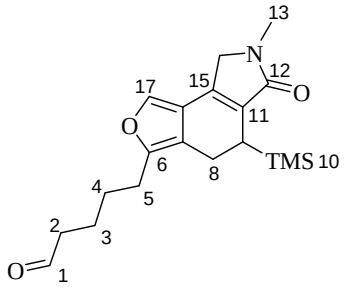
HRMS (+ESI) $[MNa]^+$ $C_{13}H_{18}O_3Na$ requires 245.1148. Found 245.1148 (0 ppm error).

IR (neat, cm^{-1}) ν_{max} 2936, 1717 (CO), 1654, 1367, 1307, 1265, 1179, 1147, 1139, 1096, 980, 727.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.29 (1H, m, OC*H*=CH), 6.95 (1H, dt, *J* 15.6, 7.0 Hz, C*H*=CHCO$_2$Et), 6.27 (1H, m, OCH=C*H*), 5.97 (1H, m, OCH=CHC*H*C), 5.81 (1H, dt, *J* 15.6, 1.4 Hz, CH=C*H*CO$_2$Et), 4.18 (2H, t, *J* 7.1 Hz, OC*H*$_2$CH$_3$), 2.63 (2H, t, *J* 7.4 Hz, CC*H*$_2$), 2.22 (2H, m, C*H*$_2$CH=CHCO$_2$Et), 1.68 (2H, m, CC*H*$_2$CH$_2$), 1.52 (2H, m, C*H*$_2$CH$_2$CH=CH, 1.29 (3H, t, *J* 7.1 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 166.6 (*C*O), 155.8 (*C*), 148.8 (*C*H=CHCO$_2$Et), 140.8 (O*C*H), 121.5 (CH=*C*HCO$_2$Et), 110.0 (OCH=*C*H), 104.8 (OCH=CH*C*HC), 60.1 (O*C*H$_2$CH$_3$), 31.8 (*C*H$_2$CO$_2$Et), 27.7 (C*C*H$_2$), 27.5 (CCH$_2$*C*H$_2$), 27.4 (C(CH$_2$)$_2$*C*H$_2$CH$_2$CHO), 14.2 (OCH$_2$*C*H$_3$).

5-(7-Methyl-6-oxo-5-trimethylsilanyl-5,6,7,8-tetrahydro-4H-2-oxa-7-aza-as-indacen-3-yl)-pentanal



264

To a solution of alcohol **183** (127 mg, 0.37 mmol) in dry dichloromethane (2 mL) was added the Dess-Martin periodinane (170 mg, 0.40 mmol) and the mixture was stirred at 0 ^{o}C for 1 h. Saturated solutions of sodium thiosulfate (1 mL) and potassium carbonate (1 mL) were added and the mixture was then partitioned between ether and water. The aqueous layer was further extracted with diethyl ether (3 x 5 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with MeOH: CH_2Cl_2/ 1:30 to afford the title compound **264** as a yellow oil (93 mg, 73%).

HRMS (+ESI) $[MMeOHNa]^+$ $C_{20}H_{31}NO_4NaSi$ requires 400.1915. Found 400.1935 (5.0 ppm error).

IR (neat, cm^{-1}) ν_{max} 2947, 1722 (CHO), 1668, 1622, 1447, 1419, 1395, 1279, 1248, 1128, 1111, 1067, 909, 840, 726, 695, 645.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.72 (1H, app. s, H-1), 7.22 (1H, s, H-17), 4.16 (1H, d, *J* 18.2 Hz, H-14), 3.94 (1H, d, *J* 18.2 Hz, H-14'), 3.04 (3H, s, H-13), 2.71 (2H, s, H-8), 2.65-2.49 (2H, m, H-5), 2.48-2.38 (2H, m, H-2), 2.35-2.29 (1H, m, H-9), 1.71-1.57 (4H, m, H-3 and H-4), -0.12 (9H, s, H-10).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 202.0 (C-1), 171.1 (C-12), 149.4 (C-6), 136.2 (C-15), 134.4 (C-11), 133.7 (C-17), 119.5 (C-16), 115.2 (C-7), 51.8 (C-14), 43.5 (C-2), 29.3 (C-13), 27.6 (C-4), 26.0 (C-5), 22.4 (C-9), 21.6 (C-3), 19.7 (C-8), -2.3 (C-10).

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