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Chemoenzymatic Routes to Enantiopure Hydroxytetrahydrofurans: Muscarine and its Analogues



Denis Beecher. B.Sc.

A Thesis Presented for the Degree of

Doctor of Philosophy

to

The National University of Ireland

Department of Chemistry

University College Cork

Supervisors: Dr. D. G. McCarthy and Prof. A. R. Maguire

Head of Department: Prof. Martyn Pemble

October 2015

Declaration

This thesis is my own work and has not been submitted for another degree, at either University College Cork or elsewhere.

Denis Beecher

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The Technical Staff of the Department of Chemistry UUC deserve a special mention. Thanks in particular to Derry for the glassblowing, German translations and of course for being Derry. Terry for keeping an eye on me supervising first years and keeping me entertained, Pat for his help, and chatting about Cork heritage, Chrissie for glassware and gossip provision, Johnny for electrical maintenance (who was recruited many times), Noel for chemicals, Lorraine for the NMR service, expertise and always willing go the extra mile, John Caffrey for the chats in the hallway, Mick for his Mass Spec. help and worldly advice.

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Finally, and most importantly, a special thank-you to my other half, Deirdre. Without her encouragement, none of this would have been possible.

Abstract

Muscarine was identified as an active principle of the poisonous mushroom *Amanita muscaria* over 170 years ago and has been identified as an agonist of acetylcholine. The synthesis of all stereoisomers of muscarine have been accomplished at this stage by chemical methods and the biological activity of these compounds tested. A number of synthetic routes to enantiomerically pure muscarine and its analogues have been published. In this work, we are focussed on the use of a novel biotransformation strategy to access these compounds. Asymmetric synthesis involves targeting a synthetic pathway leading to one enantiomer of a compound and biocatalysis is one strategy used in asymmetric synthesis.

Chapter 1 consists of a review of the relevant literature pertaining to the synthesis and stereoselective transformations of 3-hydroxytetrahydrofurans. A review of synthetic routes to these compounds is presented, with a particular focus on routes to the natural product muscarine and its analogues.

Chapter 2 discusses the preparative routes to the 3-hydroxytetrahydrofurans *via* 3(2*H*)-furanones. Steps amongst which include Rh(II) mediate cyclisation and kinetic resolution *via* baker's yeast mediated carbonyl reduction, resulting in enantioenriched 3-hydroxytetrahydrofuran derivatives. Finally, application of this methodology to the preparation of all four enantiomers of an analogue of desmethylnuscarine and the synthesis of epimuscarine is described.

Chapter 3 consists of a detailed experimental section outlining the synthetic procedures employed

Abbreviations

ABq	AB quartet
Ac	Acetyl
aq.	Aqueous
Ar	Aryl
AIBN	2,2'-Azo-bis-(isobutyronitrile)
Bn	Benzyl
br. s	Broad singlet
br. t	Broad triplet
CDCl ₃	Deuterated chloroform
COSY	Correlated spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N</i> -Dicyclohexylcarbodiimide
DCM	Dichloromethane
dd	Doublet of doublets
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless enhancement by polarisation transfer
DIAD	Di- <i>isopropyl</i> azodicarboxylate
DIBAL-H	Di- <i>isobutyl</i> aluminium hydride
DMF	Dimethylformamide
DMAP	<i>N,N</i> -Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
dq	Doublet of quartets
d.r.	Diastereoisomeric ratio
dt	doublet of triplets
e.e.	Enantiomeric excess
EDG	Electron-donating group
equiv. or eq.	Equivalents
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron withdrawing group
g	Gram
GC	Gas chromatography

h	Hour
HETCOR	Heteronuclear chemical shift correlation
HRMS	High resolution mass spectroscopy
Hz	Hertz
IR	Infrared
KH	Potassium hydride
LDA	Lithium di-isopropylamide
Lit.	Literature
m	Multiplet
m-CPBA	3-Chloroperoxybenzoic acid
MeOH	Methanol
mg	Milligram
MHz	Megahertz
ml	Millilitre
mmol	Millimole
mol	Mole
μw	Microwave
NEt ₃	Triethylamine
NOE	Nuclear Overhauser effect
Oxone	Potassium peroxymonosulfate, potassium hydrogensulfate, potassium sulfate complex (2KHSO ₅ .KHSO ₄ .K ₂ SO ₄)
p	pentet
PMB	<i>para</i> -methoxybenzyl
PTSA	<i>p</i> -Toluene sulfonic acid
q	Quartet
r.t.	Room temperature
s	Singlet
t	Triplet
t-Bu	<i>t</i> -Butyl
sat.	Saturated
TBAF	Tetra- <i>n</i> -butyl ammonium fluoride
TBDMS or TBS	<i>t</i> -Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TES	Triethylsilyl

Tf	Triflate (trifluoromethylsulfonyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMS	Tetramethylsilane or Trimethylsilyl
Ts	Tosyl (<i>p</i> -toluenesulfonyl)

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1 Introduction

1.1 General Introduction

3(2*H*)-Furanones are ketonic dihydrofurans with the general structure shown in **Figure 1.1.1(b)**. The term “2*H*” refers to the site of hydrogenation in the parent heterocycle, furan, while the “3” refers to the position of the carbonyl group. The 4,5-dihydro derivatives of these compounds are saturated at the 4- and 5-positions. 3-Hydroxytetrahydrofurans have a hydroxyl substituent at the 3-position, in place of the carbonyl group.

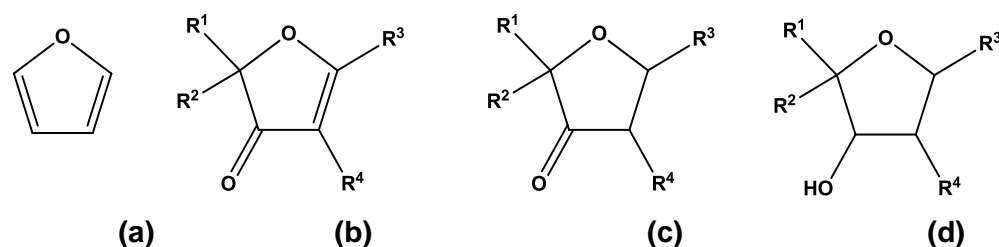


Figure 1.1.1

(a) Structure of furan.

(b) General structure of a 3(2*H*)-furanone.

(c) General structure of 4,5-dihydro-3(2*H*)-furanone.

(d) General structure of a 3-hydroxytetrahydrofuran.

3(2*H*)-Furanones, their 4,5-dihydro derivatives and 3-hydroxytetrahydrofurans have all attracted a substantial amount of interest due to their presence as structural units in a number of compounds. These compounds include natural products, such as bullatenone **1**, geiparvarin **2** and ascofuranone **3**. Furanones possess widespread cytotoxic and antitumour activity as well as other pharmacological properties. The food and beverage industry also use furanone additives, such as Furaneol® **4**, because of its flavouring properties.¹

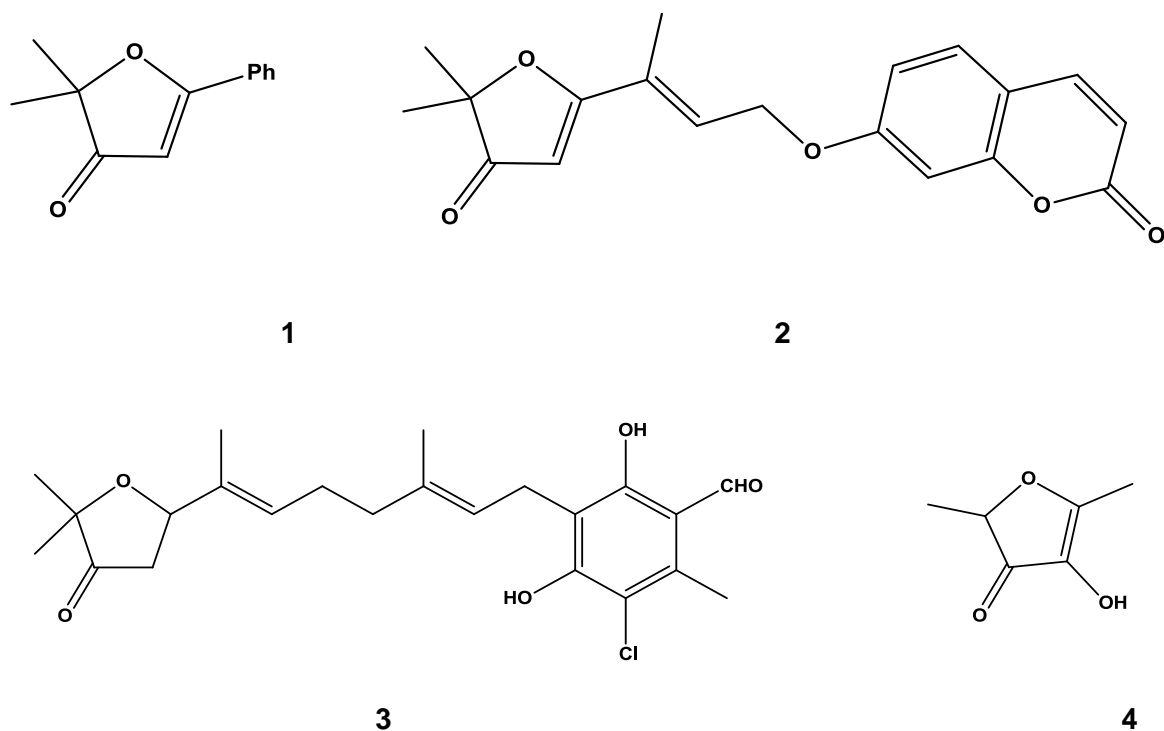


Figure 1.1.2 **(1)** Bullatenone.
(2) Geiparvarin.
(3) Ascofuranone.
(4) Furaneol®.

Interest arose in this class of compounds when bullatenone **1** was isolated in 1954 from the blistered leave myrtle *lophomyrtuis bullata*.² Raphael and Parker³ correctly identified its structure by I.R. analysis which was then confirmed with the first synthesis of the compound in 1958.

Ascofuranone **3**, a dihydrofuranone, is a hypolipidemic antibiotic, which lowers serum lipid levels. Ascofuranone was first isolated from the fungus *Ascochyta viciae* by Sasaki and co-workers⁴ who also elucidated its structure in 1972.

(+)-Eremantholide A **5** was first isolated from the stem of the Brazilian plant *Eremanthus elaeagnus* in 1975 by Le Quense and co-workers.⁵ Its molecular structure was determined by spectroscopic methods including x-ray analysis which elucidated the absolute stereochemistry. Studies have shown that the compound has *in vitro* activity against carcinoma of the nasopharynx in humans, targeting the cell membrane. Takoa and co workers⁶ published a stereoselective synthesis of (+)-eremantholide A from the starting

material D-glucose. They achieved this synthesis using an intramolecular vinylogous aldol reaction to form the nine-membered ring **Figure 1.1.3**.

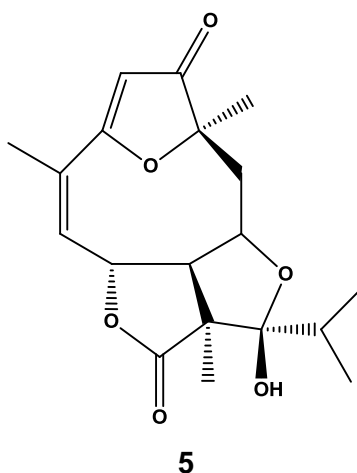


Figure 1.1.3

Steel⁷ reported the first total synthesis of (±)-longianone **6** from tetronic acid. The compound was isolated from a fungal strain *Xylaria longiana* which is found in various temperate climates around the world. (±)-Longianone possesses a 1,7-dioxaspiro[4,4]non-2-ene-4,8-dione skeleton.

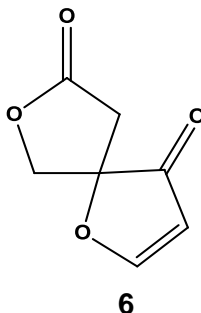
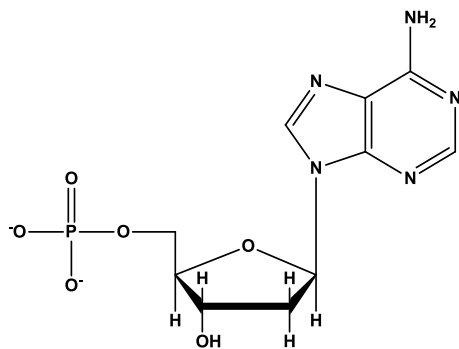


Figure 1.1.4

3-Hydroxytetrahydrofurans, the reduced form of 3(2*H*)-furanones, are widely found in nature. Each DNA nucleoside contains a 3-hydroxytetrahydrofuran moiety at its core. The 2-deoxyribose sugar has a hydroxytetrahydrofuran moiety, which in turn is bound to a base - guanine, adenine, thymine or cytosine and two phosphate functional groups, e.g. adenosine mono phosphate **7**. Many anticancer and antiviral agents such as anti HIV drugs involve the use of analogues based on a ribose or 3-hydroxytetrahydrofuran pharmacophore.^{8,9}



7

Figure 1.1.5

Anticancer drugs such as floxuridine **8**, developed by Roche Pharmaceuticals, marketed by Mayne Pharma, is used in the treatment of colorectal cancer. Its mechanism of action and pharmacokinetics are very similar to that of fluorouracil, as floxuridine is the deoxyribonucleotide of fluorouracil. Floxuridine is a fluorinated pyrimidine antagonist which inhibits DNA and RNA synthesis along with the methylation of deoxyuridylic acid to thymidylic acid.¹⁰

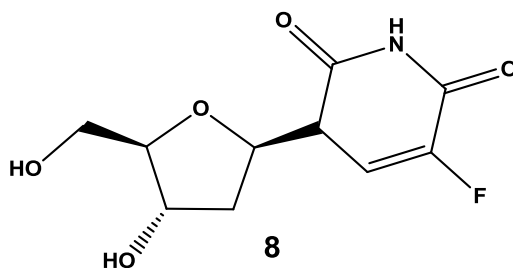
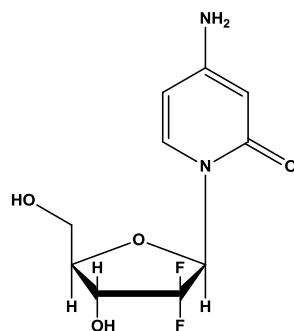


Figure 1.1.6

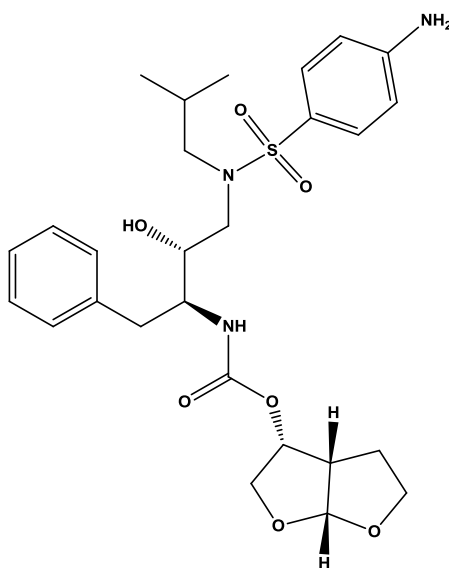
Gemcitabine **9**, commonly known as Gemzar® is a nucleoside analogue and an antimetabolite in the replication of DNA. The drug is marketed by Eli Lilly. The prodrug, Gemcitabine, is converted to the active form by phosphorylation in the body to produce an analogue of cytidine. The active drug inhibits ribonucleotide reductase, which is involved in the production of deoxyribonucleotides for DNA replication and repair. Cell apoptosis is then induced as a result of this "faulty" nucleoside.¹¹



9

Figure 1.1.7

Darunavir **10**, more commonly known as Prezista[®], developed by Tibotecis, is a drug used in treatment against the HIV virus and belongs to the protease inhibitor class. The compound is a second-generation protease inhibitor. It was designed to surpass the obstacles associated with earlier drugs such as Indinavir, which had severe side effects and drug toxicities. The drug was designed to form robust interactions with the protease enzyme from many HIV strains taken from patients with multiple resistance mutations to protease interactions.¹²

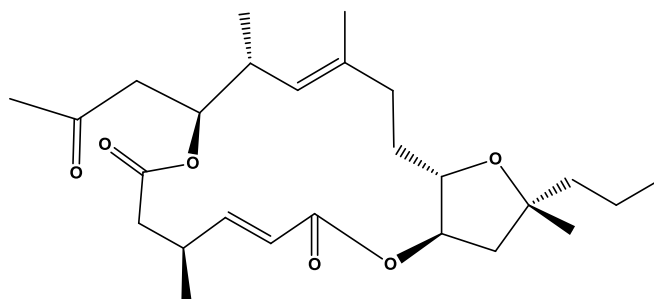


10

Figure 1.1.8

Amphidinolide X **11**, a natural product, was first synthesised by Fürster and co-workers.¹³ They are cytotoxic compounds found in the marine dinoflagellates *Amphidinium*

sp., which lives in a symbiotic relationship with the Okinawan flatworm *Amphiscolops* sp. The marine species produces a number of metabolites, amongst which are the amphidinolide class of compounds, which are highly active against various forms of cancer.¹⁴



11

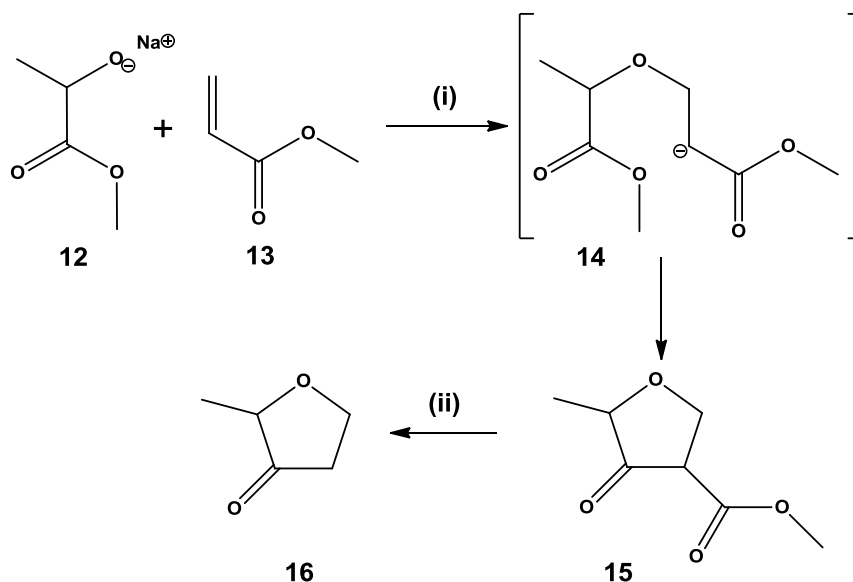
Figure 1.1.9

1.2 Synthesis of 4,5-Dihydro-3(2*H*)-furanones

Various methods have been utilised in the synthesis of 4,5-dihydro-3(2*H*)-furanones, such as cyclisation of diols,¹⁵⁻¹⁷ Nazarov-type cyclisations,¹⁸ radical mediated reactions,^{19,20} intramolecular Michael-Dieckmann condensations^{21,22} and transition metal catalysed O-H insertion reactions.²³ One of the most direct and elegant approaches detailed by Guinturco and co-workers²¹ will be explored in this section along with the O-H insertion which has been adapted in our work.

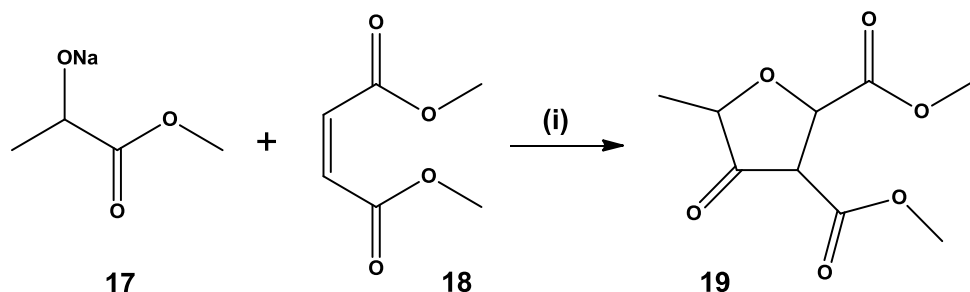
1.2.1 Intramolecular Michael-Dieckmann Condensation

This is a versatile method used to create 4,5-dihydro-3(2*H*)-furanones. It is based upon the Michael addition, in which an anion derived from an α -hydroxyester is reacted with α,β -unsaturated substrates. Following the Michael addition, the ring is closed affording the Dieckmann cyclised product. This approach was utilised by Guinturco and co-workers,²¹ where deprotonated methyl lactate **12**, underwent a Michael type addition with methyl acrylate **13**. This afforded an intermediate **14**, which spontaneously underwent a Dieckmann condensation to give **15**. Hydrolysis was achieved under acidic conditions followed by decarboxylation to yield 2-methyl-4,5-dihydro-3(2*H*)-furanone **16**.



Scheme 1.2.1 Reagents: (i) Et₂O, 0°C, (ii) H₂SO₄, heat.

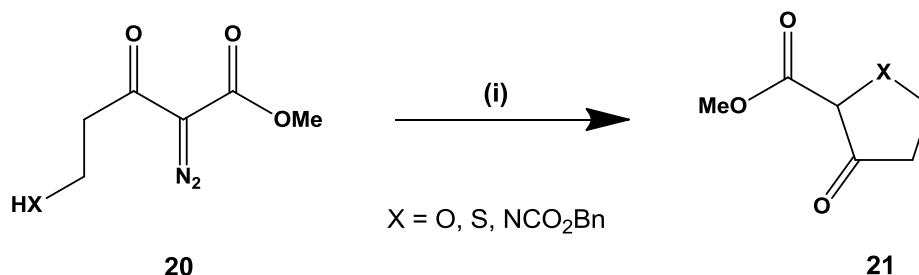
The Michael-Dieckmann cyclisation was also used by De Amici and co-workers²² in the synthesis of muscarine. The sodium salt of methyl lactate **17** was reacted with dimethyl malate **18** and following cyclisation, 3(2*H*)-furanone **19** was isolated.



Scheme 1.2.2 Reagents: (i) THF, heat.

1.2.2 Transition Metal Catalysed O-H Insertion Reactions

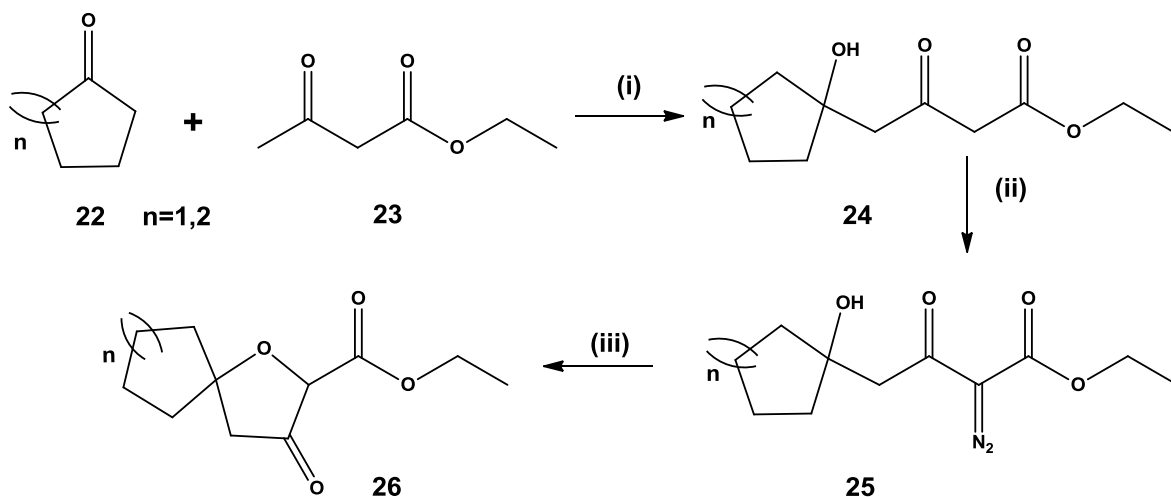
The use of transition metal complexes as catalysts for diazo decompositions have received considerable attention in recent years. Copper,²⁴ cobalt,²⁵ ruthenium²⁶ and palladium²⁷ complexes have all been reported as catalysts in diazo decompositions. Dirhodium catalysts have also been used effectively for these types of reactions.^{28,29} First prepared and characterised in the 1960's,³⁰ Dirhodium acetate [Rh₂(OAc)₄], has become one of the most widely used catalysts for diazo decompositions. In 1985, Rapoport²³ reported a successful O-H insertion reaction in the synthesis of 3(2*H*)-furanone **21** from α -diazo- β -ketoester **20**, in quantitative yields using Rh₂(OAc)₄. The corresponding sulphur and nitrogen heterocycles were also satisfactorily prepared by the same method.



Scheme 1.2.3 Reagents: (i) Rh₂(OAc)₄, PhH, Reflux, 20 min.

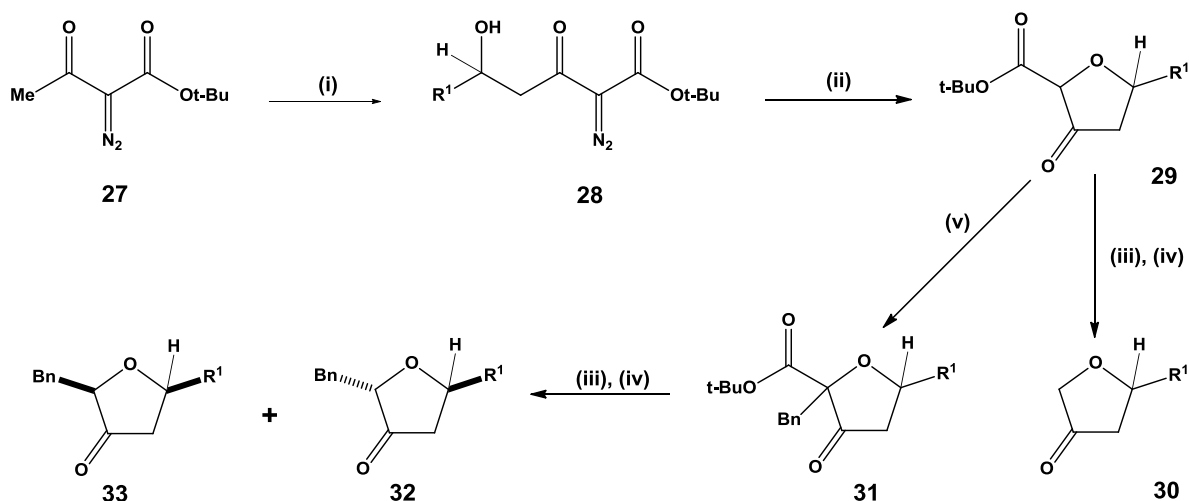
Jones and co-workers³¹ used Rh₂(OAc)₄ mediated diazo decomposition in the synthesis of oxaspirodecane **26**, a natural product subunit. The initial α -diazo- β -ketoester

was prepared by treatment of the dianion of ethyl acetoacetate, (generated *via* double deprotonation of ethyl acetoacetate **23** with two molar equivalents of LDA) with cyclopentanone or cyclohexanone **22** ($n=2$) to yield the aldol addition product **24**. This was then treated with tosyl azide to give the α -diazo- β -ketoester **25** followed by treatment with $\text{Rh}_2(\text{OAc})_4$ to give the 3(2*H*)-furanone **26**.



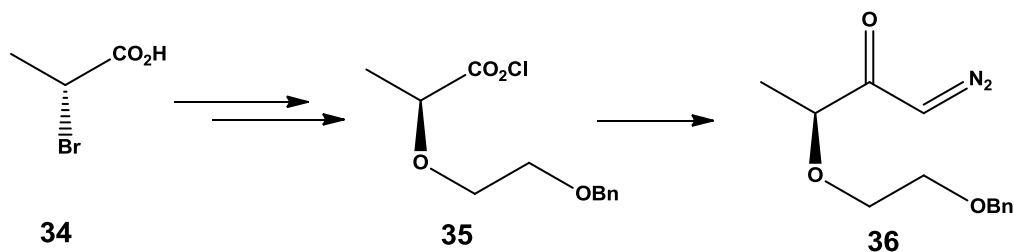
Scheme 1.2.4 Reagents: (i) 2 eq. LDA, -78°C , THF, (ii) TsN_3 , K_2CO_3 , MeCN, (iii) $\text{Rh}_2(\text{OAc})_4$, PhMe.

Utilizing the rhodium catalyzed carbene formation and O-H insertion, Calter and co-workers³² synthesised molecules which contained this 3(2*H*)-furanone core. The intermediates in this work were structurally similar to those synthesised by Jones and co-workers,³¹ however the approach to these compounds was different. In Calter and co-workers synthesis, a reaction sequence involving an aldol addition of an α -diazo- β -ketoester with appropriate aromatic or aliphatic aldehydes was used to synthesise a large number of 3(2*H*)-furanones. Upon synthesis of the aldol addition product **28**, the furanone **29** was generated by Rh(II)-catalysed O-H insertion using 1 mol % $\text{Rh}_2(\text{OAc})_4$ in refluxing benzene. Cleavage of the *t*-butyl ester with trifluoroacetic acid followed by decarboxylation in refluxing acetonitrile yielded the 3(2*H*)-furanone **30**. The treatment of 2-*tert*-butylester-3(2*H*)-furanone **29** with benzyl bromide and potassium carbonate afforded the 2,2,5-trisubstituted 3(2*H*)-furanone **31**. This was treated with trifluoroacetic acid mediating decarboxylation, which yielded the disubstituted 3(2*H*)-furanones **32** and **33** (Scheme 1.2.5).

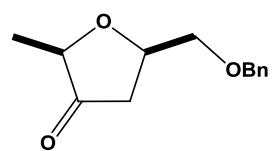


Scheme 1.2.5 Reagents: (i) Aldehyde, PhBCl_2 , NEt_3 , CH_2Cl_2 , (ii) $\text{Rh}_2(\text{OAc})_4$, PhH / CH_2Cl_2 , (iii) TFA, (iv), CH_3CN , reflux, (v) BnBr , K_2CO_3 , CH_3CN .

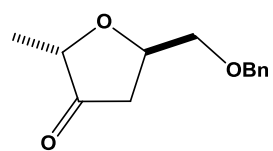
In a paper by Adams and co-workers,³³ a synthesis of 3(2*H*)-furanones *via* rhodium catalyzed C-H insertion from ethers was explored. The authors report the synthesis of muscarine from (*R*)-2-bromopropionic acid. Displacement of the bromide with the sodium salt of 2-benzyloxyethanol and subsequent treatment with oxalyl chloride afforded the acid chloride 35. Diazoketone formation was effected by standard methodology with diazomethane (**Scheme 1.2.6**). The authors proposed intermediates for the observed diastereoselectivity in this reaction. **Figure 1.2.1** shows the *cis*-isomer is 37 in favored in terms of steric requirements in the transition state. The ether oxygen, α - to the carbonyl group in 39, determines the preferred conformation of the process by co-ordinating with the rhodium metal. This places the C-2 α -hydrogen in either a pseudo-axial 39(a) or pseudo-equatorial 39(b) position. The steric repulsion is expected to be greater for 39(b) (due to the bulkier methyl group interacting with the methylene group next to the ether), which leads to the minor (*trans*-) isomer 38. The more favoured conformation proceeds *via* 39(a) leads to major diastereoisomer 37.



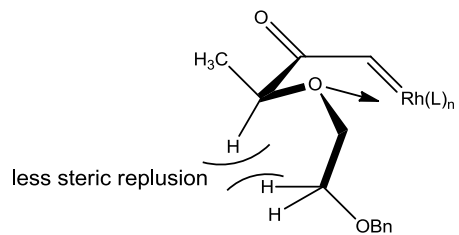
Scheme 1.2.6



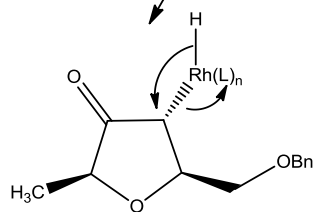
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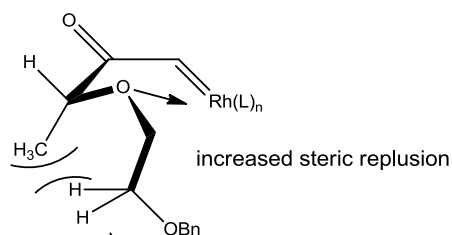
38



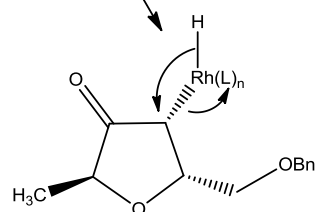
39 (a) favoured



Cis



39 (b) disfavoured



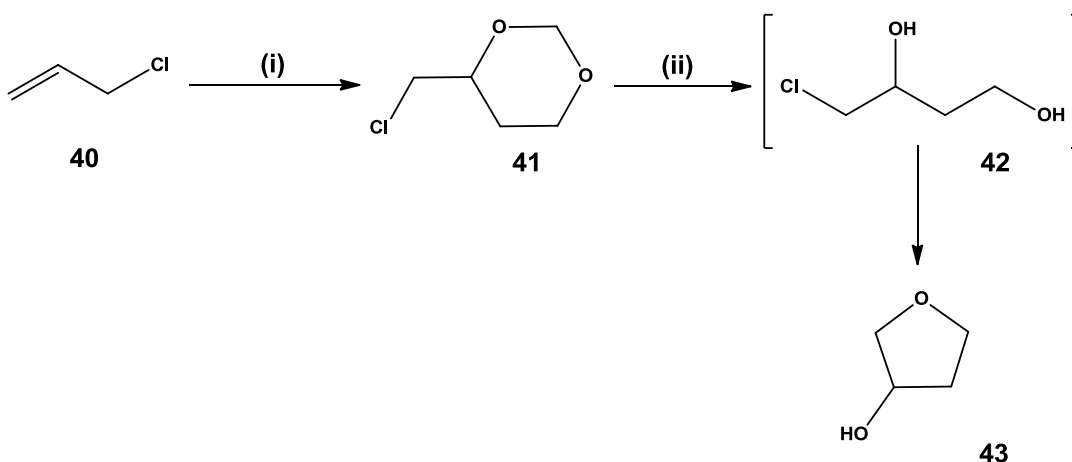
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Figure 1.2.1

1.3 3-Hydroxytetrahydrofurans

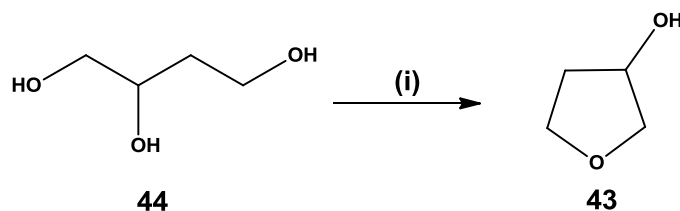
1.3.1 Synthesis of 3-Hydroxytetrahydrofurans

One of the first syntheses of 3-hydroxytetrahydrofurans published in literature was by Price and co-workers³⁴ in 1950. The authors treated allyl chloride **40** with formaldehyde in the presence of concentrated sulphuric acid, affording 4-chloromethyl-1,3-dioxane **41** in moderate yields. The authors attempts to replace the chlorine atom with cyanide or iodide resulted in the recovery of starting material. The authors then subjected 4-chloromethyl-1,3-dioxane **41** to hydrolysis with 2M HCl in the presence of 2,4-dinitrophenylhydrazine to produce chloroglycol **42**, which spontaneously cyclised to produce 3-hydroxytetrahydrofuran **43** (Scheme 1.3.1).



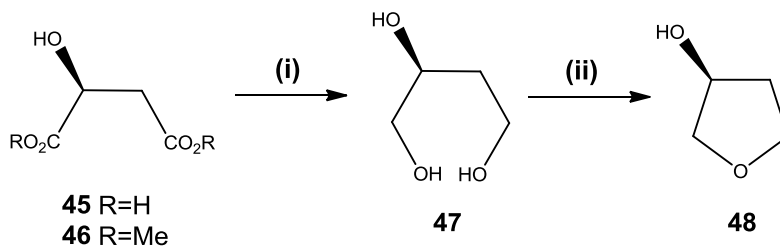
Scheme 1.3.1 Reagents: (i) H₂SO₄, paraformaldehyde, (ii) 2M HCl, 2,4-dinitrophenylhydrazine.

A second synthesis was published in 1958 in which Wynberg and co-workers³⁵ synthesised 3-hydroxytetrahydrofuran **43** by heating 1,2,4-trihydroxybutane **44** to 180 - 220 °C in the presence of *p*-toluenesulfonic acid. The authors isolated the product in 88% yield (Scheme 1.3.2).



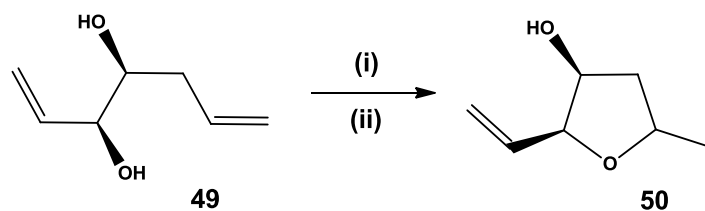
Scheme 1.3.2 Reagents: (i) *p*TsOH.

In 1983, Wynberg and co-workers³⁶ were the first group to synthesise enantiopure (*S*)-(+)-3-hydroxytetrahydrofuran **48** from malic or tartaric acid. Depending on the enantiomer of 3-hydroxytetrahydrofuran which was needed, (*S*-) or (*R*-) malic acid or tartaric acid was used as starting material. To produce the (*S*)-(+)-3-hydroxytetrahydrofuran **48**, the authors used (*S*)-(-)-dimethylmalate **46** with an e.e. of 94%. To synthesise (*R*)-(-)-3-hydroxytetrahydrofuran the authors used (*R*)-(+)-dimethylmalate, with an e.e. of 99%. The authors reduced the optically active form of tartaric acid or malic acid with lithium aluminium hydride, to afford the optically active 1,2,4-butanetriol which was subsequently cyclised to produce the optically active 3-hydroxytetrahydrofuran **48** using *p*-toluenesulfonic acid in 85 to 87% yield (**Scheme 1.3.3**).



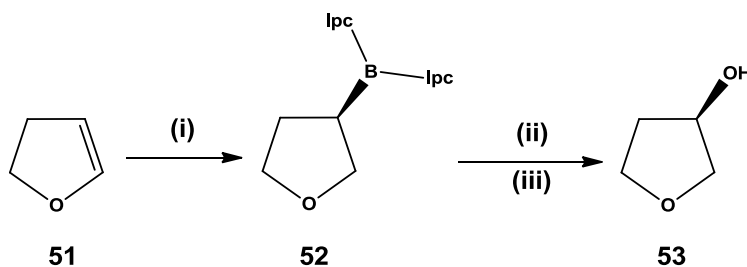
Scheme 1.3.3 Reagents: (i) LiAlH₄, THF, (ii) *p*TsOH, heat.

In 1998, a paper published by Lee and co-workers³⁷ explored the one pot synthesis of 2,5-disubstituted 3-hydroxytetrahydrofuran from hex-1,5-dien-3,4-diol **49**. Treatment of hex-1,5-dien-3,4-diol with mercury(II) trifluoroacetate at room temperature followed by reduction with sodium borohydride in the presence of triethyl borane or triethylammonium benzyl bromide at -78 °C afforded the 3-hydroxytetrahydrofuran **50** (**Scheme 1.3.4**).



Scheme 1.3.4 Reagents: (i) $\text{Hg}(\text{O}_2\text{CCF}_3)_2$, (ii) NaBH_4 , BEt_3 , -78°C .

During the 1980's, a series of papers were published by Brown documenting the synthesis of 3-hydroxytetrahydrofuran **53** from 2,3-dihydrofuran **51**. A paper in 1986 described the asymmetric synthesis of (*R*)-(-)-3-hydroxytetrahydrofuran. This transformation was achieved using (-)- Ipc_2BH , which described a route that afforded **53** in 92% yield (100% e.e). Conversely, if (+)- Ipc_2BH was used (*S*)-(+)-3-hydroxytetrahydrofuran would be formed in 68% yield (100% e.e). This procedure afforded (*R*)-(-)-3-hydroxytetrahydrofuran in a higher e.e. than the procedure utilised by Wynberg and co-workers³⁵ (**Scheme 1.3.5**).



Scheme 1.3.5 Reagents: (i) (-)- Ipc_2BH , THF, (ii) CH_3CHO , (iii) NaOH , H_2O_2 .

In a follow-up paper, published in 1988,³⁹ a synthesis of (*S*)-(+)-3-hydroxytetrahydrofuran and (*R*)-(-)-3-hydroxytetrahydrofuran from 2,3-dihydrofuran was detailed. The authors used different chiral borane reagents to afford the individual 3-hydroxytetrahydrofurans, which were produced *via* similar hydroboration reactions as in the aforementioned paper. To synthesise (*S*)-(+)-3-hydroxytetrahydrofuran, (1*S*)-di-2-isocaranylborane **54** was used while to synthesise (*R*)-(-)-3-hydroxytetrahydrofuran (1*S*)-di-4-isocaranylborane **55** was employed. Both enantiomers of 3-hydroxytetrahydrofuran were obtained in high e.e. up to 83% yield.

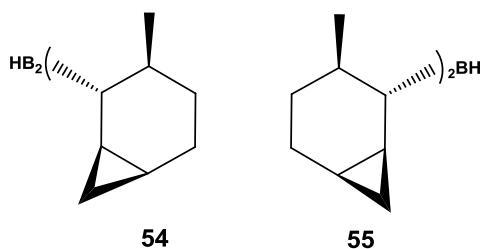
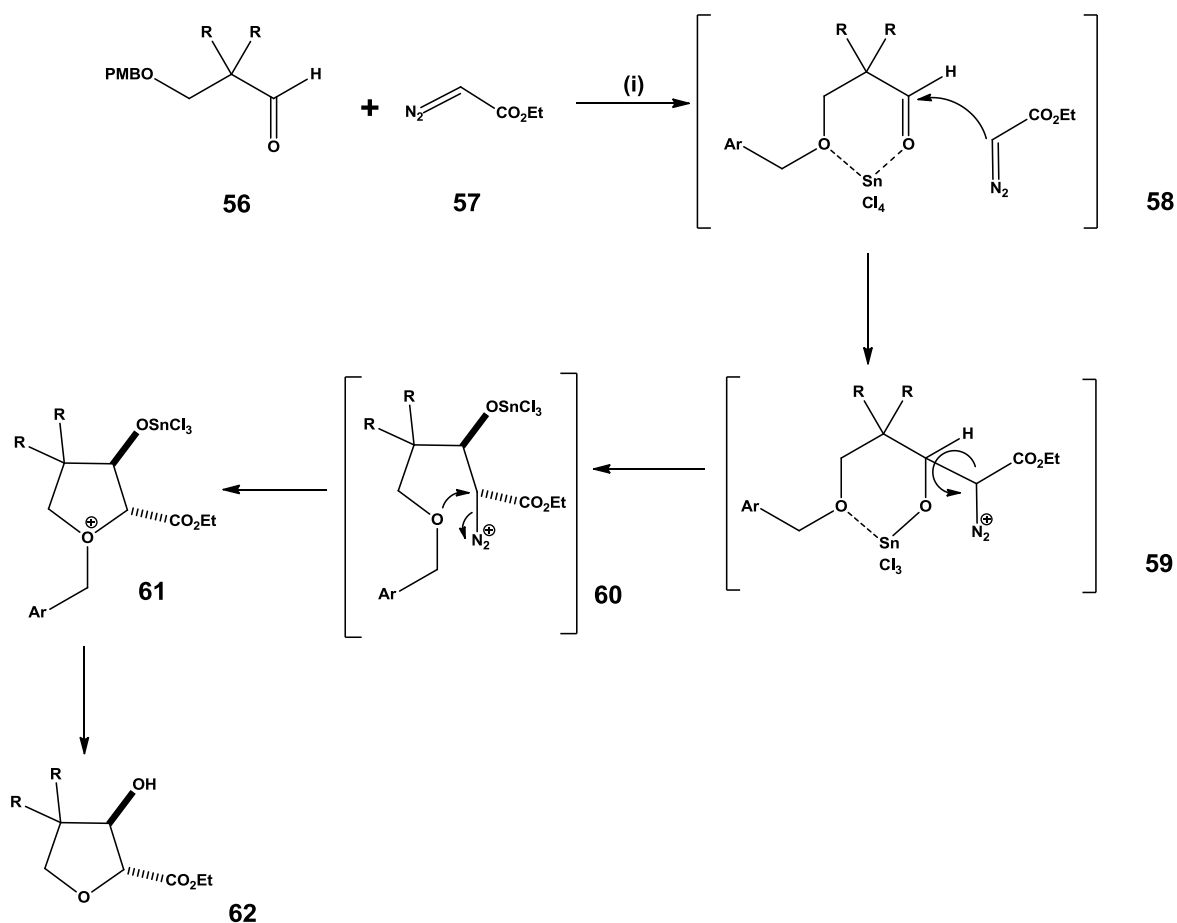


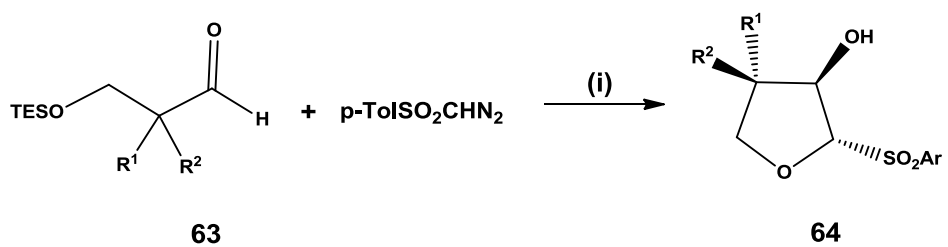
Figure 1.3.1

Angle and co-workers⁴⁰ synthesised a range of 3-hydroxytetrahydrofurans from β -(triethylsilyloxy)aldehydes and aryldiazomethanes. In a subsequent paper, the authors postulate the origins and the diastereoselectivity.⁴¹ The Lewis acid co-ordinates to the oxygens of the aldehyde and the benzylic ether, which creates a more electrophilic carbon to allow the diazo carbene carbon to condense with the aldehyde. This transition state minimises steric interactions and should afford **59**. Rotation about the new carbon-carbon bond to place the diazo-group *anti* to the oxygen of benzylic ether should afford **60**. S_N2 type intramolecular displacement of the diazo- yields the oxonium ion **61**. The benzyl group is displaced from the oxonium ion by a nucleophile such as the chloride anion to afford the 3-hydroxytetrahydrofuran **62** in 77 to 80% yield (**Scheme 1.3.6**). This mechanism accounts for the observed *trans*- orientation between the ester and alcohol functionalities. The stereochemical outcome for aldehyde **56**, with an α -stereogenic centre is consistent with a chelation controlled addition of the α -diazoester to the aldehyde.



Scheme 1.3.6 Reagents: (i) SnCl_4 (alternatively ZrCl_4 or $\text{BF}_3 \cdot \text{OEt}_2$), DCM, -78°C .

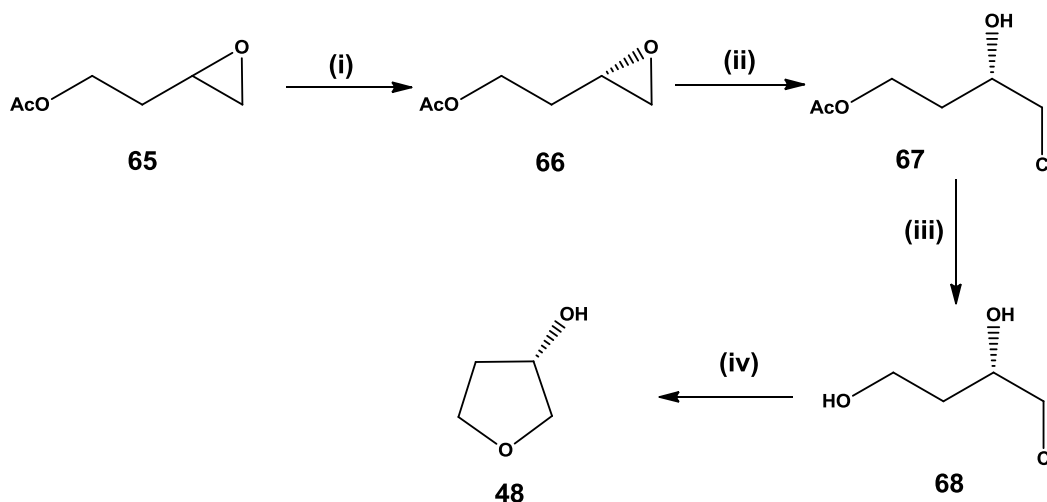
Angle and co-workers⁴² published another paper in which they described the synthesis of a range of 2,4-disubstituted 3-hydroxytetrahydrofurans from β -(triethylsilyloxy)aldehydes **63** and *p*-tolylsulfonyldiazomethane. This route yielded 3-hydroxy-2-sulfonyltetrahydrofurans **64**. The authors used various Lewis acids such as tin tetrachloride and boron trifluoride diethyletherate (**Scheme 1.3.7**), they confirmed the stereochemistry by NOE experiments. They note that the diastereoselectivity arises in the 3-hydroxytetrahydrofuran products from the steric bulk of the α -substituents of the aldehyde; increasing from methyl to *tert*-butyl.



Scheme 1.3.7 *Reagents:* (i) $SnCl_4$ or $ZrCl_4$ or $BF_3 \cdot OEt_2$.

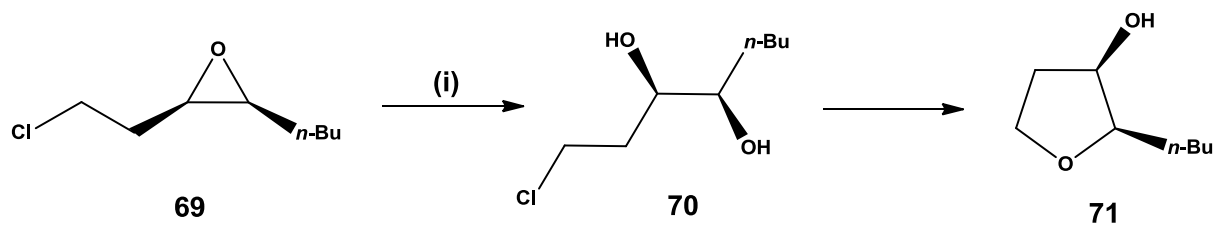
1.3.2 Synthesis of 3-Hydroxytetrahydrofurans *via* Biotransformations

Botes and co-workers,⁴³ in 2008, published a paper in which epoxide hydrolyases were used to resolve an epoxy ester to afford an enantioenriched epoxy ester (97.8% e.e.). Once obtained, the epoxy ester was treated with lithium chloride in acetic acid and THF to give the chlorohydrin **67**. The ester was cleaved with a lipase and the resulting diol **68** and underwent acid catalysed cyclisation to afford the enantioenriched 3-hydroxytetrahydrofuran in 79% yield (**Scheme 1.3.8**).



Scheme 1.3.8 *Reagents:* (i) epoxide hydrolyase, buffer, (ii) LiCl, acetic acid, (iii) lipase buffer, (iv) H₃O⁺, heat.

Faber and co-workers⁴⁴ reported the asymmetric bio-hydrolysis of an epoxide using epoxide hydrolyase. The authors used racemic chloroalkyl oxiranes as a substrate for the epoxide hydrolyase (*Rhodococcus* sp.) to give the (3*R*,4*R*) (*vic*-)chloroalkyl diol which cyclised to afford the 2-butyl-3-hydroxytetrahydrofuran. The authors confirmed the stereochemistry with the use of NOE experiments. It was also Faber and co-workers who noted that the rate of cyclisation was faster than the rate of enzymatic hydrolysis. Overall this allowed the development of a one pot synthesis (**Scheme 1.3.9**).



Scheme 1.3.9 Reagents: (i) *Rhodococcus* sp., buffer.

1.4 Bakers' Yeast Transformations

Saccharomyces cerevisiae, a form budding yeast, was the first eukaryotic genome to be completely sequenced in 1996. The yeast genome database⁴⁵ is highly annotated and remains a very important tool for developing basic knowledge about the function and organisation of eukaryotic cell genetics and physiology. Another important *S. cerevisiae* database is maintained by the Munich Information Centre for Protein Sequences. The genome is composed of about 13,000,000 base pairs and 6,275 genes, although only about 5,800 of these are believed to be true functional genes. It is estimated that yeast shares about 23% of its genome with humans.⁴⁵ It is the most intensively studied eukaryotic model organisms in molecular and cellular biology. It is perhaps the most important yeast thanks to its use since ancient times in baking and brewing. "Saccharomyces" is derived from the Greek word meaning "sugar mould" while "cerevisiae" comes from the Latin word meaning "of beer".

It was not until 1874 that the reducing properties of *Saccharomyces cerevisiae* were first observed by Dumas.⁴⁶ He reported that on addition of finely powdered sulphur to a suspension of fresh yeast hydrogen sulphide was liberated. The use of Bakers' yeast as a reagent in organic synthesis has been known since the beginning of the 20th century.^{47,48} In recent years, the advantages of using enzymatic catalysts in preparative organic chemistry have become well known and documented comprehensively in review articles.⁴⁷⁻⁴⁹ *S. cerevisiae* is ideal for non-microbiologists since it is readily available at a reasonable price and does not require sterile conditions to allow it to be used with most laboratory equipment. Often organic chemists seeking a stereoselective transformation prefer organisms such as bakers' yeast and enzymes such as lipases to traditional chemical reagents. Hydrolytic enzymes do not require co-factor regeneration and are easy to use.

Two biocatalytic systems are available to chemists for the reduction of prochiral ketones; 1) whole cell and 2) enzymes. Reductase enzymes, such as ketoreductases, require reduced nicotinamide cofactors, which must be provided in stoichiometric amounts or *via* a regeneration system (**Figure 1.4.1**).

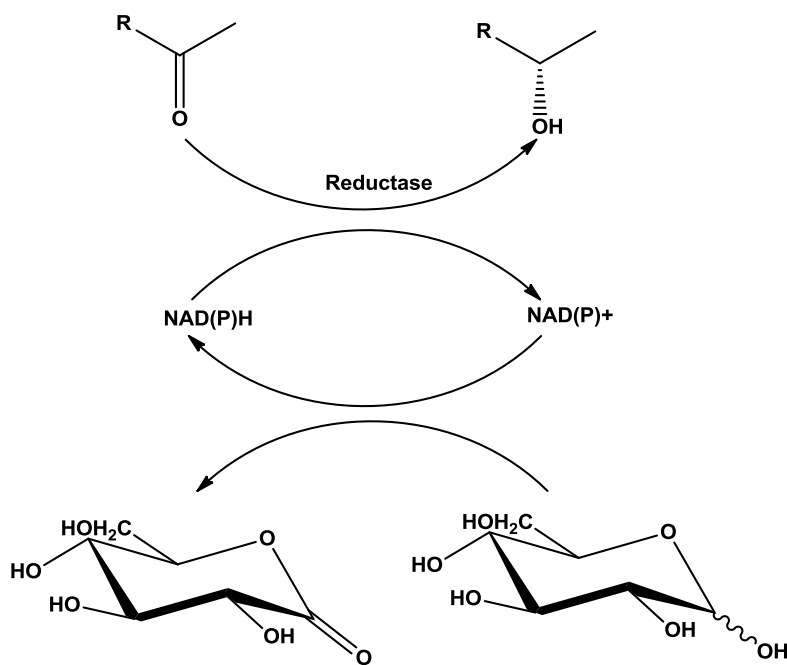


Figure 1.4.1

Whole cell systems, such as bakers' yeast, do not need extra co-factors, as they possess all the necessary enzymes for co-factor regeneration. A subset of the approximately 6,000 proteins produced by this organism catalyse the reduction of ketones and aldehydes to the corresponding alcohols. These transformations often proceed with very high efficiencies and stereoselectivities.⁵⁰ Simple aliphatic and aromatic ketones are reduced by fermenting yeast, according to Prelog's rule,⁵¹ to give the corresponding (*S*)-alcohol, normally optically pure. Only a carbohydrate substrate such as glucose is needed as an energy source, the overall reaction can be considered as a formal reduction reaction.

The use of purified yeast enzymes for carbonyl group reductions avoids problems associated with competing catalyst processes, such as giving differing stereoselectivities. A variety of reductase enzymes have been purified from bakers' yeast.⁵² Unfortunately, bakers' yeast alcohol dehydrogenase is the only commercially available organism and has a very limited substrate range.

Work carried out by Shieh and co-workers⁵³ showed that a fatty acid synthase, one of the bakers' yeast reductase enzymes, was the main enzyme responsible for the enantioselective reduction of 4-chloroacetoacetic esters to 4-chloro-3-hydroxy esters. Fatty acid synthase, aldo-keto reductase and *R*-acetoxy keto reductase have been identified as three of the major β -keto ester reductases in bakers' yeast. Further work by Kayser and

Stewart^{54,55} has demonstrated the utility of these purified enzymes in providing chiral β -hydroxy ester building blocks.

Through disabling fatty acid synthase by mutation, the (S)-configuration of the alcohol was produced. Work carried out by Kayser and co-workers⁵⁴ demonstrated that deactivation of the gene responsible for the fatty acid synthase, which is responsible for producing *R* alcohols, produced β -hydroxy esters with the (S)-configuration at the 3-position. This group also found that it was possible to achieve this selectivity by over expressing the gene Gre2p responsible for acetoxy ketone reductase, in strains of bakers' yeast from which the fatty acid synthase gene had been eliminated by previous mutations.⁵⁵

The first industrial application of bakers' yeast was in the synthesis of trimegestone (17- α -methyl-17- β -(2(S)-hydroxy-1-oxopropyl)-estra-4,9-dien-3-one),⁵⁶ a progesto-mimetic molecule developed by Roussel Uclaf for postmenopausal therapies. The key step of the synthesis is the chemo-, regio-, and stereospecific bioreduction of triketone **73** to the desired 21-(S) alcohol **72**, trimegestone (d.e.= 99%). This bioreduction is performed with bakers' yeast in water. It was found that once pH was maintained between 4 and 7, the reduction would take place. Outside of this pH range, the reduction did not take place. The optimum temperature was 40 ± 2 °C for the process. Glycerol was used as the energy source and as a formal source of the hydride for the process. Oxidation of the glycerol allows the reduction of NAD(P)⁺ to NAD(P)H. Regeneration of the co-factor, NAD(P)H, allows for the reductase enzyme to carry out the reduction of the ketone. The advantage of using glycerol is that foaming, associated with the liberation of carbon dioxide, is not observed during the reaction. The use of carbohydrates as a nutritional source for the bakers' yeast acidifies the reaction medium, with glycerol this does not happen.⁵⁷ Also, the rate of metabolism is the same as the rate in the presence or absence of a prochiral ketone⁶⁵ (**Figure 1.4.2**). Ethanol has also been used as a source of reductant for NAD(P)H, where ethanol is oxidised to acetate and finally to carbon dioxide.⁵⁸

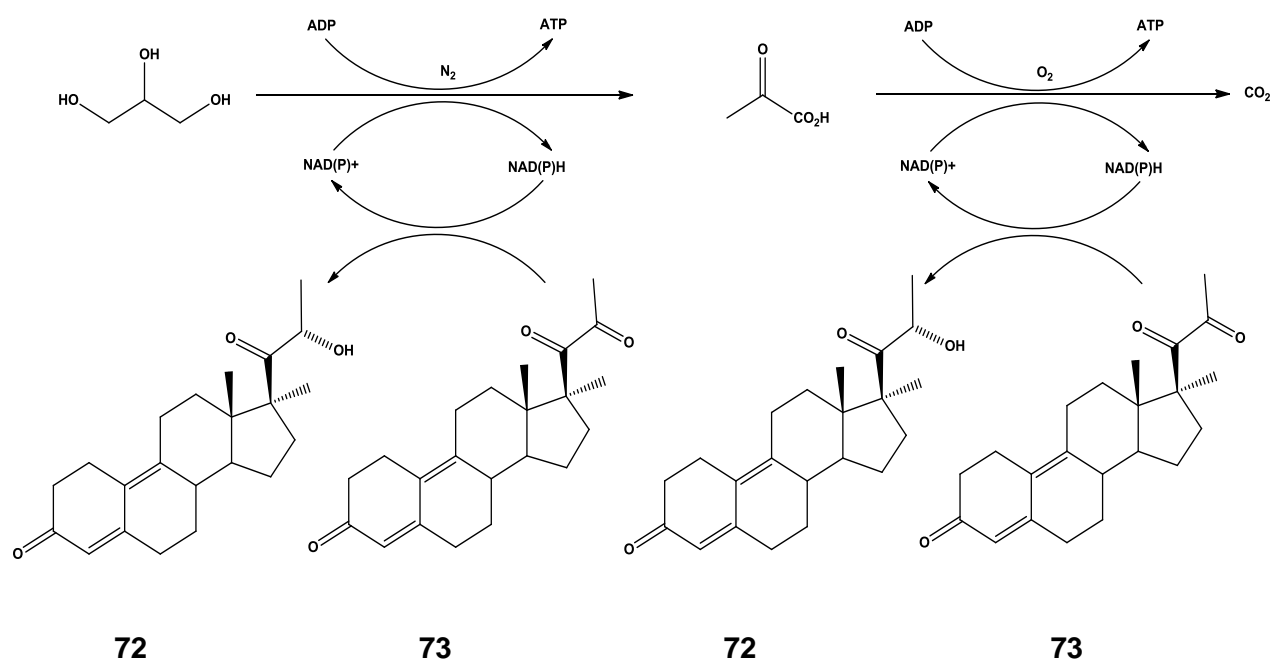
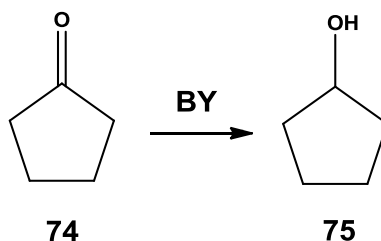


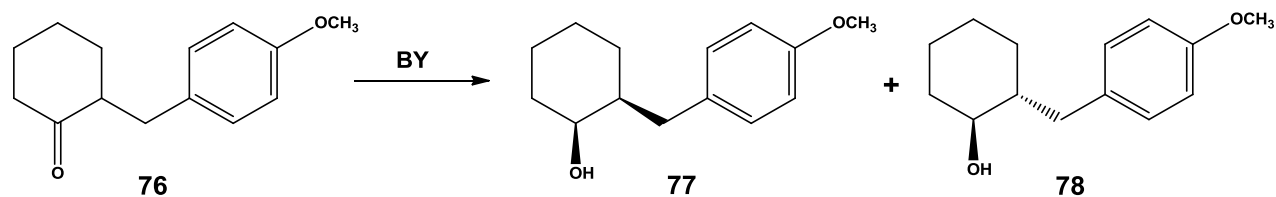
Figure 1.4.2

The asymmetric reduction of carbonyl containing compounds by bakers' yeast is one of the most common applications of the organism. For instance, Neuberg and co-workers observed reduction of cyclopentanone **74** to cyclopentanol **75** with 42% yield⁵⁹ (**Scheme 1.5.3**).



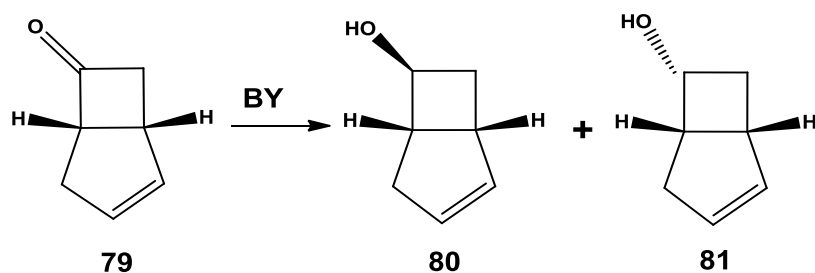
Scheme 1.4.3

Bakers' yeast has a preference for the reduction of prochiral ketones to the corresponding alcohol to give (*S*)-configured alcohol. Racemic 2-(4-methoxybenzyl)cyclohexanone **76** was reduced by bakers' yeast to yield a 1:1 mixture of *cis*-(1*S*,2*S*)-2-(4-methoxybenzyl)-1-cyclohexanol **77** (91.6% e.e.) and *trans*-(1*S*,2*R*)-2-(4-methoxybenzyl)-1-cyclohexanol **78** (97.5% e.e.) in a study carried out by Romanuk and co-workers⁶⁰ (**Scheme 1.4.4**).



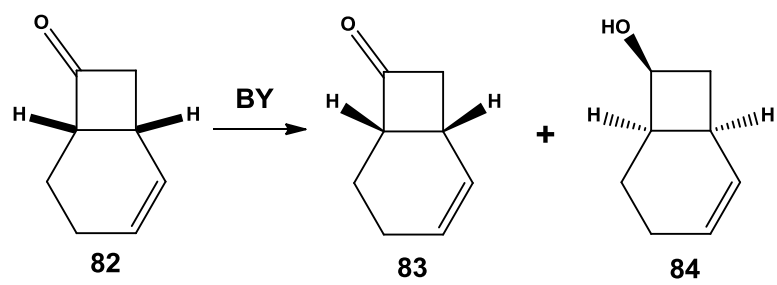
Scheme 1.4.4

Bicycloheptenones are important building blocks in the synthesis of prostaglandins PGE₂, PGFA_{2α} and PGA₂. Roberts and co-workers carried out the enzymatic reduction of (±)-bicyclo[3.2.0]hept-2-en-6-one to **80** in 90% e.e with the diastereoisomer **81** in 18% yield, its diastereoisomer was not detected however starting material was recovered (**Scheme 1.4.5**).⁶¹



Scheme 1.4.5

Kluge and co-workers carried out the reduction of bicyclo[4.2.0]octenones and it found to be highly diastereoselective for reduction from the ketone's *exo*-face, in addition to being highly enantioselective. Thus, reduction of racemic **82** afforded ketone **83**, yield 32% (40% e.e.), and yield of 25% of the alcohol **84** (92% e.e.)⁶² (**Scheme 1.4.6**).



Scheme 1.4.6

1.5 Muscarine

Due to its pharmacological activity, muscarine, has been investigated extensively well into the last century and beyond.⁶³⁻⁶⁶ Muscarine is the principal agent of the poisonous mushroom Fly Agaric, *Amanita muscaria* and was recognised as this over 170 years ago.⁶⁷ In 1914, while studying the pharmacological actions of acetylcholine, Dale and co-workers observed two distinct types of activity, which he termed as muscarinic and nicotinic.⁶⁸ The muscarinic actions of acetylcholine are those that can be reproduced by the injection of muscarine. So called 'natural' muscarine poisoning is caused by *L*-(+)-muscarine **85**, which is responsible for the poisoning caused by *Inocybe* and *Clitocybe* mushrooms.

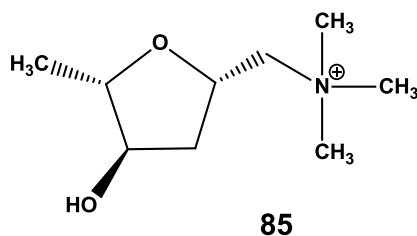


Figure 1.5.1

(+)-(2*S*,3*R*,5*S*)-Muscarine **85**, a hydroxytetrahydrofuran, is amongst the most widely studied alkaloids due to its presence in a range of fungi. It is found as a secondary metabolite in poisonous mushrooms of the *Amanita* species, e.g. *Amanita phalloides* (death cap) and *Amanita muscaria* (fly agaric). Several synthetic and structural investigations have been directed at this compound since the early 1800's. In 1954, Eugster and Waser isolated pure muscarine chloride by precipitation from the alcoholic extract of *Amanita muscaria* with Reinecke acid.⁶⁹ This breakthrough resulted in a series of experiments which elucidated the muscarine structure. This was followed by its synthesis and determination of its pharmacological profile.

Muscarine is a selective agonist of acetylcholine receptors in the smooth muscle of the gastrointestinal tract, eye, exocrine glands and heart. Muscarine activity on smooth muscle resembles that of acetylcholine to the extent that direct action on cholinergic receptors in the autonomic nervous system. This has become known as muscarinic activity. Pharmacological investigations with selective agonists have demonstrated that subtypes

of the muscarinic receptor exist. The muscarinic receptors in cardiac muscle tissue are different to those that exist in the gastrointestinal tract. For this reason the receptors have been divided into different subtypes (M_1 - M_4).⁷⁰

M_1 -receptors are found mainly in central nervous system and peripheral neurons and gastric parietal cells. These receptors mediate excitatory effects. Deficiency of acetylcholine-mediated effects in the brain is associated with dementia. Identification of a connection between cholinergic deficits and the pathology of Alzheimer's disease has led to a renewed interest in compounds possessing muscarinic activity. The renewed interest has been centred around muscarine and its analogues. It is hoped that the information gathered from the selective interactions with individual muscarine receptors would lead to chemotherapeutically useful agents which could be employed as muscarinic agonists and antagonists.^{70,71}

Conformations of naturally occurring compounds are important for their biological activity. A large number of conformational studies have been carried out on muscarine. Quantum mechanical studies of the perturbative configuration interaction have suggested that the positive charge on the quaternary nitrogen atom is distributed over the surrounding *N*-methyl groups.⁷² X-ray diffraction studies⁷³ have shown that the cationic quaternary nitrogen is pointing away from the ring and that no electrostatic interaction occurs between it and the ether oxygen.

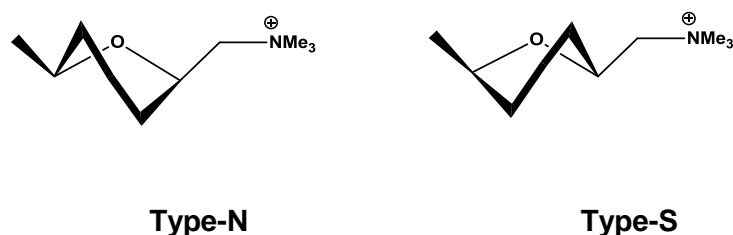


Figure 1.5.2

The tetrahydrofuran ring of muscarine exists in two conformers, type-N and type-S, (**Figure 1.5.2**). A dynamic equilibrium exists between the two interconverting conformations. Brown and Mubarak⁷⁴ proposed the type-S conformation was favoured in the muscarine ring. The barrier to ring inversion between conformers is low and as a result interconversion occurs rapidly. Due to this rapid interconversion, the influence of the population of each conformer on the pharmacological activity of muscarine is unknown.

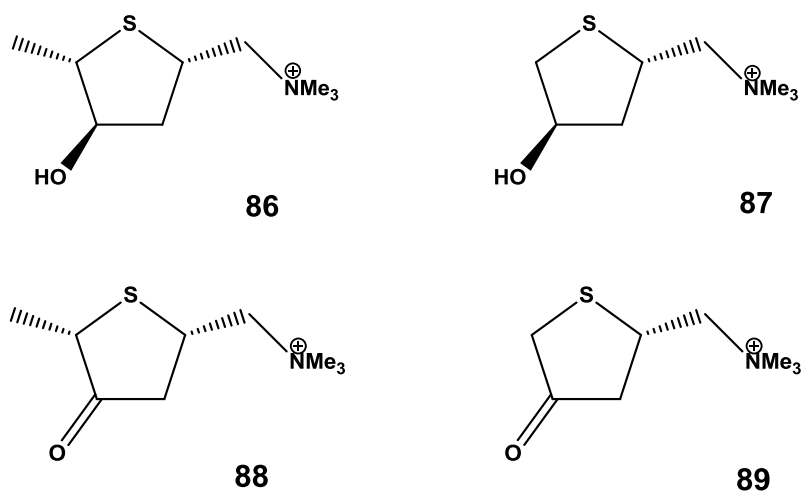


Figure 1.5.3

Sulphur analogues of muscarine **86**, desmethyl-muscarine **87** and their parent molecules **88** and **89** show significant reduction in muscarinic activity. This has been found to be as low as 0.03% activity of the potency of the tetrahydrofuran compounds. The difference is much less (3%) in muscarone compounds. This could be explained by the inability of the sulphur atom to form strong hydrogen bonds with some cholinceptive groups, as the electronegativity of sulphur (2.5) is much less than that of the ring oxygen (3.5). The increase of ring bulk by about 35%, by substitution of sulphur for oxygen naturally affects the position and biological function of the neighbouring groups and the fit of the molecule in the receptor.⁶⁶

Diminishing the chain length ($^+\text{N-C-C-O-C-C}$) from 6 atoms to 5 atoms in desmethyl-muscarine **90** and desmethyl-*epi*-muscarine **91**, and to a lesser extent in muscarone **92** and its derivatives, results in a decrease in cholinomimetic action with the exception of desmethyl-thiomuscarine and desmethyl-*epi*-thiomuscarine, which are three times more active than their corresponding methylated compounds.⁶⁶

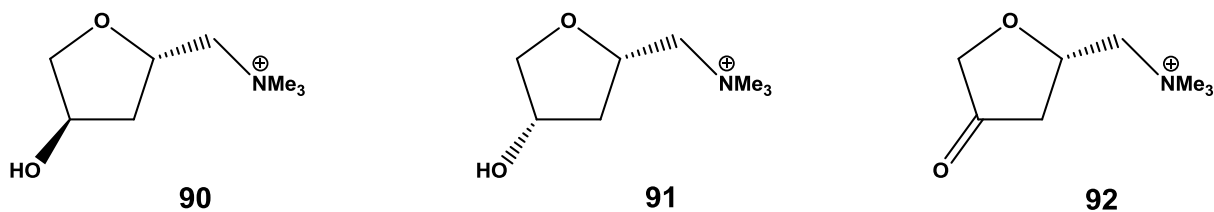


Figure 1.5.4

Chain lengthening by replacing the methyl groups with either a propyl or *isobutyl* groups leads to a significant decrease in muscarinic activity. Introduction of a (4,5) double bond into the molecules muscarine and muscarone alters the shape of the five member ring. The substituent at the C₅ position enters into a co-planar position and the charge distribution in the ring is changed. 4,5-Dehydromuscarine **93** and 4,5-dehydro-*epi*-muscarine **94** are almost as active as muscarine.⁶⁶

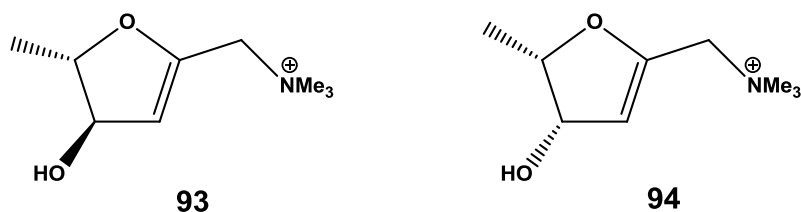


Figure 1.5.5

The potency of *epi*-muscarine is increased 100-fold by dehydrogenation at C₄-C₅. 4,5-Dehydro-muscarone **95** is as potent as muscarone. All three 4,5-dehydro compounds show stronger nicotinic activity than their saturated counterparts.⁶⁶

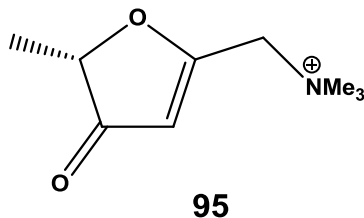


Figure 1.5.6

The oxygen in the heterocyclic ring, in muscarine and its analogues, requires a partial positive charge and the whole ring system has an electronegative character. The formation of the hydrogen bonds will be more difficult, but the charge distribution of the ring will favour binding on the ring. All substituents in the ring are co-planar and the molecule is flat. 4,5-Dehydromuscarone might consist of a partially aromatic furan ring, due to enolisation, and a hybrid structure which makes total racemisation possible⁶⁶ (**Figure 1.5.7**).

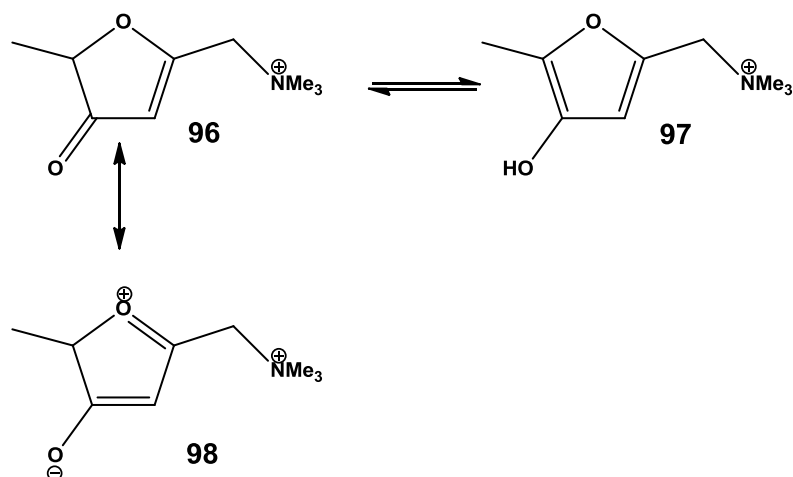


Figure 1.5.7

Nor-muscarine **99** and nor-muscarone **100** lack a quaternary nitrogen and are almost inactive. It is thought that the quaternary nitrogen is important in binding to the receptor site, which may contain an anionic pocket.⁶⁶

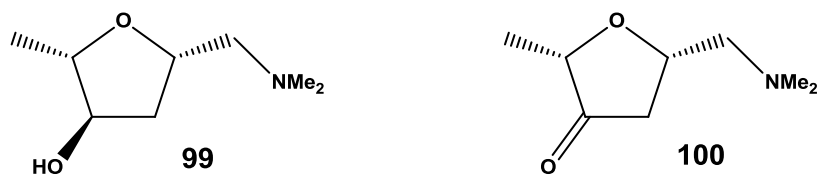
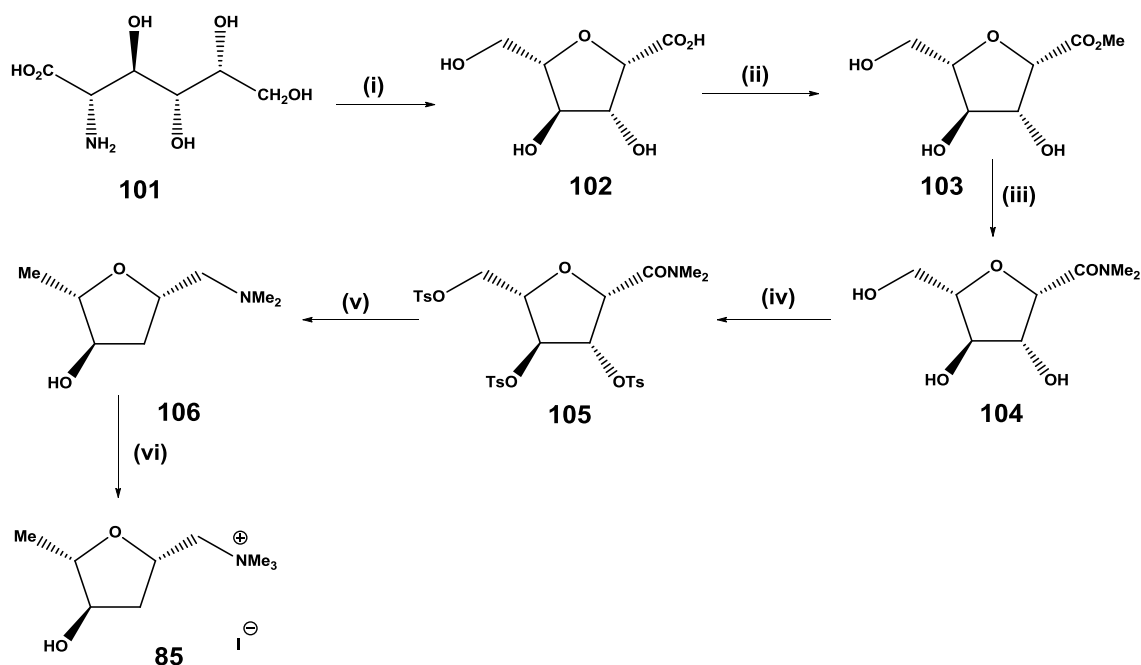


Figure 1.5.8

1.6 Synthesis of Muscarine

1.6.1 First Synthesis of Muscarine

The first total synthesis of naturally occurring (+)-muscarine was reported in 1957 by Hardegger and Lohse⁷⁵ and since then all eight stereoisomers have been reported. These syntheses will be discussed in more detail later in this chapter. The route employed by the authors began in this first synthesis by deamination of (*L*)-2-amino-2-deoxy gluconic **101** acid with nitrous acid, affording (*L*)-chitaric acid **102**. Esterification with diazomethane gave the corresponding methyl ester **103**. This ester was then converted to dimethylamide **104** by treatment with dimethylamine. Treatment with tosyl chloride afforded the tritosylate **105**. Lithium aluminium hydride reduction of **105** gave a mixture of reduction products. Purification of this mixture and quaternisation with iodomethane gave (+)-muscarine iodide **85**.

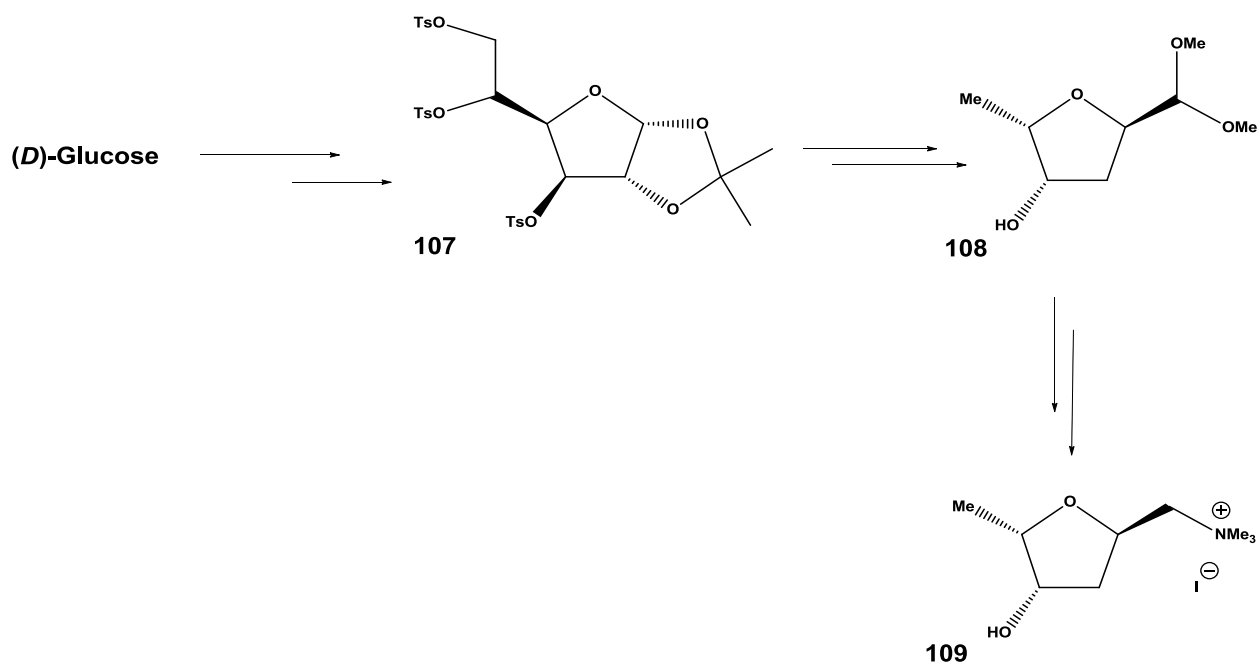


Scheme 1.6.1. Reagents: (i) HNO_2 , (ii) CH_2N_2 , (iii) Me_2NH , (iv) TsCl , Pyridine, (v) LiAlH_4 , (vi) MeI .

A number of syntheses of (+)-muscarine and its analogues have since been reported, the following gives a brief overview

1.6.2 Synthesis of Muscarine and Analogues from Carbohydrates

Joullie⁷⁶ has reported the synthesis of muscarine analogues such as epiallomuscarine **109**, isoeppiallomuscarine **114** and 3-hydroxyepiallomuscarine **117** from (*D*)-glucose. The synthesis of epiallomuscarine **109** involved a series of reactions outlined in **scheme 1.6.2**, starting from selective ketal hydrolysis, tosylations, reductions during which an epoxide functionality was formed between the 3 and 4 positions. Removal of the C₆ carbon and conversion of the remaining acetal to the trimethylammonium group afforded the desired product **109**.

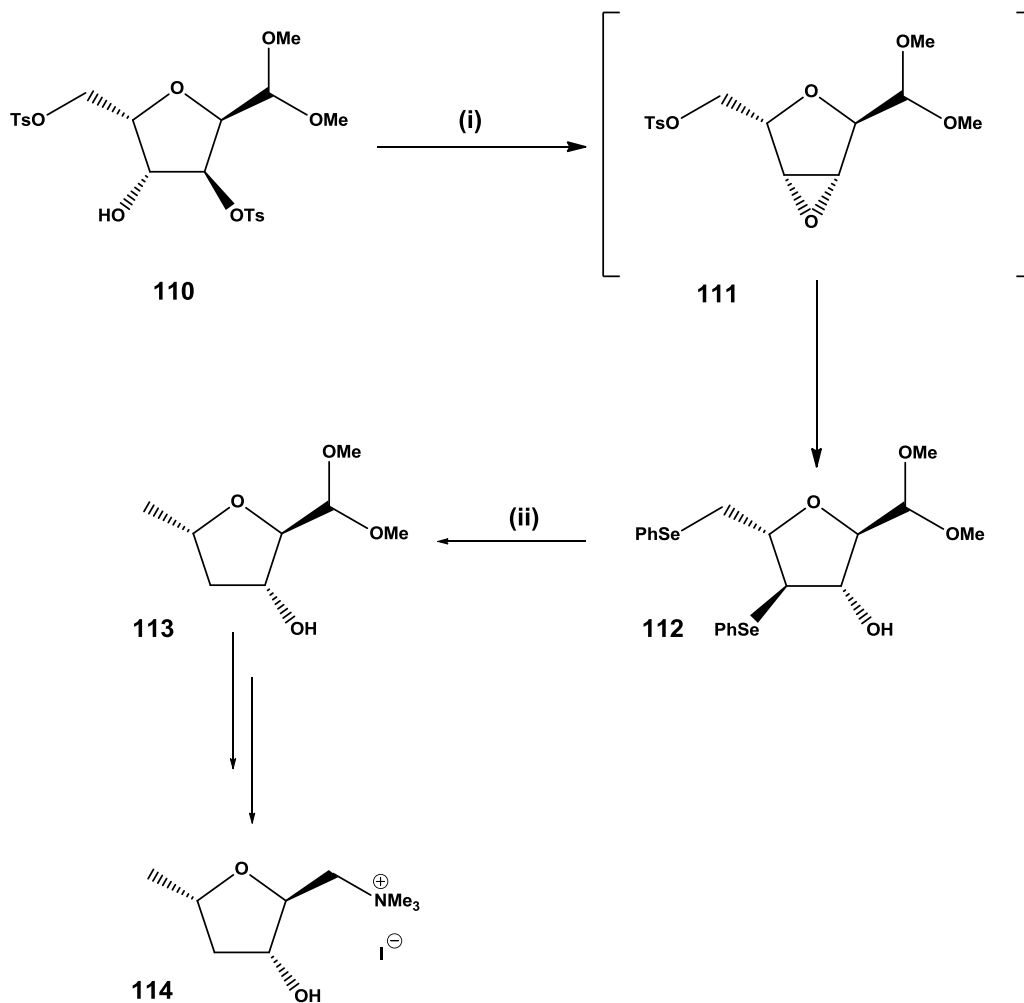


Scheme 1.6.2

The synthesis of (+)-epiallomuscarine was carried out by reduction of the ditosylate, giving two isomeric alcohols in the ratio 3 : 2 *via* an epoxy intermediate during the aforementioned synthesis of muscarine. The desired alcohol was isolated and subsequently converted to the dimethylamide. Reduction of the tertiary amide and subsequent treatment with iodomethane yielded (+)-epiallomuscarine **109**.

(2*S*,3*S*,5*S*)-Isoepiallomuscarine **114** was formed by a modification of the procedure outlined in **Scheme 1.6.2**. Efficient preparation of the isomer required a route which generated alcohol **113** as the major isomer. An excess of sodium phenyl selenide was

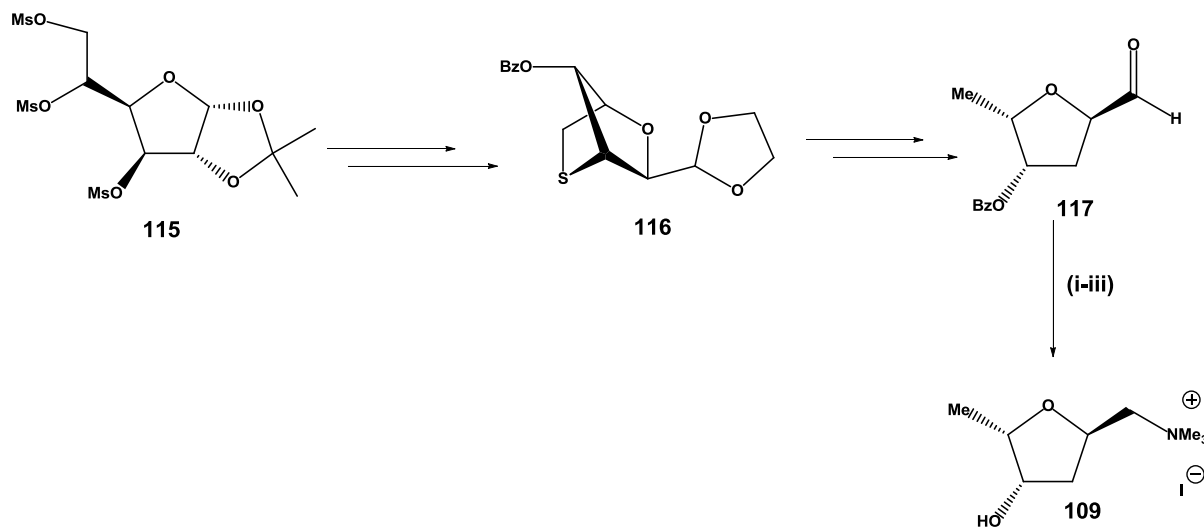
utilised to allow access to this isomer. Removal of the C-4 phenylselenenyl group with Raney Nickel gave alcohol **113** as the major isomer.



Scheme 1.6.3 *Reagents:* (i) NaSePh, DMF, (ii) W-4 Raney-Ni, EtOH.

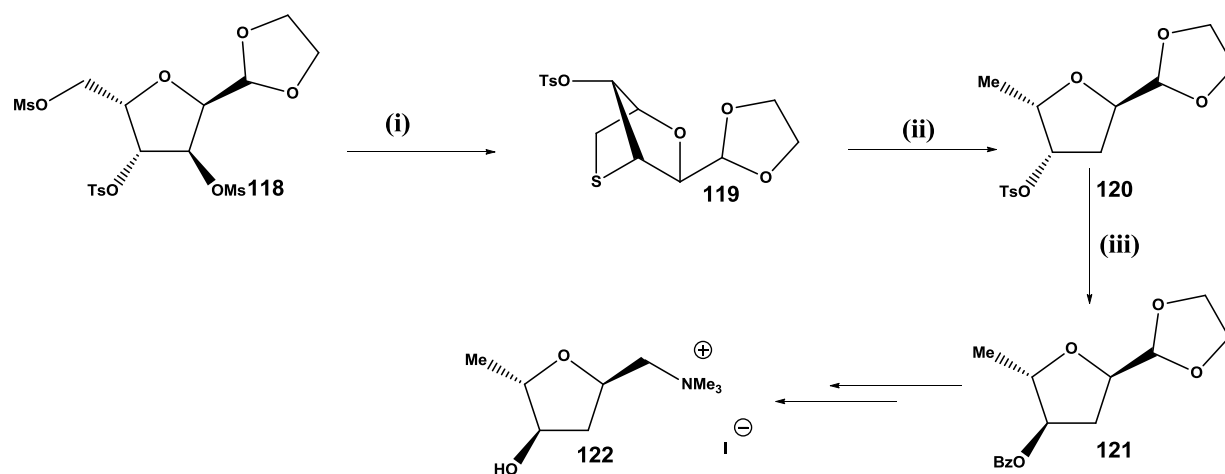
Popsavin and co-workers⁷⁷ group utilised **116** as the key chiral intermediate for their synthesis of (+)-epiallomuscarine. The group utilised (*D*)-glucose as a starting material which could be converted to the trimesylate **115** quite readily. This trimesylate was treated with ethylene glycol and catalytic PTSA. Subsequent intra- and intermolecular attack of sodium hydrosulfide on the primary alcohol led to the bicyclic oxathiane derivative **119**. Successful desulphurisation of this intermediate left all the chiral centres of **116** which contained the desired absolute stereochemistry for (+)-**109**. Subsequent hydrolysis led to

the aldehyde which was reduced to a primary alcohol. Using an Apfel reaction, this alcohol was converted to the iodide, which upon treatment with dimethylamine installed the desired amine functionality. Subsequent iodomethane treatment afforded **109** in 62% yield.



Scheme 1.6.4 Reagents: (i) NaBH₄, MeOH, (ii) I₂, imidazole, PPh₃, toluene, (iii) Me₂NH, (iv) MeI.

Popsavin and co-workers⁷⁸ also reported the synthesis of (-)-allomuscarine **122** employing similar methodology. They used the same starting material for the synthesis of allomuscarine and epiallomuscarine, which are epimers at the C₃ position of the hydroxytetrahydrofuran moiety with respect to each other. The group synthesised the 3-O-tosyl derivative **120**. Treatment of this tosylate with potassium benzoate yielded the benzoate ester. This transformation had the effect of inverting the stereochemistry at C₃. Completion of the synthesis was carried out employing the same reaction sequence as described for epiallomuscarine.



Scheme 1.6.5 Reagents: (i) NaSH, DMF, (ii) Ra-Ni, (iii) KOBz, DMF.

Popsavin and co-workers⁷⁹ have described the preparation of (+)-muscarine and (-)-epimuscarine using a stereoselective catalytic reduction of the conformationally constrained dihydrofurans **123** and **124**. Both compounds were synthesised from D-glucose.

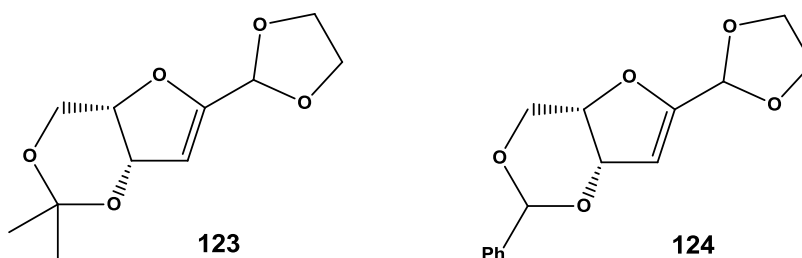
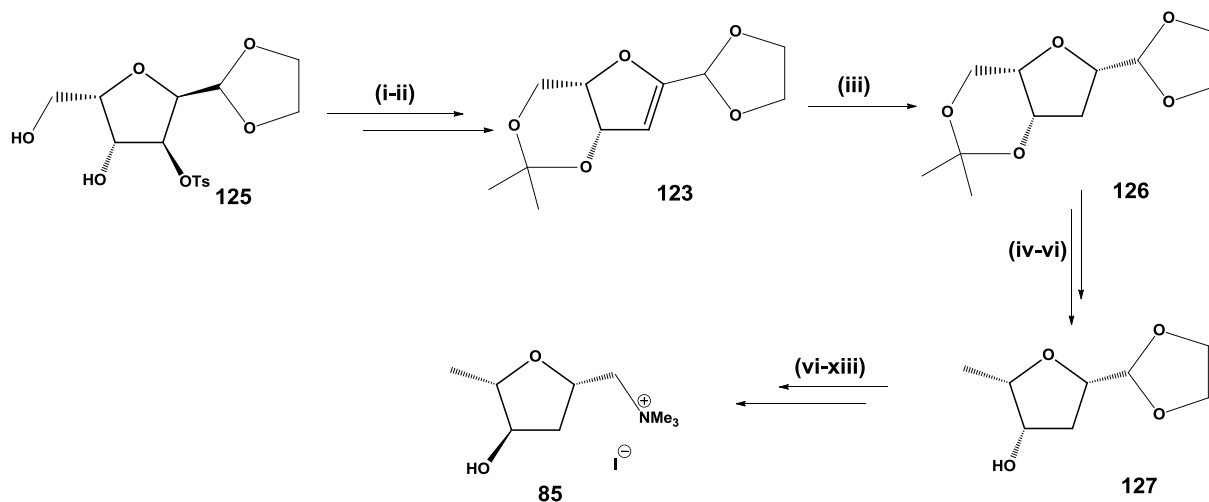


Figure 1.6.1

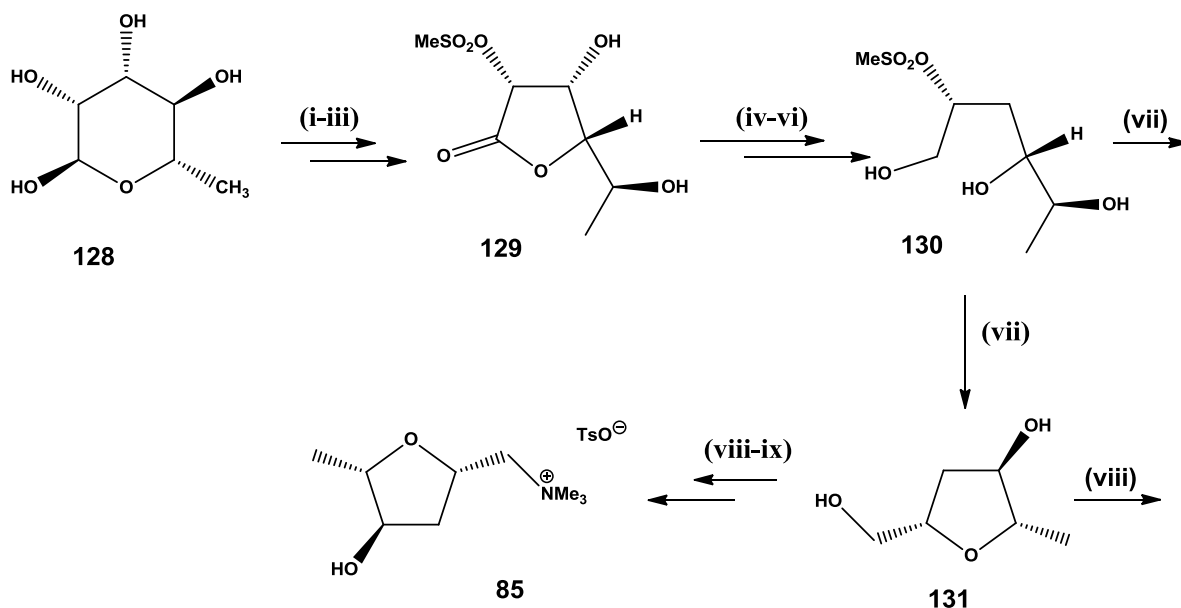
The synthetic work carried out by Popsevin and co-workers is detailed in **scheme 1.6.6**. Catalytic hydrogenation of **123** afforded the 3-deoxy derivative **126** as a single diastereoisomer. The diastereoselectivity using Adam's catalyst took place with high stereoselectivity from the less hindered β -face. The stereochemistry was confirmed by NOE NMR analysis. Selective removal of the 4,6-O-acetonide protective group followed by monotosylation of the primary alcohol and then reduction gave the 3-hydroxytetrahydrofuran **127**. The stereochemistry at C₃ was inverted using the process

described in **scheme 1.6.5**. Following inversion, **127** was subsequently converted to (+)-muscarine.



Scheme 1.6.6 Reagents: (i) $\text{Me}_2\text{C}(\text{OMe})_2$, TsOH , (ii) TBAF, MeCN, (iii) H_2 , PtO_2 , EtOH, (iv) TFA, MeOH, (v) TsCl , py, (vi) LiAlH_4 , THF, (vii) TsCl , py, (viii) KOBz, DMF, (ix) TFA, 6M HCl, (x) NaBH_4 , (xi) imidazole, Ph_3P , I_2 , Toluene (xii) K_2CO_3 , MeOH, (xiii) NMe_3 , EtOH

The following synthesis reported by Mantell and co-workers⁸⁰ shows how *L*-rhamnose **128** was recognised as a valuable starting material for asymmetric synthesis. Many syntheses that have been reported require the separation of enantiomers and diastereoisomers, however, this synthesis of muscarine seeks to minimise this problem (**Scheme 1.6.7**).

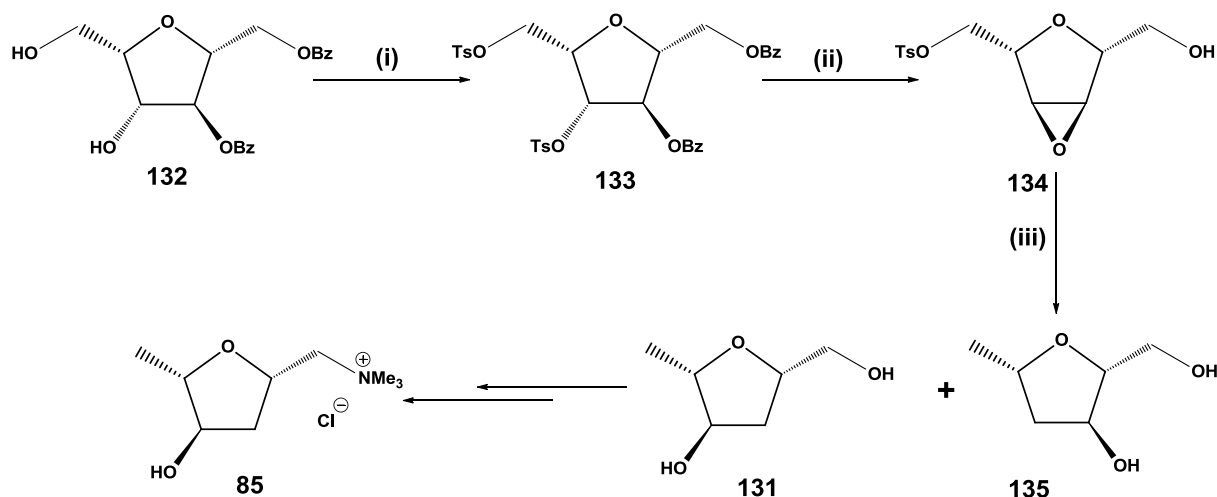


Scheme 1.6.7 Reagents: (i) Br₂, BaCO₃, H₂O, (ii) CF₃CO₂H, H₂O, (iii) MeSO₂Cl, DMAP, pyr, (iv) (CF₃CO)₂O, NEt₃, THF, then CH₃CO₂H, MeOH, (v) 10% Pd-C, EtOAc, (vi) LiBH₄, THF, (vii) NaOAc, MeCN, (viii) TsCl, pyr, (ix) Me₃N, MeOH.

L-Rhamnose **128** has the correct functionality and stereochemistry at C₂, C₄, C₅ and C₆ of the tetrahydropyran ring. *L*-Rhamnose was oxidised to the lactone and treated with acid to afford a 1,4-lactone which was *mono*-mesylated to afford **129**. The alcohol was reacted with trifluoroacetic anhydride and eliminated to afford the 2(5H)-furanone. This 2(5H)-furanone underwent hydrogenation to give the saturated lactone which when reduced, resulted in ring opening to afford **130**. This was then cyclised with sodium acetate to afford the 3-hydroxytetrahydrofuran **131**. Selective tosylation of the primary alcohol afforded the *mono*-tosylate which subsequently was treated with trimethylamine to yield muscarine **85** as its tosylate salt.

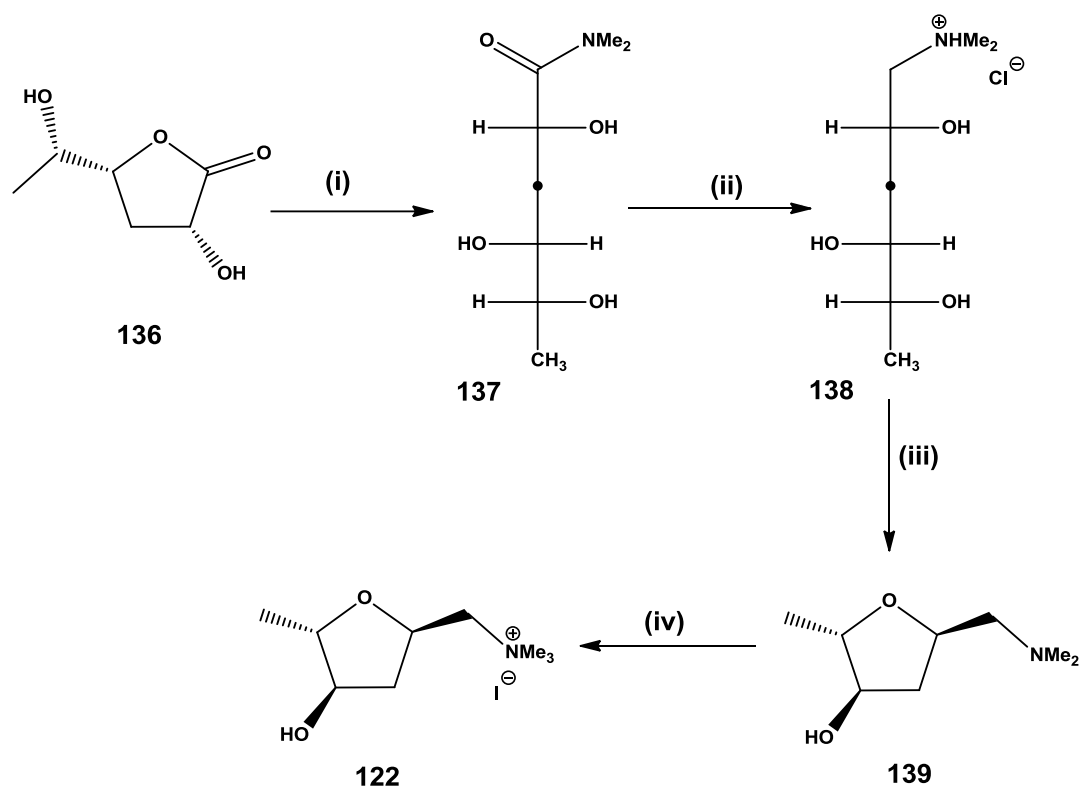
In another synthesis, Brown and co-workers⁸¹ utilised *D*-mannitol as a starting material in the synthesis of (+)-muscarine **85**. This starting carbohydrate was 2,5-anhydro-4,6-di-*O*-benzoyl-*D*-glucitol **132** which contained the necessary functional groups and chirality to complete the synthesis of (+)-muscarine. The carbohydrate **132** was di-tosylated at the C₁ and C₃ positions, the resulting 1,3-ditosylate **133** was subjected to sodium methoxide affording the epoxide **134**.

The epoxide **134** was reduced with sodium *bis*-(2-methoxyethoxy)aluminium hydride to give 2-methyl-3-hydroxy-5-hydroxymethyl-tetrahydrofuran **135** and 5-methyl-3-hydroxy-2-hydroxymethyl-tetrahydrofuran **131** in a ratio of 12 : 1. Selective tosylation of the primary alcohol of the diols **131** or **135** afforded the corresponding monotosylated alcohol. This was then subjected to methanolic trimethylamine to give muscarine chloride **85** following ion exchange (**Scheme 1.6.8**).



Scheme 1.6.8 Reagents: (i) TsCl , *py*, (ii) NaOMe , (iii) *bis*-(2-methoxyethoxy)aluminium hydride, toluene.

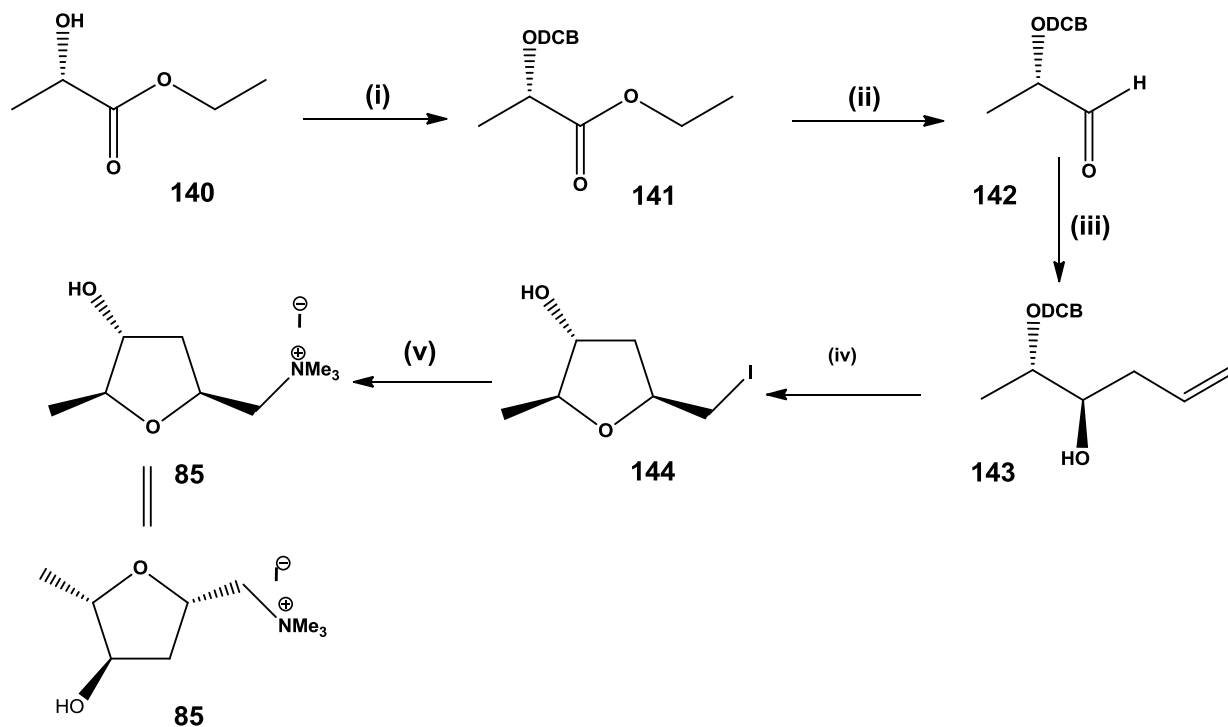
Pedersen and co-workers⁸² developed a synthesis of (-)-allomuscarine from 3,6-dideoxygalactono-1,4-lactone **136** in 30% yield. This lactone was treated with 20% dimethylamine in methanol to furnish the tertiary amide **137**. The amide **137** after reduction with borane afforded the amine **138**. Cyclisation of the triol under acidic conditions gave the 3-hydroxytetrahydrofuran **139**. Quarterisation of the amine with iodomethane furnished (-)-allo-muscarine **122** (**Scheme 1.6.9**).



Scheme 1.6.9 Reagents: (i) Me_2NH , MeOH , (ii) $\text{BH}_3 \cdot \text{SMe}_2$, HCl , (iii) HF , formic acid, (iv) MeI , Et_2O .

1.6.3 Synthesis of Muscarine from Other Chiral Starting Materials

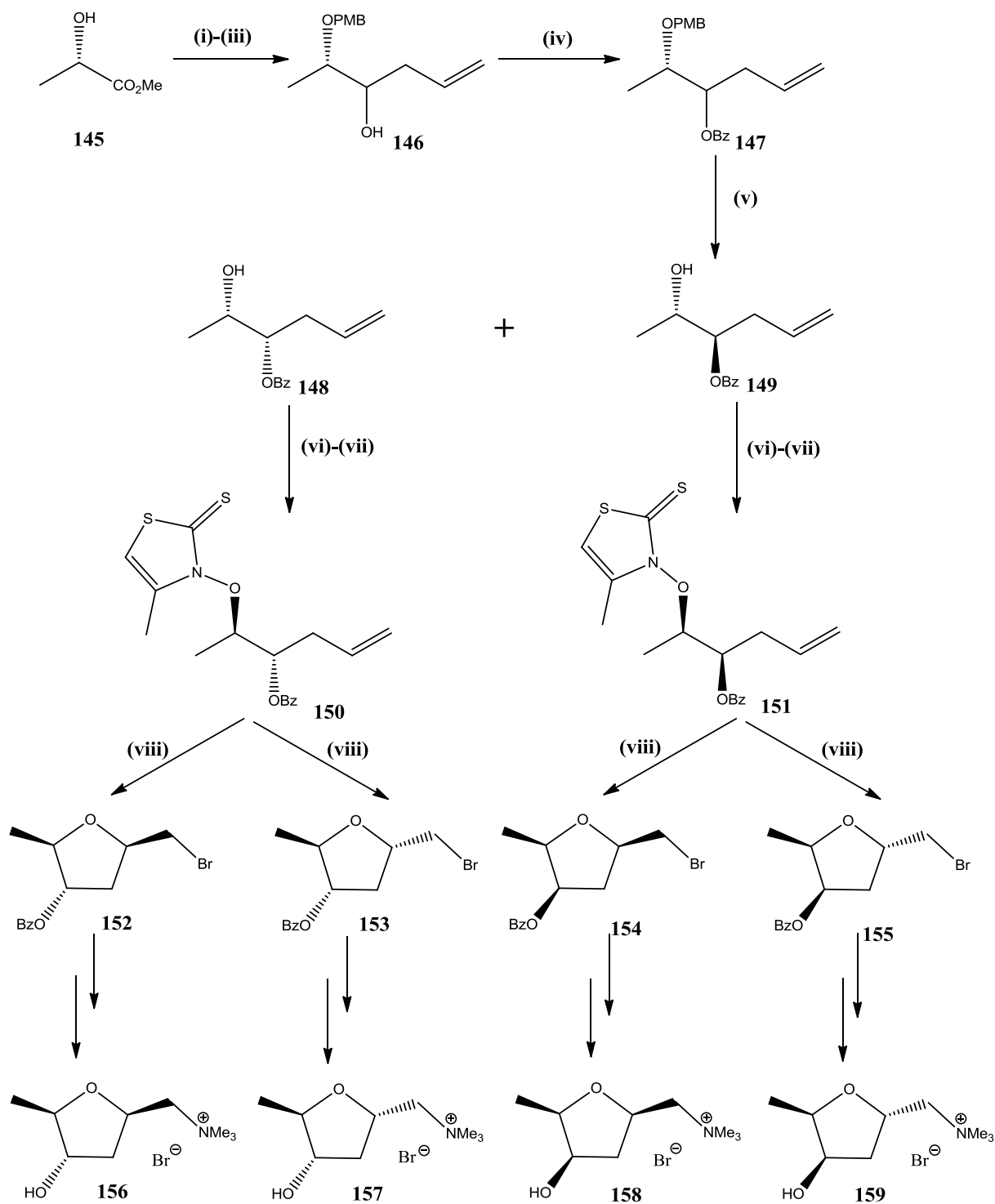
Chan and co-workers⁸³ utilised (*S*)-ethyl lactate as a precursor for their synthesis of (+)-muscarine. The key step was the application of a zinc mediated alkylation which gave the diastereoisomer in the *anti*-configuration preferentially.



Scheme 1.6.10 Reagents: (i) DCBBr, Ag₂O, Et₂O, (ii) DIBAL-H, THF, (iii) CH₂=CHCH₂Br, Zn, H₂O, NH₄Cl, (iv) I₂, CH₃CN, (v) NMe₃, EtOH.

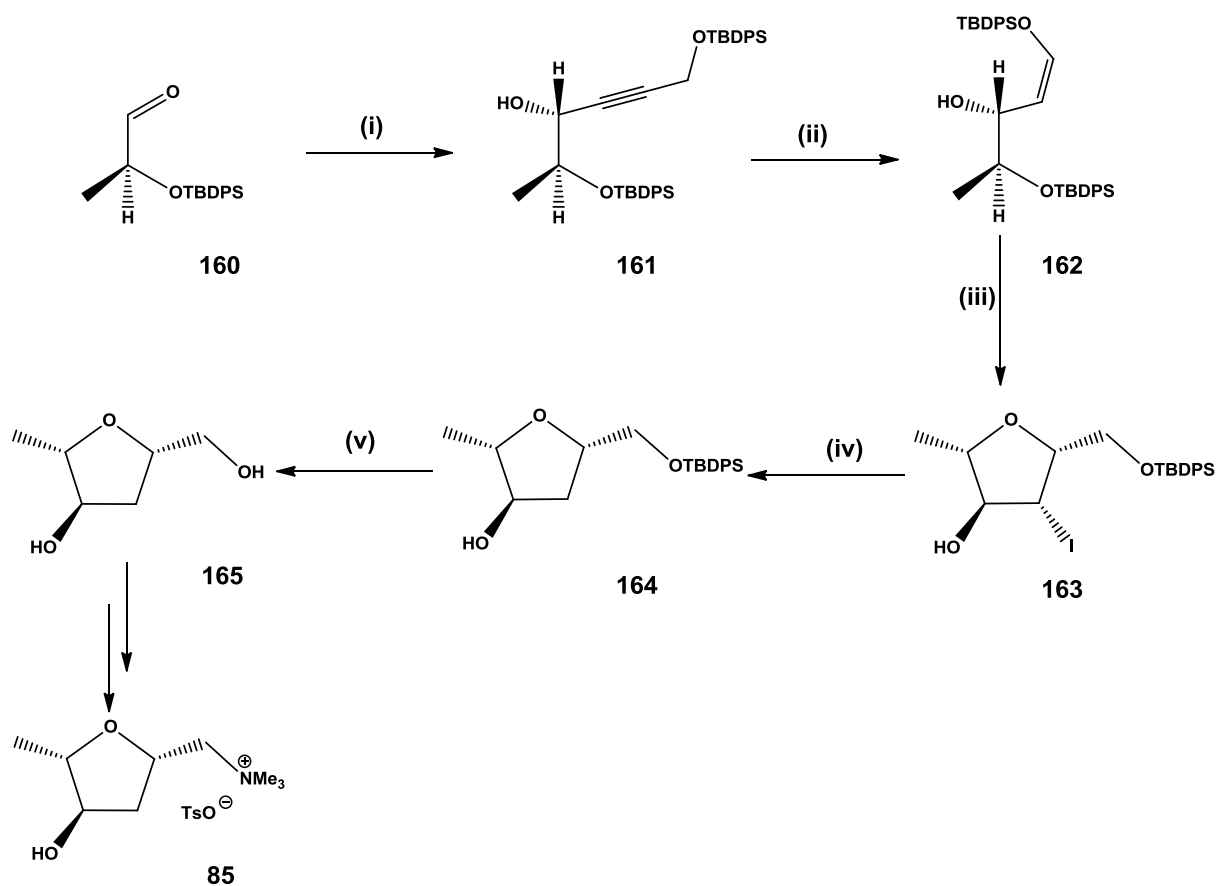
(*S*)-Ethyl lactate **140** was converted to its 2,6-dichlorobenzyl ether **141**. This compound which was subsequently reduced to the aldehyde **142** with DIBAL-H. The next step involved treatment of the crude aldehyde with allyl bromide in the presence of zinc powder using ammonium chloride as an activating agent. The allylic alcohol **143** was then treated with iodine to give the 3-hydroxytetrahydrofuran **144** by means of an iodocyclisation reaction. The iodide salt of muscarine **85** was then isolated following treatment of the iodomethyl compound with methanolic trimethylamine (**Scheme 1.6.10**).

Hartung and co-workers⁸⁴ published a synthesis of muscarine and its analogues from (S)-lactate which utilised a selective alkoxyl radical cyclisation to construct the tetrahydrofuran core. The key step in this work was a photocyclisation reaction involving the O-thiazoethione (**150** or **151**) and eight equivalents of bromochloroform. This cyclisation was carried out in a photoreactor with light of wavelength 350 nm to yield trisubstituted tetrahydrofuran in high yield as a mixture of diastereoisomers which were separable. The esters were hydrolysed to yield the corresponding 3-hydroxyltetrahydrofuran. This was followed by treatment with trimethylamine in ethanol to afford muscarine and its various diastereoisomers (**Scheme 1.6.11**).



Scheme 1.6.11 Reagents: (i) NaH, *para*-methoxybenzyl chloride, DMF, (ii) DIBAL-H, (iii) vinyl magnesium bromide, (iv) BzCl, DABCO, (v) DDQ, DCM, (vi) TsCl, DABCO, (vii) *N*-hydroxy-4-methylthiazole-2(3*H*)thione tetraethyl ammonium salt, (viii) BrCCl₃, *hν*.

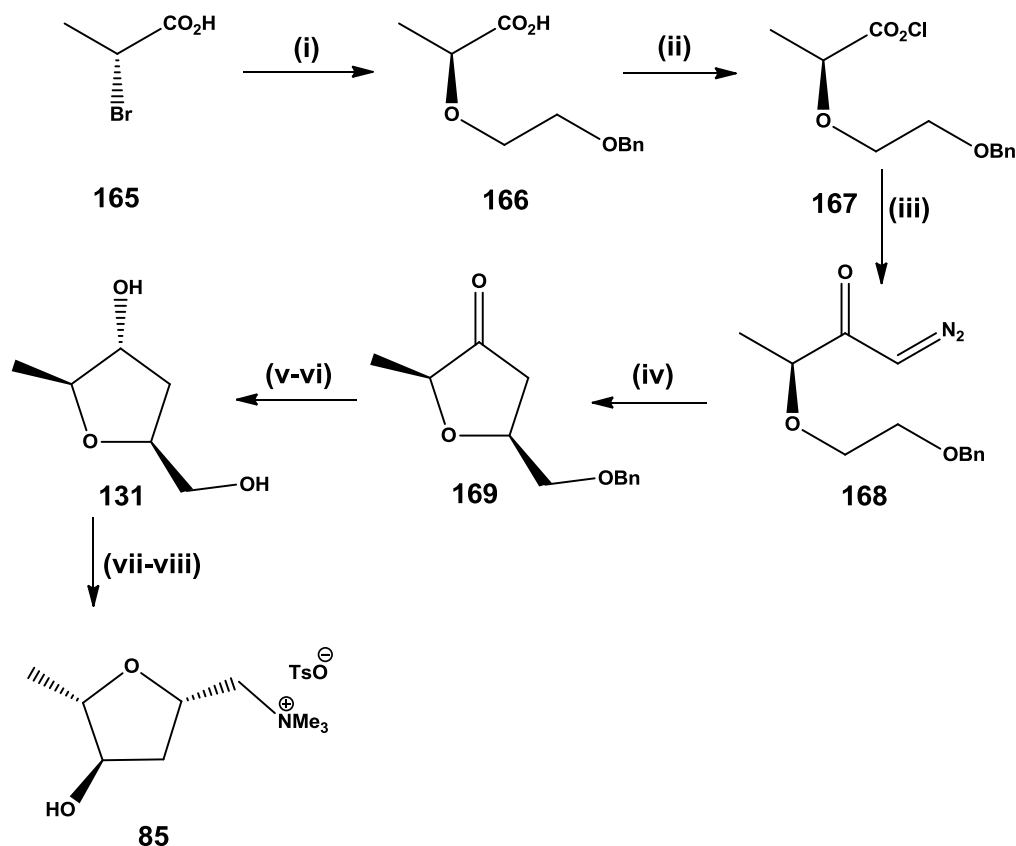
Knight and co-workers⁸⁵ synthesised (+)-muscarine utilising a 5-*endo*-trig iodocyclisation. They could control the stereochemistry at the 2- and 5- positions of the tetrahydrofuran by controlling the *cis/trans* relationship of the allylic alcohol precursor **162**. The propyl alcohol **161** was subjected to hydrogenolysis by means of treatment with Lindlar's catalyst to afford the desired (*Z*)-allyl alcohol **162**. The authors then focused on the key reaction, the iodocyclisation. They found that the reaction of the (*Z*)-allyl alcohol **162** with iodine monobromide proceeded without the need to deprotect the *O*-silylated secondary alcohol. The reaction cyclisation deprotects the secondary alcohol *in situ* to afford the 3-hydroxy-4-iodo-tetrahydrofuran **163** in high yield and as a single isomer. Removal of the iodide by hydrogenolysis followed by deprotection of the alcohol and subsequent conversion yielded (+)-muscarine (**Scheme 1.6.12**).



Scheme 1.6.12 *Reagents:* (i) BuLi, *O*-TBDPS propargyl alcohol, 12-crown-4, -78°C, (ii) H₂, Pd-CaCO₃, quinolone, MeOH, (iii) IBr, MeCN, (iv) H₂, Pd-C, NEt₃, MeOH, (v) NH₄F, MeOH.

1.6.4 Synthesis of Muscarine via Carbenoid Mediated Cyclisation Reactions.

Adams and co-workers⁸⁶ utilised a Rh(II) catalysed carbenoid C-H insertion reaction of an α -hydroxy diazoketones in their synthesis of muscarine (**Scheme 1.6.13**).



Scheme 1.6.13 *Reagents:* (i) BnOCH₂CH₂OH, NaH, DMF; (ii) (COCl)₂, DCM, (iii) CH₂N₂, Et₂O, (iv) Rh₂(OAc)₄, benzene, (v) H₂, Pd(OH)₂, EtOH, (vi) NaHB(OAc)₃, (vii) TsCl, pyr, (viii) Me₃N, MeOH.

2-Bromopropanoic acid **165** was reacted with 2-(benzyloxy)ethanol to form the ether **166**, which was subsequently reacted with oxalyl chloride to form the acyl chloride **167**. Subsequent reaction with diazomethane gave the diazoketone **168**. This was then treated with dirhodium tetraacetate to yield the 4,5-dihydro-3(2*H*)-furanone **169**. Good diastereoselectivity was observed in this key reaction. There was an 8.1 : 1 preference in favour of the *cis*- over the *trans*-isomer. This was attributed to the co-ordination of the ether co-ordinating to rhodium as previously discussed (**Figure 1.2.2**).

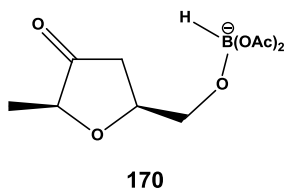
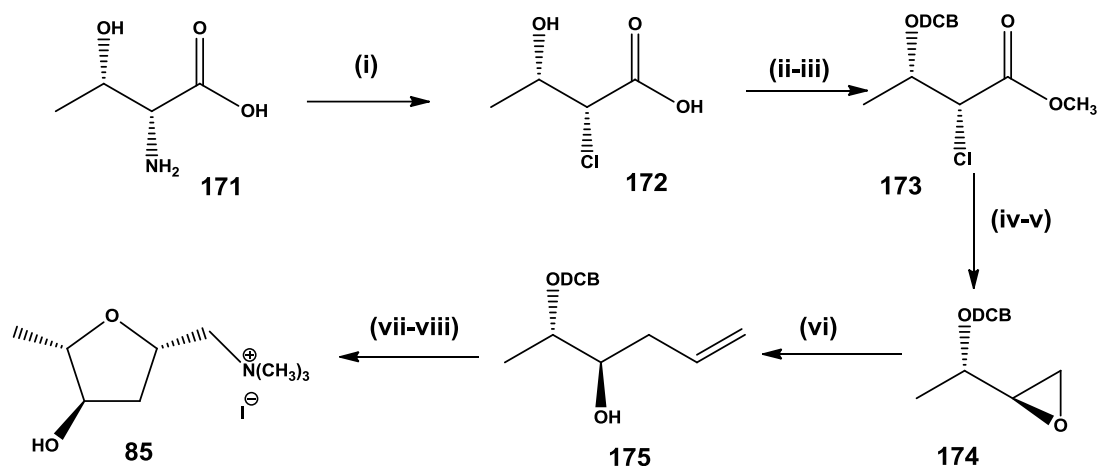


Figure 1.6.4

Following cyclisation, the benzyl moiety of the 3(2*H*)-furanone was cleaved by hydrogenolysis. This allowed NaHB(OAc)₃ to be utilised in the stereoselective reduction of the ketone **169** to afford the 3-hydroxytetrahydrofuran **131**. The primary alcohol coordinates to the NaHB(OAc)₃ and allows for the hydride transfer to occur *syn*- to the methoxy ether as shown in **figure 1.6.4**. For this reaction to occur intramolecularly the alcohol must be in close proximity to the ketone group in question. The primary alcohol was then tosylated and reacted with trimethylamine to yield (+)-muscarine **85** as its tosylate salt.

1.6.5 α-Amino Acids in the Synthesis of Muscarine

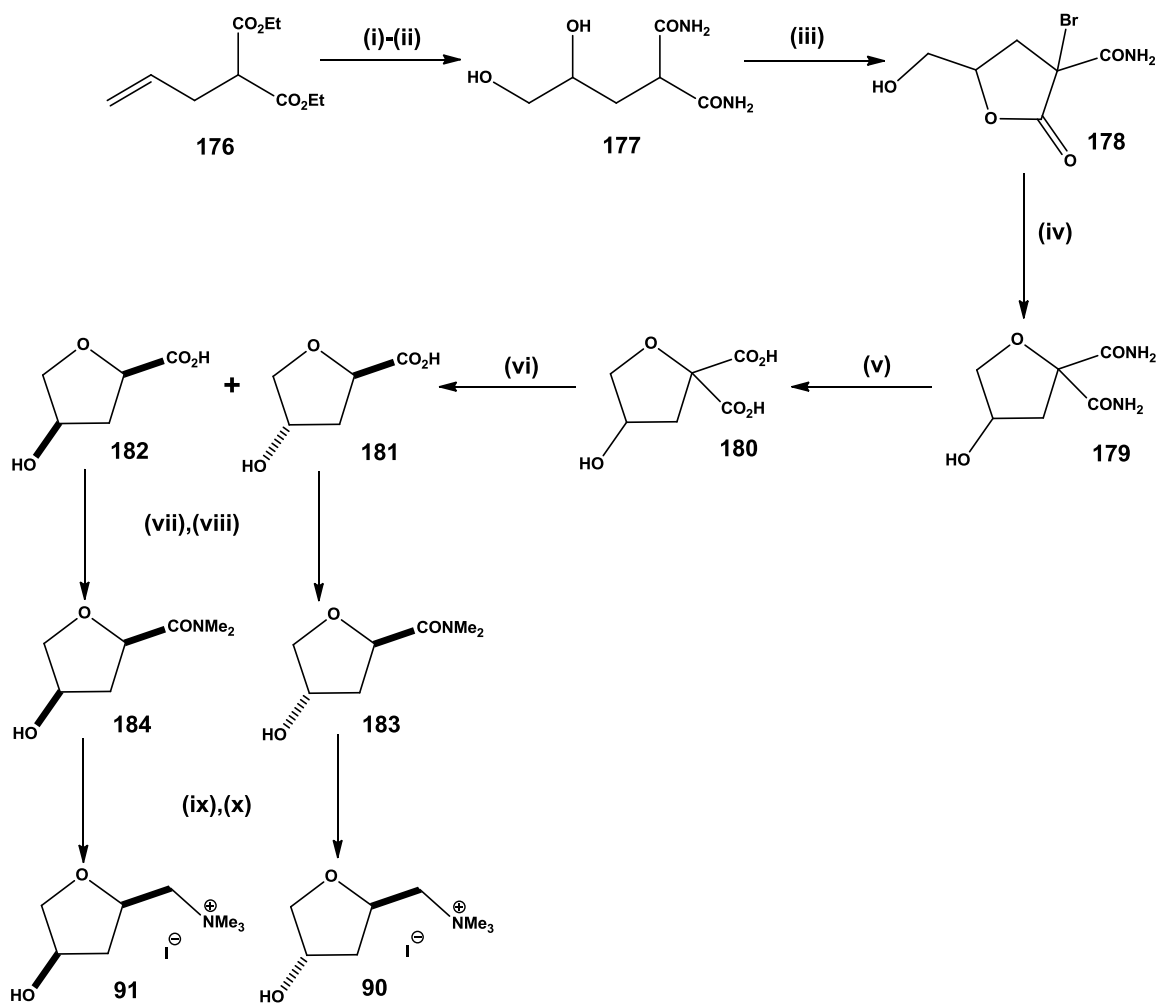
α-Amino acids have also been used in the total synthesis of muscarine,^{87,88} both the (-) and (+) isomers. The synthesis of these isomers was possible with the use of threonine **171**. The synthesis began with a deamination of threonine using sodium nitrite in 6N HCl. This reaction proceeds with the retention of configuration at the C₂ position. Protection of the carboxylic acid as a methyl ester was achieved by treatment with sodium hydrogen carbonate and methyl iodide. The alcohol at the C₂ position was protected as the 2,6-dichlorobenzyl ether by treatment with 2,6-dichloro benzyl trichloroacetimidate in the presence of trifluoromethanesulphonic acid giving **173**. The ester then was reduced with sodium borohydride and calcium chloride in isopropanol. Treatment of the α-chloroalcohol with potassium hydroxide gave the epoxyether **174** with inversion of configuration due an S_N2 reaction. The epoxide was opened regioselectively with vinylmagnesium bromide in the presence of copper iodide. The product was cyclised upon treatment with iodine in acetonitrile. Conversion to the iodide salt of muscarine was achieved when treated with trimethylamine **85** (**Scheme 1.6.14**).



Scheme 1.6.14 Reagents: (i) NaNO_2 , HCl , (ii) NaHCO_3 , MeI , DMF , (iii) 2,6-dichloro benzyl trichloroacetimidate, $\text{CF}_3\text{SO}_3\text{H}$, (iv) NaBH_4 , CaCl_2 , IPA , (v) KOH , Et_2O , (vi) vinylmagnesium bromide, CuI , (vii) I_2 , CH_3CN , (viii) NMe_3 , MeOH

1.6.6 Synthesis of desmethylnuscarine

Matsumoto and co-workers⁸⁹ synthesised analogues of desmethylnuscarine **90** and **91**. Desmethylnuscarine and its analogues have no methyl group at the C-2 position. The authors reacted allylmalonate **176** with formic acid and hydrogen peroxide to yield the diol **176** which when reacted with ammonia in ethanol afforded the diamide. This was reacted with bromine and treated again with ammonia to afford the tetrahydrofuran diamide **179**, which was subsequently hydrolysed to the diacid **180**. This was then heated with water to furnish the tetrahydrofuran carboxylic acids **181** and **182**. The author separated the *cis*- and *trans*-tetrahydrofuran carboxylic acids by selective crystallisation. The *trans*- isomer was obtained as granular crystals while the *cis*- isomer was obtained as rhombic crystals. The different isolated isomers were carried separately through the same sequence of reactions. The authors converted the carboxylic acid to the methyl ester by reaction with diazomethane, followed by treatment with dimethylamine to furnish the dimethylamide. Reduction of the amide followed by quartisation with iodomethane yielded both *cis*- and *trans*- isomers of desmethylnuscarine **90** and **91** in racemic form (**Scheme 1.8.15**).



Scheme 1.6.15 *Reagents:* (i) HCO_2H , H_2O_2 , (ii) NH_3 , (iii) Br_2 , (iv) NH_3 , (v) NaOH , (vi) heat, (vii) CH_2N_2 , (viii) Me_2NH , (ix) LiAlH_4 , (x) MeI .

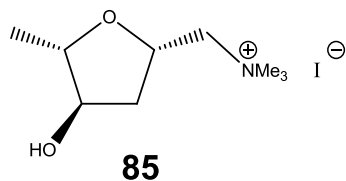
1.7 Project Objectives

The principal objective of this project is to develop a new synthesis of the natural product muscarine **85** and its analogues. This synthesis will be built on a chemoenzymatic approach with initial work concentrating on desmethylnuscarine **92**. Current research in the field of muscarinic ligands is uncovering how these ligands could be used as potential targets to disorders of intestinal motility, cardiac and urinary bladder functions, asthma analgesia, Parkinson's and Alzheimer's diseases.

Substituted 3(2*H*)-furanones will first be synthesised by chemical methodology and these will then be subjected to biotransformation using bakers' yeast to yield the 3-hydroxytetrahydrofurans in an enantioenriched form. This is due to kinetic resolution taking place during the bakers' yeast reduction. These alcohols will then be chemical modified to yield muscarine, desmethylnuscarine, their stereoisomers and analogues.

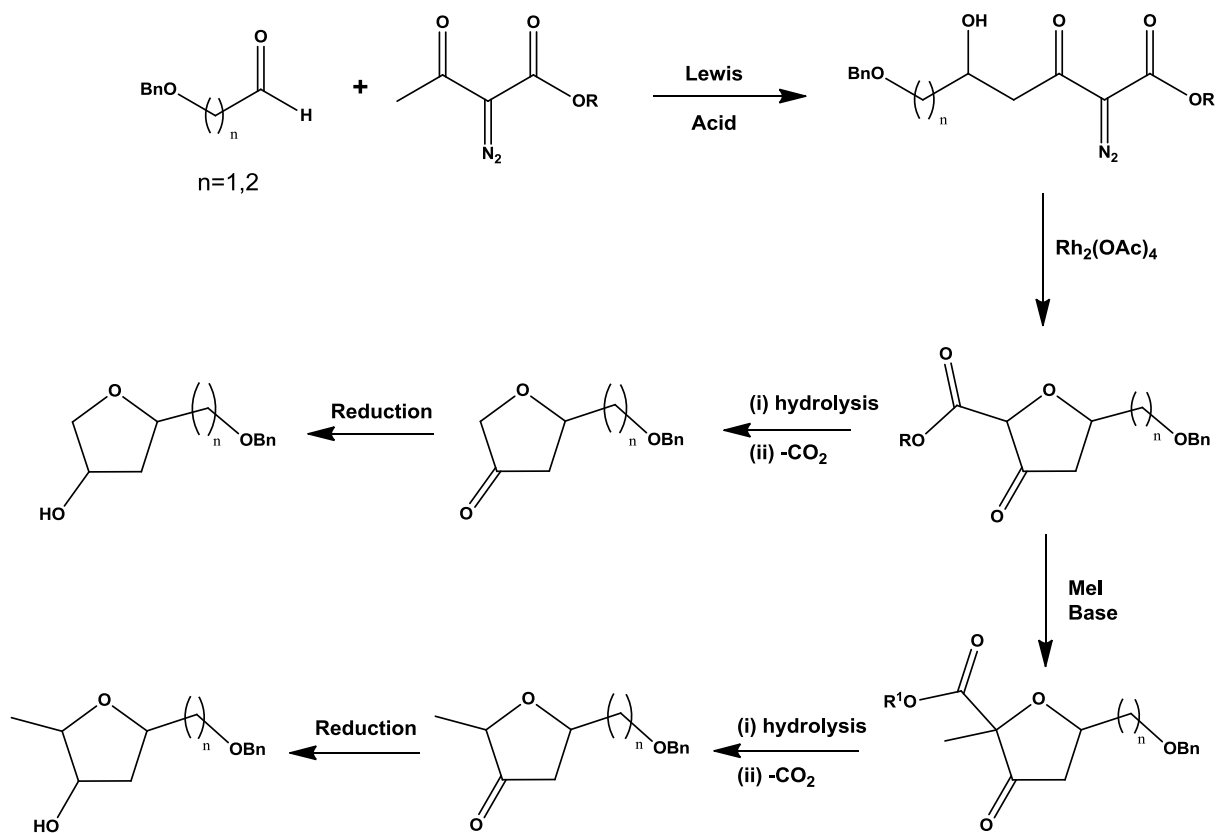
Biocatalysis is a strategy often used in asymmetric synthesis. The use of enzymes and whole cells has been important in the food and drink industries for centuries. However, in the last 30 years, the application of biocatalysts for the synthesis of high value fine chemicals has enjoyed increasing popularity.

Muscarine is the active principle of the poisonous mushroom *Amantia muscaria* and is an agonist of acetylcholine receptors. The synthesis of all stereoisomers of muscarine has been accomplished at this stage by chemical methods and the biological activity of these compounds evaluated. A number of synthetic routes to enantiomerically pure muscarine and its analogues have been published.



This research is focussed on use of a novel biotransformation strategy to access these compounds. The bioreduction involving the bakers' yeast mediated reductions of parent 3(2*H*)-furanones are the key step in the enantioselective synthesis of muscarine and its derivatives. The initial part of the synthesis focused on the generation of 3(2*H*)-furanones, to afford racemic 3-hydroxytetrahydrofurans. These racemic 3-hydroxytetrahydrofurans as references for chiral HPLC analysis of the enantioenriched

products of bakers' yeast reductions (**Scheme 1.7.1**) was carried out by O'Donovan⁹⁰ and Lambe.⁹¹



Scheme 1.7.1

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2 Results and discussion

2.1 Introduction

This chapter describes the synthesis of a number of 3-hydroxytetrahydrofurans and subsequent stereoselective transformations carried out on these compounds. The initial part of this work focused on the synthesis of a number of racemic homologues and analogues of (+)-muscarine and desmethylnuscarine. From the outset, the focus of the work was to introduce chirality to dihydrofuranone derivatives by means of baker's yeast mediated kinetic resolution, thus accessing enantioenriched hydroxytetrahydrofurans. It had been anticipated that the enzymes present in baker's yeast, such as ketoreductases, would catalyse reduction of the carbonyl moiety to the corresponding secondary alcohol. Similar transformations have been reported to proceed in a highly enantioselective manner, resulting in enantiomerically pure ketones and alcohols.^{1,2} Many obstacles had to be overcome in order to achieve this aim; namely 1) a successful aldol addition reaction needed to be developed to provide the diazo substrates required for dihydrofuranone formation; and 2) the identification of a hydrolysis/decarboxylation strategy was necessary to generate the desired 5-alkyl furanone compounds for baker's yeast reductions. Upon obtaining enantiomerically enriched alcohols, stereoinversion of the alcohol using chemical methods would produce the complementary enantiomeric alcohols. Both sets of alcohols would then be carried through to produce (+)-muscarine, desmethylnuscarine and their analogues.

Previous work in our group identified a number of routes for the preparation of racemic 3(2*H*)-furanones **1** (**Figure 2.1.1**) the variation in route was dependant on the substituent pattern of the 3(2*H*)-furanone. The investigations in our laboratories have shown that a Lewis acid catalysed cyclisation of enones of the type **2** shown in **Scheme 2.1.1**, was an efficient route to 4-substituted 3(2*H*)-furanones **3** containing an arylsulfonyl substituent at the 4-position.³

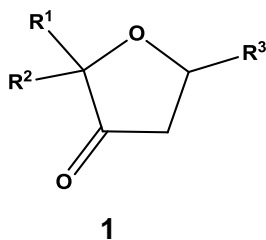
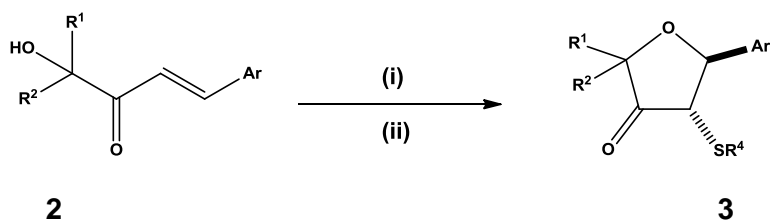
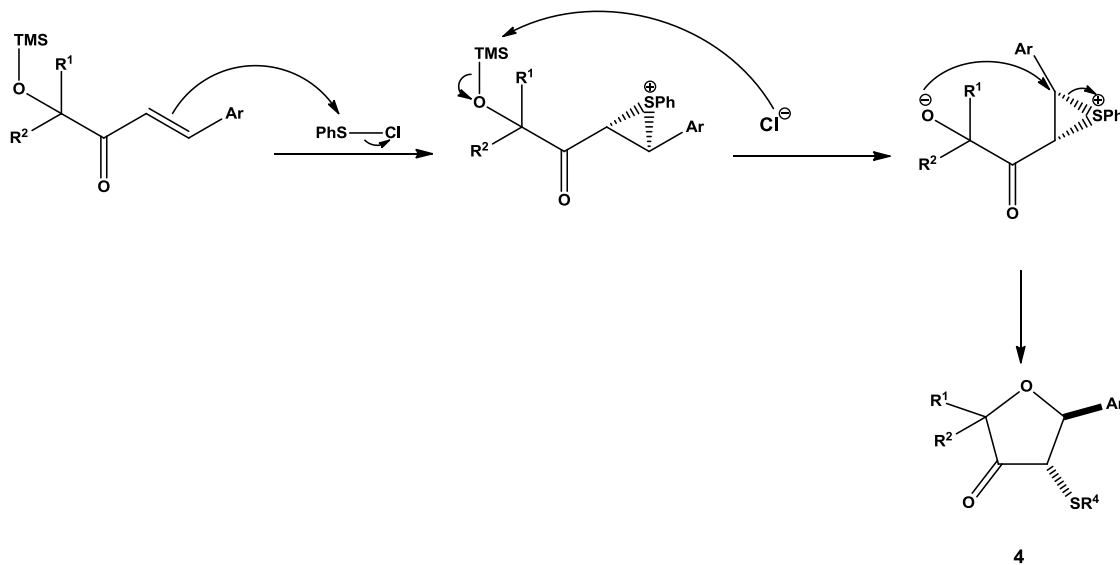


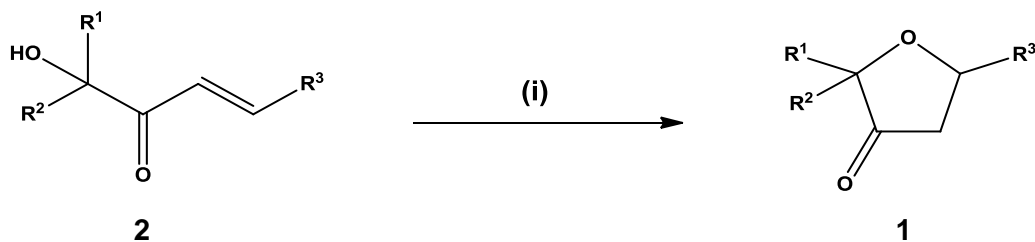
Figure 2.1.1



Scheme 2.1.1 Reagents: (i), TMSCl, DMAP, NEt₃, (ii) ArSCl.



The acid catalysed cyclisation of enones of type **2** provided a convenient route to a variety of 2,2,5-trisubstituted 3(2*H*)-furanones **1** (**Scheme 2.1.2**). Previous investigations showed that the best catalyst and solvent for this cyclisation was *p*-toluenesulfonic acid (PTSA) and 1,2-dichloroethane respectively.⁴



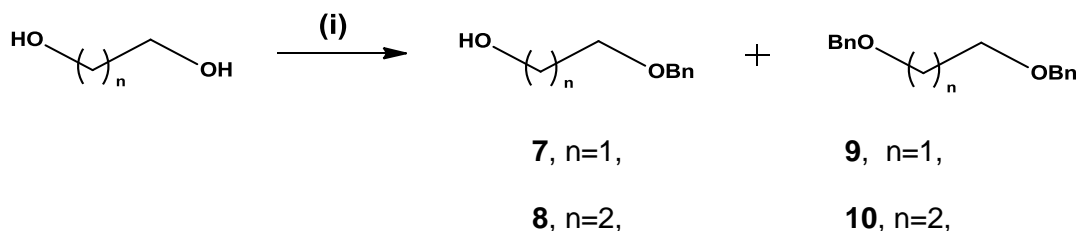
Scheme 2.1.2 Reagents: PTSA

One of the key steps in our synthesis was a carbenoid OH insertion to form a furanone. Carbenes formed *via* rhodium catalysed decomposition of diazo compounds

have been reported to undergo insertion into alcohols, amines and thiol functionalities⁵ as well as double bonds (cyclopropanation).⁶

2.2 Preparation of Aldehydes

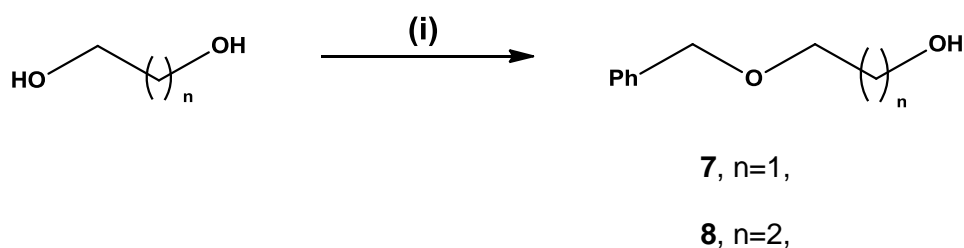
The work began with the synthesis of aldehydes **12**, **13** and **14** from benzyl protected alcohols **7**, **8** and **11**. Benzyloxyacetaldehyde **12** and benzyloxypropanal **13** were prepared from benzyloxyethanol **7** and benzyloxypropanol **8** respectively. The benzyl protecting group was selected because of its stability under various conditions, including both acidic and alkaline media. It can, however, also be cleaved easily and quantitatively using hydrogenolysis. Initially benzyloxyethanol **7** was prepared by reacting ethylene glycol with one equivalent of sodium hydride and benzyl bromide in a mixture of (10 : 7) THF : DMF (**Scheme 2.2.1**). This transformation was carried out using a procedure documented by Wu and co-workers.⁷ Following a 12 h reaction, aqueous work-up and purification by flash chromatography benzyloxyethanol **7** was isolated as a clear liquid in 42% yield. The relatively poor yield of benzyloxyethanol **7** may be explained by the isolation of a less polar compound, whose NMR spectrum was consistent with the structure of the *bis*-benzyl ether. The same procedure was also utilised for the synthesis benzyloxypropanol **8**.



Scheme 2.2.1 Reagents: (i) NaH, BnBr.

In an effort to combat the poor yields obtained in the protection reaction, we revised the reaction conditions. Benzyloxyalkyl alcohols **7** and **8** were synthesised following a procedure which was adopted from Kotsuki and co-workers.⁸ The reaction was carried out using diol (4 eq), potassium hydroxide (2 eq) and benzyl bromide (1 eq). The potassium hydroxide was allowed to dissolve before addition of the benzyl bromide. After heating overnight at 80 °C, the resultant black solution was partitioned across water and ethyl acetate, with the aqueous portion being further extracted with ethyl acetate. Following work-up, crude analysis (¹H NMR) of the product showed no ethylene glycol present. There was no evidence of the *bis*benzylated ethers **9** and **10** in the respective

crude ^1H NMR spectra. The yields of the desired products were increased when compared to the previous procedure by Wu and co-workers. The products were isolated by flash column chromatography. Yields from both methods are given in **Table 2.2.1**.



Scheme 2.2.2 *Reagents:* (i) KOH, BnBr.

For ease of purification of various intermediates of the desmethylnuscarine and its analogues, a *p*-nitrobenzyl group was utilised, as it was thought the nitro group would add crystallinity and provide an option for obtaining intermediates of higher purity by crystallisation.

Diol	Benzyl halide	Solvent*	Mono-alkylated alcohol (yield)	Bis-alkylated diether (yield)
Ethane-1,2-diol (1 eq)	Benzyl bromide	(10:7) THF:DMF	2-(benzyloxy)ethanol (42%)	1,2- <i>bis</i> (benzyloxy)ethane (37%)
Ethane-1,2-diol (4 eq)	Benzyl bromide	-	2-(benzyloxy)ethanol (72%)	Not formed
Ethane-1,2-diol (4 eq)	Benzyl chloride	-	2-(benzyloxy)ethanol (67%)	Not formed
Propane-1,3-diol (1 eq)	Benzyl bromide	(10:7) THF:DMF	3-(benzyloxy)propanol (37%)	1,3- <i>bis</i> (benzyloxy)ethane (34%)
Propane-1,3-diol (4 eq)	Benzyl bromide	-	3-(benzyloxy)propanol (68%)	Not formed
Ethane-1,2-diol (1 eq)	4-nitro-benzyl bromide	(10:7) THF:DMF	No product formed	Not formed
Ethane-1,2-diol (4 eq)	4-nitro-benzyl bromide	-	2-(4-Nitro-benzyloxy)propanol (71%)	Not formed

*Where no solvent is entered, the diol was used as the solvent

Table 2.2.1 Table of yields of mono-alkylated alcohols and Bis-alkylated diether

7, Ar=Ph, n=1,

8, Ar=Ph, n=2,

11, Ar=*p*-NO₂-C₆H₄, n=1,

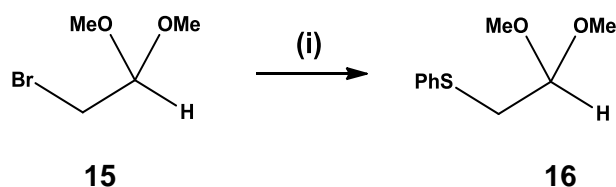
12, Ar=Ph, n=1,

13, Ar=Ph, n=2,

14, Ar=*p*-NO₂-C₆H₄, n=1

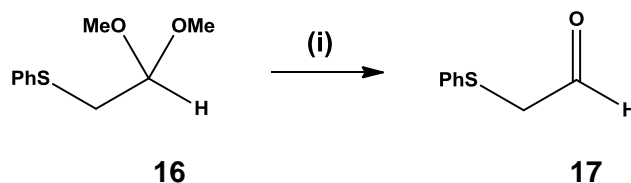
sodium hypochlorite with potassium bromide. This reaction resulted in 63% starting material remaining.

To synthesise sulphur analogues of desmethylnuscarine, thiophenyl analogues of benzyloxyethanal **12** and benzyloxypropanal **13** were employed and were obtained via a different strategy. To synthesis **17**, we first needed to synthesise the acetal **16**. This substrate was made by reacting thiophenol (2.3 eq) with bromoacetaldehyde dimethylacetal **15**, employing sodium ethoxide as base, in refluxing ethanol for 16 h (**Scheme 2.2.6**). The product **16** was isolated following bulb to bulb distillation. The resultant fraction remaining in the round bottom flask which had contained the crude product, following bulb to bulb distillation, was diphenyl disulphide. The diphenyl disulphide originated due to aerobic oxidation of thiophenol. In order for the aldol addition to take place, the dimethyl acetal **15** needed to be hydrolysed to afford the aldehyde **17** (**Scheme 2.2.7**).



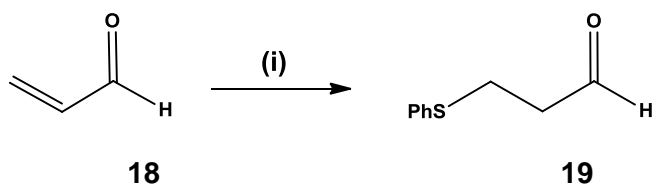
Scheme 2.2.6 Reagents: (i) PhSH, NaOEt, ethanol.

Hydrolysis of **16** using 2M HCl obtained **17** in moderate yield (54%). The reaction was carried out in 1,4-dioxane and isolated following bulb to bulb distillation. 1,4-Dioxane was chosen as a solvent as it is a high boiling polar solvent and therefore could be heated to push the reaction as much to completion as possible.



Scheme 2.2.7 Reagents: (i) 2M HCl, 1,4-dioxane, reflux.

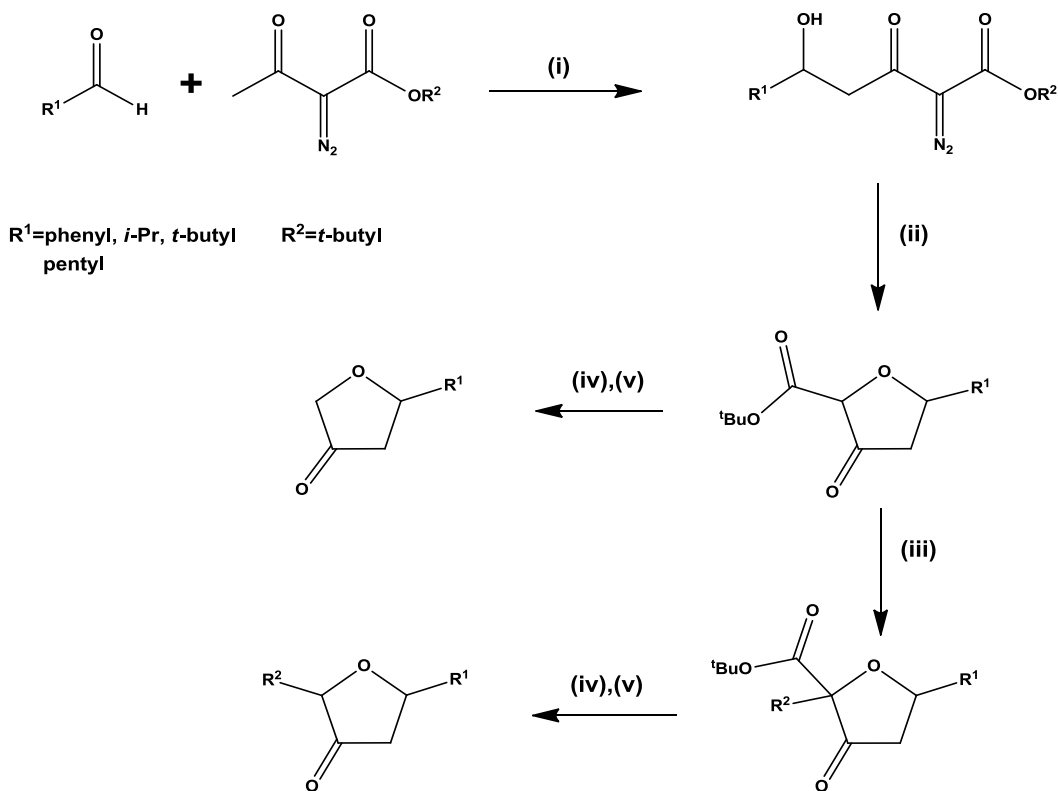
3-Benzenesulphenylpropanal **19** was prepared following treatment of acrolein **18** with thiophenol using trimethylamine in anhydrous chloroform (**Scheme 2.2.8**). Following work-up, 3-benzenesulphenylpropanal **19** was isolated in moderate yield (65%) following bulb to bulb distillation.



Scheme 2.2.8 *Reagents:* (i) PhSH, NEt₃, CHCl₃.

2.3 Preparation of the α -Diazo- β -Keto Esters

To synthesise desmethylnuscarine and its analogues, a reaction sequence outlined by Calter and co-workers⁹ was followed. This synthesis provided the basis for much of our investigations. The key steps in Calter's synthesis of 3(2*H*)-furanones involves an aldol addition reaction of an α -diazo- β -ketoester with an aldehyde, followed by a Rh(II) catalysed O-H insertion. The prerequisite, α -diazo- β -ketoester, was prepared by base catalysed diazo transfer from *p*-toluenesulfonyl azide (tosyl azide) to *t*-butyl acetoacetate. Such reactions have previously been found to proceed in high yield using potassium carbonate/acetonitrile as the base/solvent system.¹⁰ The synthesis is outlined in **Scheme 2.3.1**. Calter's work involves coupling of an α -diazo- β -keto ester to an aldehyde, followed by cyclisation to afford a 2,5-disubstituted-3(2*H*)-furanone which could then be derivatised further.



Scheme 2.3.1 Calters Scheme: *Reagents:* (i) Dichlorophenylborane, NEt_3 , $-78^\circ C$, DCM, (ii) $Rh_2(OAc)_4$, benzene, DCM, reflux (iii) Base, R^2I , (iv) TFA, $0^\circ C$, (v) heat.

During investigation of the key aldol reaction, a range of α -diazo- β -keto esters were synthesised. Initially 2-diazo-3-oxobutyric acid *tert*-butyl ester **20** was synthesised from *t*-butyl acetoacetate. Other α -diazo- β -keto esters were also synthesised for reasons which will be outlined later in this chapter. The diazo transfer reactions were carried out using acetonitrile as the solvent. The appropriate β -keto ester was charged to acetonitrile, then potassium carbonate. The resulting mixture was cooled to 0 °C and tosyl azide was added as a solution in acetonitrile. Upon addition of the tosyl azide, a yellow colour accompanied by a large exotherm was observed. After 2 h at 0 °C hexane and ether were added to precipitate the sulphonamide salts, a side product of this reaction. Following filtration of the suspension, concentration of the filtrate *in vacuo* and wet flash chromatography, using 5 - 10% ethyl acetate in hexane as eluent, the desired products were isolated as bright yellow oils. 2-Diazo-3-oxobutyric acid benzyl ester proved an exception and was isolated as a low melting solid. Yields and selected spectroscopic data associated with these products are shown in **Table 2.3.1**.

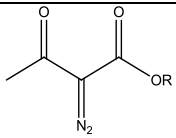
	Yield (%)	$\nu_{\text{max}}/\text{cm}^{-1}$ CN_2	$\delta_{\text{H}}/\text{ppm}$
R = Methyl (21)	62	2142	2.46 (3H, s, OCH_3), 3.85 (3H, s, OCH_3).
R = Ethyl (22)	75	2140	1.31 (3H, t, OCH_2CH_3), 2.48 (3H, s, CH_3), 4.32 (2H, q, OCH_2CH_3).
R = <i>t</i>-Butyl (20)	75	2133	2.46 (3H, s, CH_3), 1.53 [9H, s, $\text{C}(\text{CH}_3)_3$]
R = Benzyl (23)	79	2143	2.48 (3H, s, CH_3), 5.27 (2H, s, OCH_2Ph), 7.35-7.38 (5H, m, ArH).

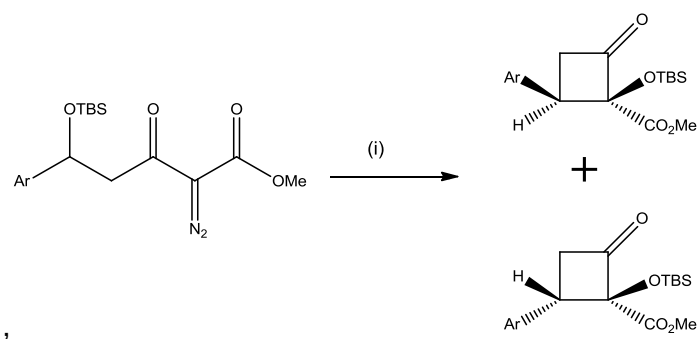
Table 2.3.1 Table of α -diazo- β -keto esters and spectroscopic data

The IR spectra of the various diazo β -keto esters show strong absorbances at approximately 2130 - 2145 cm^{-1} . The IR spectrum of 2-diazo-3-oxobutyric acid benzyl ester shows both carbonyl absorbances for both the ketone and the ester, at 1649 and 1709 cm^{-1} respectively, as well as showing an absorbance for the diazo functionality at

2145 cm^{-1} . The carbonyl functionalities absorb at low wavenumbers due to the extended conjugation between the ketone, ester and the diazo group. Due to this conjugation, the molecule has adopted a planar configuration. The IR spectrum for **23** also shows characteristic absorbances for a mono substituted phenyl ring at 701 and 749 cm^{-1} . It was also noted that the signal corresponding to the diazo carbon was not observed from the ^{13}C spectra for all the compounds prepared. The absence of this signal can be attributed to the prolong relaxation times associated with diazo carbon signals.

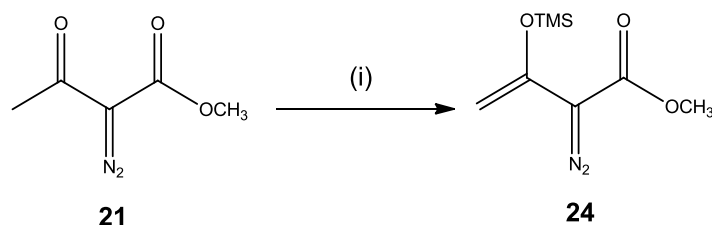
2.4 Preparation of Silyl Enol Ethers

One route which was undertaken to gain access to the desired 3(2*H*)-furanone was a procedure outlined by Doyle and co-workers.¹¹ Herein the aldol addition product (see **scheme 2.4.1**) contained a secondary silyl ether. The aldolisation addition product synthesised by Doyle was similar to the aldol addition intermediate in our synthesis, prior to rhodium(II) mediated cyclisation. To carry out this preparation Doyle and co-workers used a silyl enol ether derivative of an α -diazo- β -keto ester in a Mukaiyama addition reaction. Doyle and co-workers synthesised a number of the Mukaiyama addition products, which were subsequently cyclised to afford functionalised cyclobutanoates (**Scheme 2.4.1**).



Scheme 2.4.1 Reagents: (i) $Rh(OAc)_4$.

Trimethylsilyl trifluoromethanesulfonate was employed as the silylating reagent in the synthesis outlined Doyle and co-workers, however due to the expense of this reagent the reaction would be inefficient from atom economy perspective. As a result, various attempts to synthesise silyl enol ethers were made from more readily available silylating reagents. These included trimethylsilyl chloride, triethylsilyl chloride and *tert*-butyldimethylsilyl chloride. These attempts involved the use of a variety of bases, such as *n*-butyl lithium, lithium di-*isopropyl*amide, potassium *tert*-butoxide, di-*isopropyl*ethylamine, DABCO and triethylamine amongst others. The α -diazo- β -keto ester was recovered when mild bases were used. Successful synthesis of TMS silyl enol ethers was achieved when following a procedure outlined by Calogeropoulou and co-workers.¹² This procedure uses sodium iodide to exchange the iodide for the chloride in the trimethylsilylchloride, in a Finkelstein reaction (**scheme 2.4.2**).



Scheme 2.4.2 Reagents: (i) TMSCl, NEt₃, NaI.

The α -diazo- β -keto ester was dissolved in acetonitrile followed by addition of sodium iodide and triethylamine. Trimethylsilylchloride was added and a colour change of yellow to orange was observed. The work-up procedure which Calogeropoulou and co-workers¹² outlined was attempted, but the desired product was not isolated. Trimethylsilyl enol ethers decomposed upon contact with water to regenerate the starting materials. Optimisation of the reaction which involved investigation of alternative work-ups was undertaken. Following a 2 h reaction, hexane was added to the reaction mixture. Hexane is immiscible with acetonitrile, forms a biphasic mixture. The acetonitrile layer is sufficiently polar to allow for the salts to dissolve while hexane was used to extract the silyl enol ether. The combined hexane layers were filtered through a plug of celite®. The filtrate was concentrated *in vacuo*, however, not all of the hexane could be distilled as this would cause decomposition of the silyl enol ether. The formation of triethylsilyl analogues were found to be stable to the aqueous work-up. The reaction was monitored by I.R. spectroscopy. The reaction was found to be completed when a shift from 2133 to 2105 cm⁻¹ was observed and the disappearance of the peak in the 1660 cm⁻¹ region. The lowering of the wavenumber was due to the extended conjugation in the molecule.

The ¹H NMR analysis showed the disappearance of a 3H singlet and the appearance of two sets of doublets, one set at approximately 4.25 ppm and the other set at approximately 5 ppm. Both protons have a coupling constant of 2 Hz which is indicative of geminal coupling. The two protons, even though attached to the same carbon, are magnetically inequivalent. The proton *cis* to the silyloxy functional group appears further downfield at 5 ppm due to the deshielding effect of the oxygen and the proton *cis* to the diazo functional group appears up at 4.2 ppm. In **Figure 2.4.1**, a ¹H NMR spectra of methyl 3-*tert*-butyldimethylsilyloxy-2-diazobut-3-enoate is shown, which includes an expansion highlighting the region between 4.1 and 5.1 ppm, where the chemical shifts of the silyl enol protons appear. The formation of *tert*-butyldimethylsilyl analogues was unsuccessful when *tert*-butyldimethylsilyl chloride was used in the protocol. Starting

materials were recovered from the reaction. The formation of the TMS and TES analogues of the silyl enol ethers were high yielding.

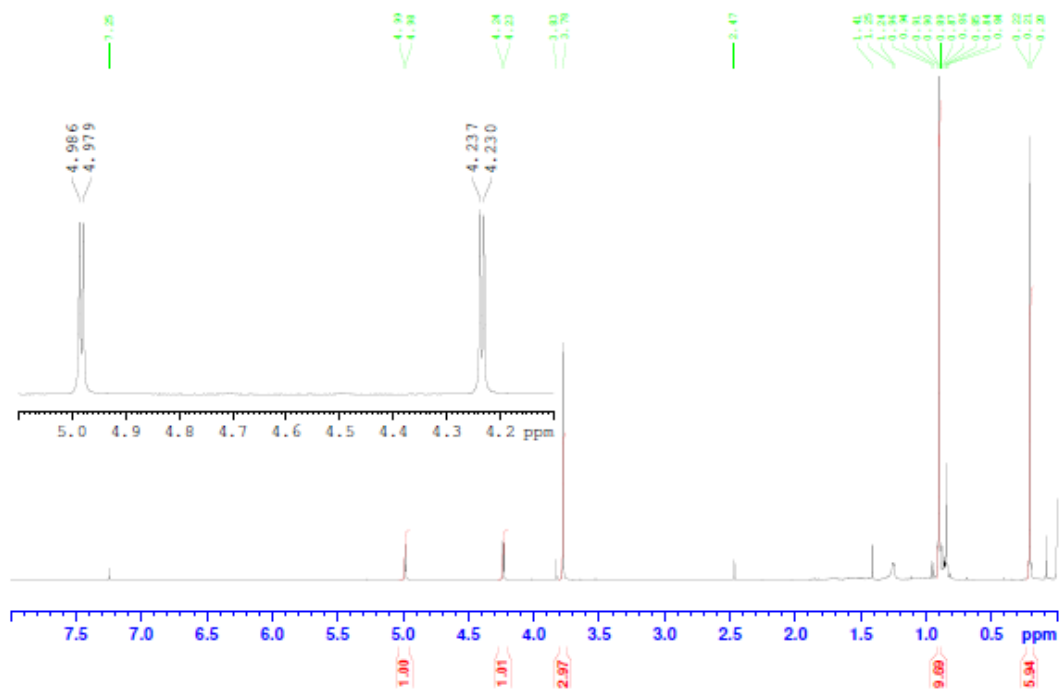


Figure 2.4.1 ^1H NMR of methyl 3-*tert*-butyldimethylsilyloxy-2-diazobut-3-enoate **25**.

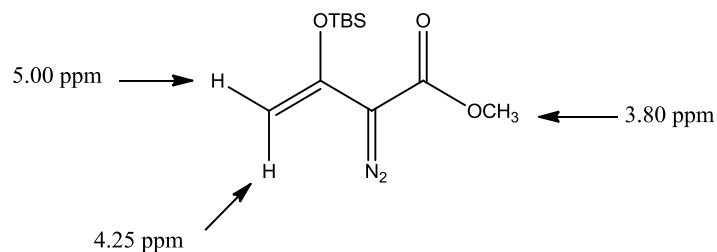
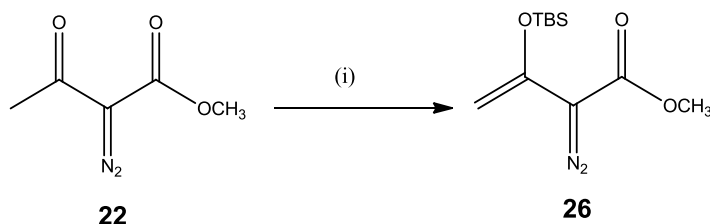


Figure 2.4.2. δH of selected resonances observed in the ^1H NMR spectrum of **25**

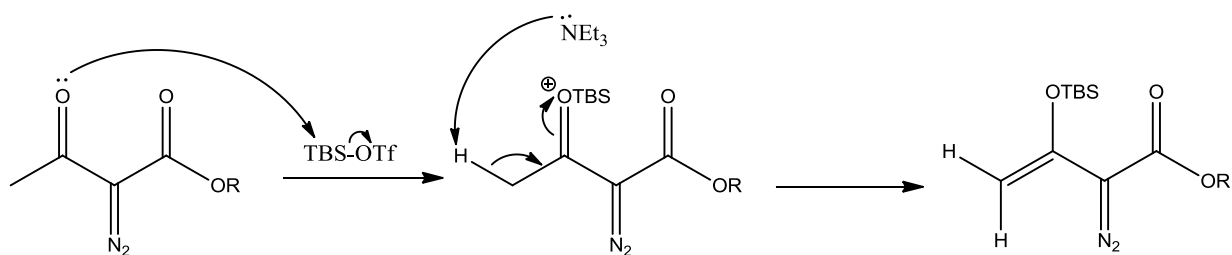
The *tert*-butyldimethylsilyl enol ether analogues were synthesised using *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of trimethylamine, following a procedure outlined by Davies and co-workers¹³ (**Scheme 2.4.3**). *tert*-Butyldimethylsilyl trifluoromethanesulfonate was added dropwise to a stirring solution of triethylamine and

α -diazo- β -keto ester in DCM at 0 °C. The silylating reagent was added dropwise due to the large exotherm which occurs upon silylation. In instance where *tert*-butyldimethylsilyl trifluoromethanesulfonate was added too quickly, decomposition of the diazo functionality was observed. This is most likely attributed to the exothermic nature of the reaction.

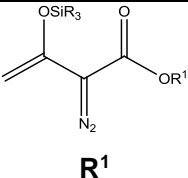


Scheme 2.4.3 Reagents: (i) TBDMSOTf, NEt₃, DCM.

The desired silyl enol ethers were isolated in good yield (**Scheme 2.4.4**). All of the silyl enol ethers were used without further purification. Attempted purification by column chromatography or distillation led to decomposition resulting in recovery of the starting material. Yields of silyl enol ethers are outlined in **Table 2.4.1**.



Scheme 2.4.4

 R¹	SiR	Yield (%)	$\nu_{\text{max}}/\text{cm}^{-1}$ N₂
Methyl	TMS (26)	quantative*	2102
	TES (27)	78	2103
	TBDMS (25)	92	2102
Ethyl	TMS (28)	quantative*	2102
	TES (29)	74	2104
	TBDMS (30)	89	2102
<i>tert</i>-Butyl	TMS (31)	quantative*	2102
	TES (32)	85	2099
	TBDMS (33)	92	2104
Benzyl	TMS (34)	quantative*	2100
	TES (35)	79	2103
	TBDMS (36)	87	2103

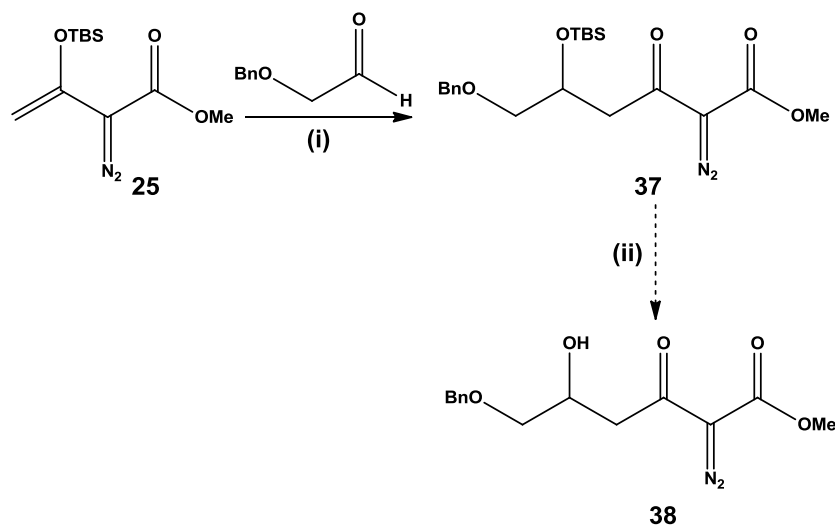
*No detectable TMS silyl enol ethers of α -diazo- β -keto ester were present in the acetonitrile

Table 2.4.1 *Table of silyl enol ethers and selected spectroscopic data*

2.5 Mukaiyama Aldol Addition

Following a publication by Doyle and co-workers¹¹ which outlined the synthetic scheme for preparation of highly functionalised cyclobutanoates, as described in **Scheme 2.4.1**, the next step of our chosen synthesis involved reaction of the silyl enol ether with the appropriate aldehyde. Only recently have methods involving Lewis acids such as boron(III)⁹ and titanium(IV)¹⁴ been used for the reaction of diazoacetates with aldehydes. Enolates of diazoacetates underwent aldol addition with aldehydes, however, stoichiometric amounts of the Lewis acids were required to achieve conversion. The majority of these reactions were conducted at -78 °C.

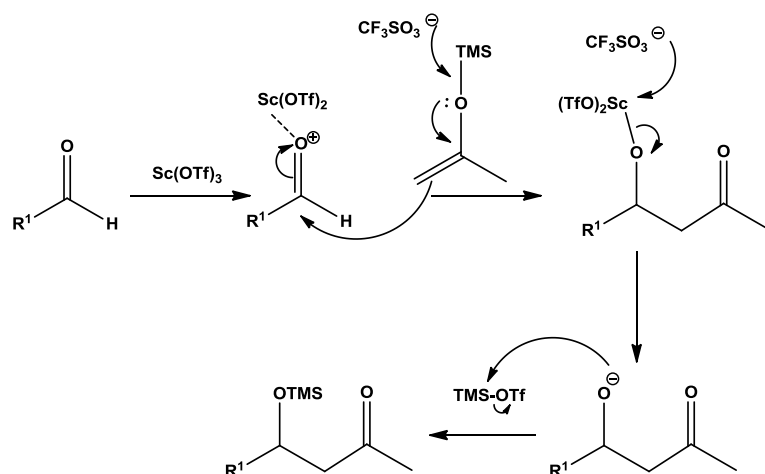
According to Doyle and co-workers,¹¹ lanthanide triflates, especially scandium(III) triflate, in low catalytic loading are highly effective in Mukaiyama aldol addition reactions of methyl 3-(*tert*-butyldimethylsilyloxy)-2-diazobut-3-enoate with both aliphatic and aromatic aldehydes and aromatic imines at room temperature. Following addition to the aldehyde, Doyle and co-workers decomposed the diazo functional group of the Mukaiyama aldol adducts in the presence of 1.0 mol% rhodium(II) acetate, which led to the formation of highly substituted cyclobutanones in high yields and high diastereoselectivities (**Scheme 2.4.1**). In a subsequent paper, Doyle and co-workers¹⁵ generated asymmetric Mukaiyama addition products of the type outlined in **Scheme 2.5.1** in high enantiomeric excess. The authors used chiral promoters, such as binaphthyl type ligands in the presence of potassium fluoride to induce chirality in the addition product. Silver fluoride was chosen as the Lewis acid over copper and titanium Lewis acids. As an alternative synthesis to the intermediate **38**, it was envisaged to synthesise **37** and then deprotect the secondary silyl ether to afford the aldol product, which could then be cyclised to the desired 3(2*H*)-furanone.



Scheme 2.5.1 Reagents: (i) Sc(OTf)₃ or Zn(OTf)₂, (ii) Source of F⁻

The Mukaiyama addition reactions were first attempted using TMS enol ethers. These were the first silyl enol ether prepared in our laboratory. Doyle and co-workers^{11,15} outlined procedures which utilised Lewis acids such as silver(I) triflate, copper(II) triflate, zinc(II) triflate, scandium(III) triflate amongst others as catalysts for this reaction. However for the purpose of this work a variety of alternatives were investigated. These include copper(II) triflate, scandium(III) triflate, zinc(II) chloride, aluminium(III) chloride and boron(III) trifluoride, which were used both in catalytic and stoichiometric quantities. In each case the desired product was not formed. THF and DCM were used as solvents for the reactions as Doyle and co-workers had also utilised these solvents. All reactions were carried out under anhydrous conditions. Unfortunately, none of the aldol addition products were obtained using variations of this protocol. Possible residual chloride, present in the silyl enol ether, was identified as a potential contributory factor.

The Lewis acid functions by co-ordination to the carbonyl group of the aldehyde, the triflate activates the silyl enol ether generating a nucleophile. This nucleophile undergoes an aldol addition to the aldehyde generating a ketone, an oxyanion and TMSOTf. The alkoxide then reacts with TMSOTf to generate secondary silyl ether (**Scheme 2.5.2**).



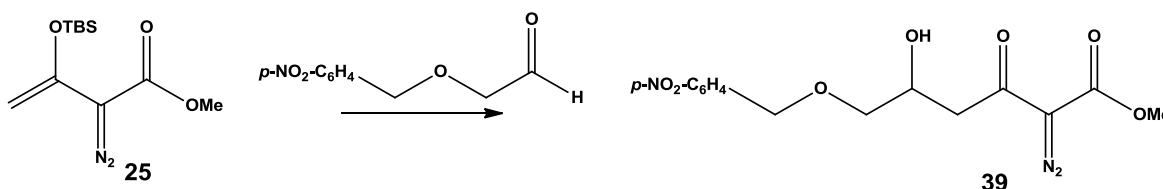
Scheme 2.5.2

Following the initial unsuccessful reactions carried out on TMS derived silyl enol ethers, TBS and TES silyl enol ether derivatives were synthesised and subsequent work focused on these analogues. The reactions focused on the use of scandium(III) triflate as the chosen Lewis acids. Doyle and co-workers had identified scandium(III) triflate to be high yielding at low catalyst loading. TBS enol ethers were used initially as they were the most stable to hydrolysis when compared to TES and TMS enol ethers. Later experiments utilised TES enol ethers as they were more economical alternative. Exact conditions outlined by Doyle and co-workers¹¹ were followed, however the reactions were not successful. This could not be explained as the aldehydes were repurified using bulb to bulb distillation. The silyl enol ethers could not be purified further, however additional care was taken during the work-up. The Mukaiyama reactions were repeated and the reactions were followed by NMR. NMR analysis after 4, 8, and 20 h showed some hydrolysis of the silyl enol ether and no evidence for formation of the desired product. This partial hydrolysis could have hindered the Mukaiyama cycle, and may be attributed to trace amounts of water present in the DCM or catalyst.

When a solvent screen was undertaken, it was found that dry THF gave the desired Mukaiyama addition product. Hexane, DMSO, DMF and chloroform were also screened as possible solvents. Doyle had reported the use of THF, however, he noted that when DCM was used as the solvent a higher yield was achieved. Subsequently we investigated the use of scandium(III) triflate as Lewis acid and THF as solvent of choice. 3 - 5 mol% catalyst loading was found to be the optimum to afford the Mukaiyama aldol addition product. The silyl enol ether and the appropriate aldehyde, both as solutions in

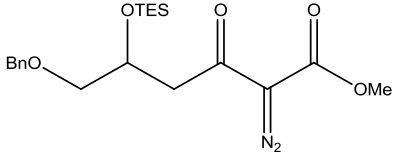
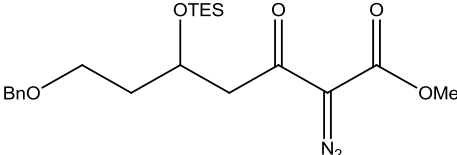
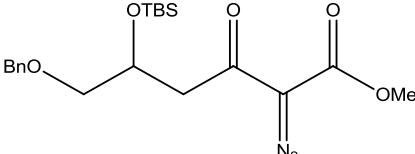
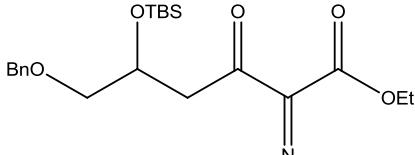
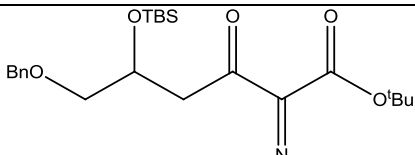
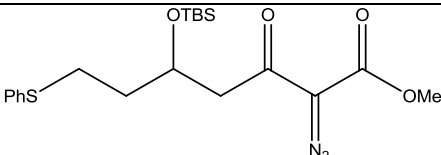
THF, were added simultaneously to a stirring suspension of scandium(III) triflate and the mixture were allowed to stir overnight. After 2 h, a colour change from orange to light yellow was observed. NMR analysis of the reaction mixture after 2 h indicated about 30 - 50% formation of the Mukaiyama aldol addition product. Upon completion of the reaction, IR analysis of the crude mixture showed a shift from $\sim 2105\text{ cm}^{-1}$ to $\sim 2133\text{ cm}^{-1}$. The reaction was filtered through celite[®] which was subsequently washed with diethylether. Flash column chromatography using 5% ethyl acetate in hexane afforded the desired product as a yellow oil.

When 2-(*para*-nitrobenzyl)acetylaldehyde **14** and methyl 3-*tert*-butyldimethylsilyloxy-2-diazobut-3-enoate **25** were reacted in the presence of scandium(III) triflate, only the deprotected aldol addition product (**Scheme 2.5.3**), 6-(4-nitrobenzyloxy)-2-diazo-5-hydroxy-3-oxohexanoic acid methyl ester **39**, was recovered. The low yield could be a result of the nitro group on 2-(*para*-nitrobenzyl)acetylaldehyde **17** chelating to the scandium triflate halting or hindering the catalytic cycle and reducing the yield.



Scheme 2.5.3 Reagents: (i) Sc(OTf)₃, THF.

As touched on earlier, Doyle and co-workers¹⁵ utilised zinc(II) triflate as the Lewis acid for this group of reactions. Zinc(II) triflate is a cheaper catalyst to scandium(III) triflate while affording similar yields. Doyle used this zinc catalyst to construct highly functionalised diazoacetoacetates *via* catalytic Mukaiyama-Michael reactions. α -Diazo- β -keto esters were converted to silyl enol ether **25**, which was subsequently reacted with various α,β -unsaturated ketones to afford the desired Michael addition product. When silyl enol ethers were reacted with aldehydes **13** and **14**, reactions ran with zinc(II) triflate as the Lewis acid gave higher yields in DCM, as opposed to THF as solvent. All reactions followed a similar course, with similar observations. All reactions were monitored using IR and the disappearance of the diazo peak for the silyl enol ether peak at 2105 cm^{-1} and the appearance of the diazo peak at 2133 cm^{-1} were observed.

Mukaiyama Aldol Addition Product	Catalyst*	Isolated Yield (%)
 <p>40</p>	Sc(OTf) ₃	68
	Zn(OTf) ₂	60
 <p>41</p>	Sc(OTf) ₃	58
	Zn(OTf) ₂	73
 <p>37</p>	Sc(OTf) ₃	69
 <p>42</p>	Sc(OTf) ₃	65
 <p>43</p>	Sc(OTf) ₃	60
 <p>44</p>	Zn(OTf) ₂	43

*When Sc(OTf)₃ was used, THF was solvent the of choice, when using Zn(OTf)₂, DCM was the chosen solvent using Doyle's procedure.

Table 2.5.1 Table of aldol products **37** and **40 – 44**.

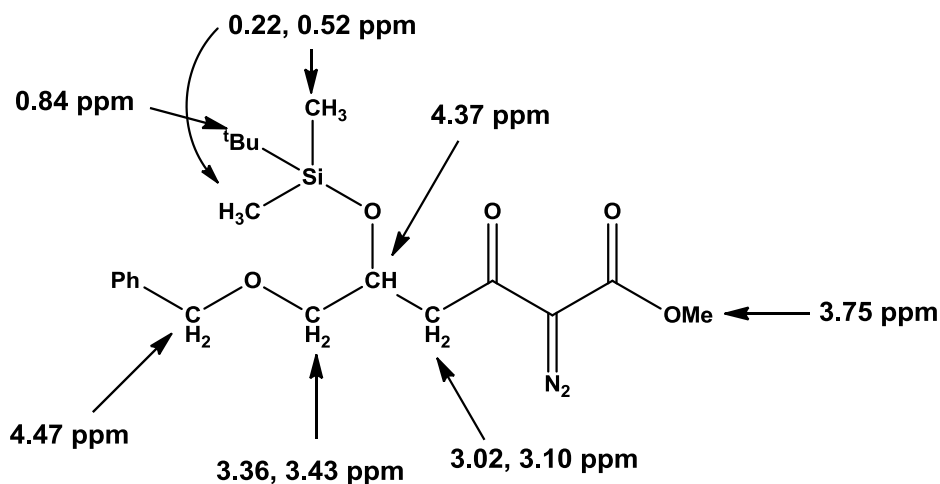


Figure 2.5.1. δH of selected resonances observed in the 1H NMR spectrum of **37**

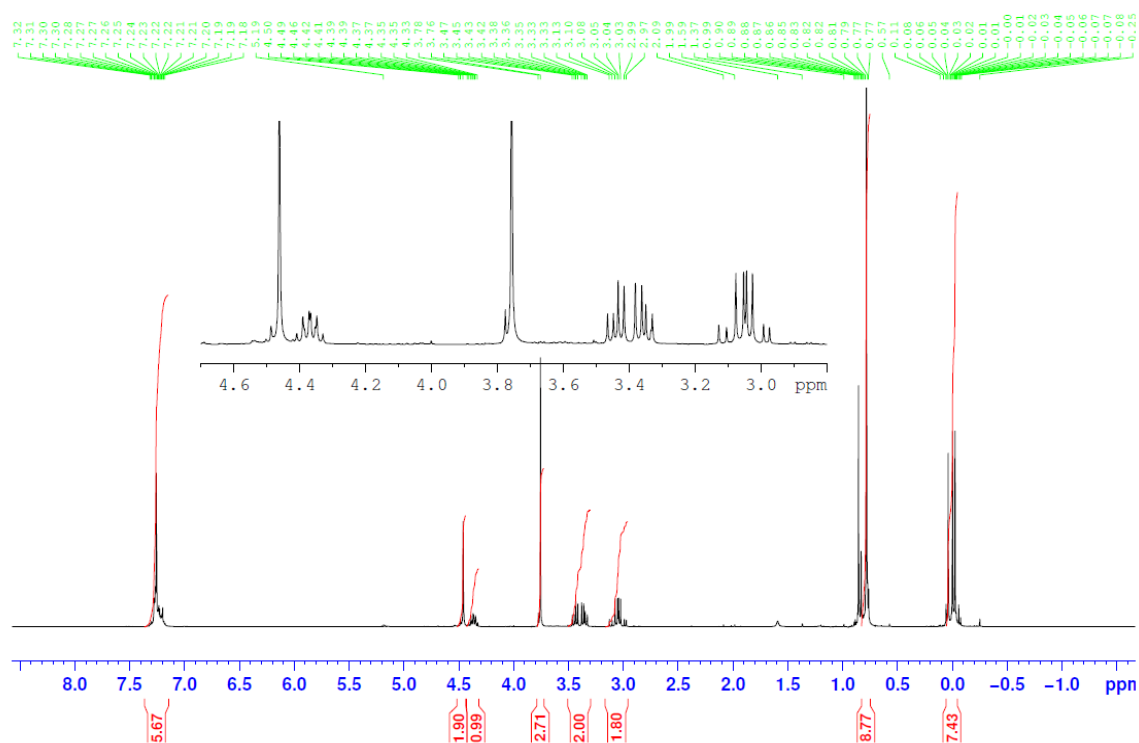


Figure 2.5.2 1H NMR of methyl 6-(benzyloxy)-5-tertbutyldimethylsilyloxy-2-diazo-3-oxohexanoate **37**.

Shown in **Figure 2.5.2** is the 1H NMR spectrum of methyl 6-(benzyloxy)-5-tertbutyldimethylsilyloxy-2-diazo-3-oxohexanoate **37**. Two ABX systems are present in the molecule, arising from the C4 and C6 protons, which appear as doublets of doublets due

to their diastereotopic nature. The protons attached to the C6 carbon appear more downfield, at 3.4 ppm, due to the deshielding nature of the benzyl ether group. While protons attached to the C4 carbon appear more upfield at 3.1 ppm. The two sets of protons attached to the C4 and C6 carbons are both coupled to the same proton, the C5 proton.

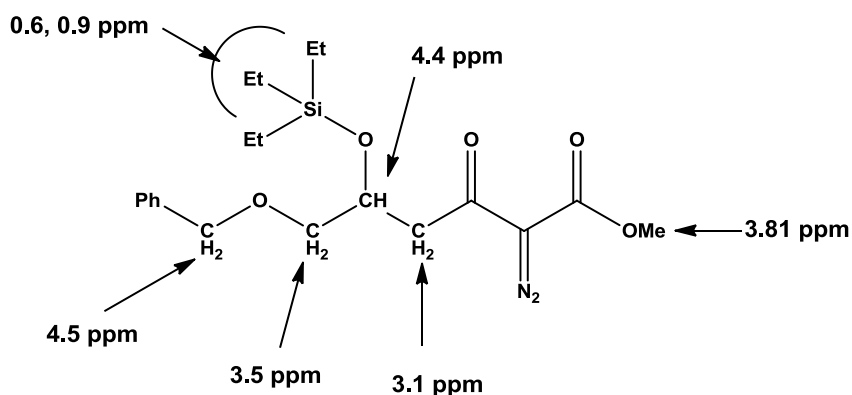


Figure 2.5.3. δH of selected resonances observed in the 1H NMR spectrum of **40**.

In **Figure 2.5.4**, a 1H NMR spectrum of methyl 6-(benzyloxy)-5-(triethylsilyloxy)-2-diazo-3-oxohexanoate **40**, the ABX system of the C4 protons does not appear as a doublet of doublets but instead appears as a doublet. The protons attached to the C6 carbon show a splitting pattern consistent with the diastereotopic nature of the protons and appear downfield of the C4 protons.

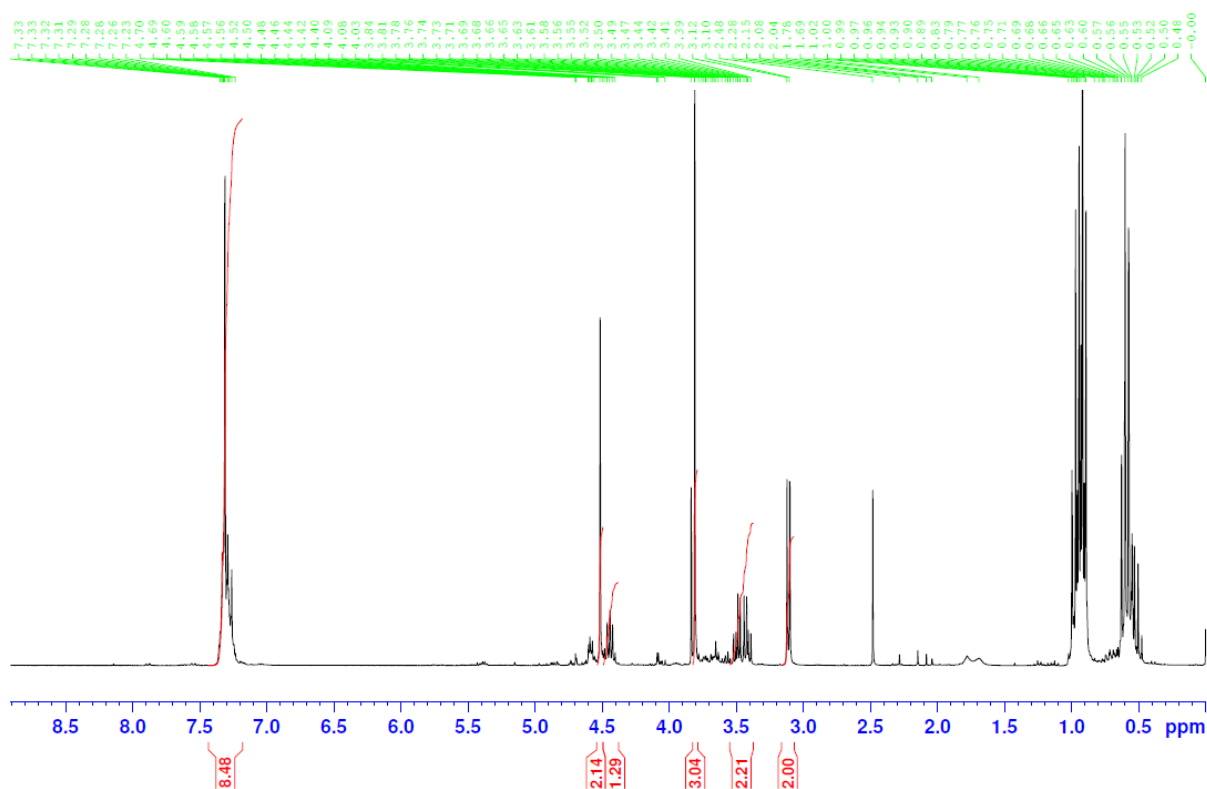


Figure 2.5.4 ^1H NMR of methyl 6-(benzyloxy)-5-triethylsilyloxy-2-diazo-3-oxohexanoate **40**.

The nominal mass spectrum of compound **40** shows a parent ion of 407 ($\text{M}+\text{H}^+$) and a daughter ion, 293 $[\text{M}-(\text{TES})+2\text{H}]^+$ following hydrolysis of the triethylsilyl ether. Another daughter peak was observed at 265 $[\text{M}-\text{TES}-\text{N}_2+2\text{H}]^+$, which follows loss of nitrogen. This spectrometric pattern was evident for all analogues and homologues of methyl 6-(benzyloxy)-5-triethylsilyloxy-2-diazo-3-oxohexanoate **42**, hydrolysis of the silyl ether followed by loss of nitrogen (N_2).

2.6 Preparation of Aldol Addition Products

During the course of this work a variety of routes for the synthesis of aldol intermediates were explored. Initially, one of the key steps in a synthetic procedure outlined by Calter and co-workers¹⁰ was utilised to synthesise the 3(2*H*)-furanone **46**. This method involved the use of dichlorophenylborane as a Lewis acid for the aldol addition reaction (**Scheme 2.6.1**). Calter and co-workers reported the synthesis of compounds of type **47**. Molecules of this type have recently been reported as intermediates in the synthesis of C-nucleosides.¹⁷

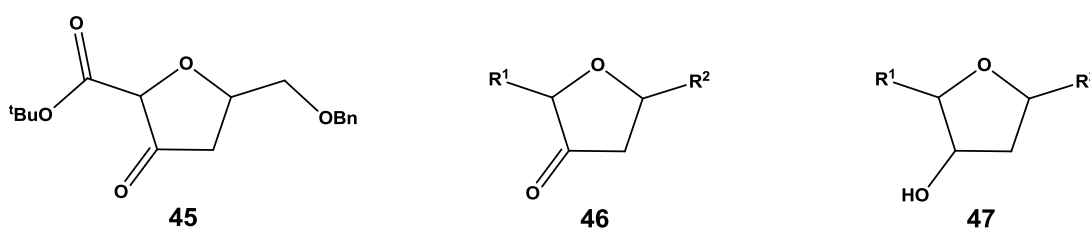
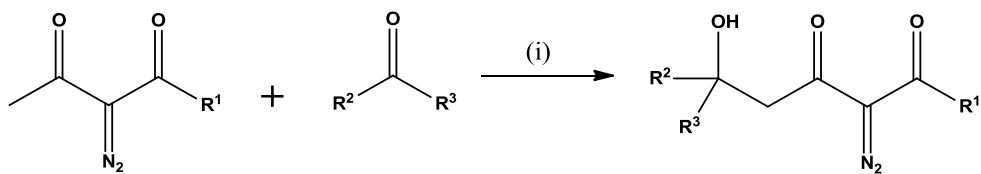


Figure 2.6.1

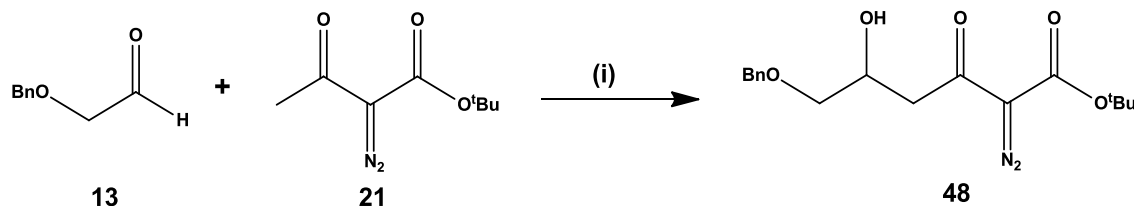
C-Nucleosides are known to be active anti-cancer and anti-HIV agents. Therefore, the development of efficient routes to compounds such as **47** in an enantiomerically pure state is considered to be potentially highly valuable.



Scheme 2.6.1 Reagents: (i) dichlorophenylborane, NEt₃.

O'Donovan¹⁸ and Lambe¹⁹ utilised dichlorophenylborane as the Lewis acid of choice for the aldol addition of 2-benzyloxyacetaldehyde **12** and *tert*-butyl 2-diazo-3-oxobutyric acid **21** (**Scheme 2.6.2**). Following procedures outlined by Calter and O'Donovan, yields of 49 - 65% were achieved in the coupling of **12** and **21**. Esters of 2-diazo-3-oxobutyric acid **20-23** were dissolved in DCM, cooled to -78 °C and triethylamine was added. During this reaction when dichlorophenylborane was added, a dark red colour was observed. This dark colour persisted even after the addition of the aldehyde.

It was important that all reagents used in the experiments were dried to the highest standard. Dichlorophenylborane is a moisture sensitive reagent and fumes, as a result, the reagent was handled under a nitrogen. The reaction was quenched at -78 °C with pH 7 buffer and methanol, then allowed to warm to 0 °C. The products were isolated following column chromatography and were recovered in moderate yields (**Table 2.6.1**). Calter and co-workers had noted that if the reaction was not quenched at -78 °C and left to warm to room temperature, it would lead to a drop in yield due to decomposition of the diazo functional group. The reaction goes *via* co-ordination of the Lewis acid to the α -diazo- β -keto esters allowing for deprotonation of the α -carbon by triethylamine to afford intermediate **49**.



Scheme 2.6.2 Reagents: (i) PhBCl_2 , NEt_3 , DCM -78 °C.

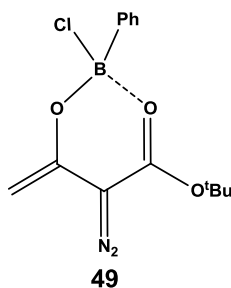


Figure 2.6.2

It was desirable to find an alternative reagent to dichlorophenylborane, as it is was a highly expensive Lewis acid. To this end other Lewis acids were screened, such as aluminum trichloride, zinc(II) chloride, freshly fused zinc(II) bromide, magnesium(II) chloride, titanium(IV) diisopropoxide dichloride (which was prepared from a disproportion reaction of titanium(IV) tetrachloride and titanium(IV) isopropoxide in hexane), triethylborane, boron trifluoride, boron trichloride amongst others. An aldol addition

reaction was also carried out with titanium(IV) tetrachloride used as the Lewis acid. This reaction was conducted in accordance with the procedure laid out by Deng and co-workers,²⁰ requiring the reaction to be run at -78 °C. Addition of the titanium(IV) tetrachloride resulted in a black colour. TLC and IR analysis of the mixture indicated that the α -diazo- β -keto ester **20** had not decomposed but remained fully intact. 2-(Benzyoxy)acetaldehyde **12** was then added to the reaction mixture. Following work-up no formation of the aldol addition product **48** was identified nor was there any 2-(benzyoxy)acetaldehyde **12** present in the crude ¹H NMR spectrum.

2-(Benzyoxy)acetaldehyde **12** is an unstable aldehyde and had to be freshly prepared before each reaction in which it was employed. The unstable nature of the aldehyde could be attributed to the α -enolisable protons of the carbonyl group. These protons are quite acidic which facilitates formation of an enol or enolate more readily. Following column chromatography, none of the aldehyde was recovered.

It was found that in addition to dichlorophenylborane, methyl aluminium dichloride also afforded the aldol addition product. As a result, the procedure outlined by Calter was adapted to use methyl aluminium dichloride. However, yields for the methyl aluminium dichloride mediated aldol additions were found to be significantly lower than the corresponding dichlorophenylborane mediated reactions (**Table 2.6.1**). This set of reactions established a criteria for the Lewis acid catalyst for all subsequent aldol addition reactions. This criteria stipulated that a Group(III) metal must possess a halide, such as a chloride, as well as one alkyl or aryl group.

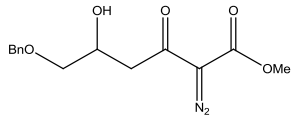
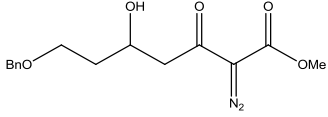
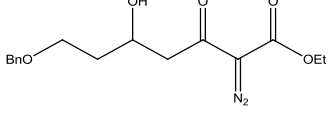
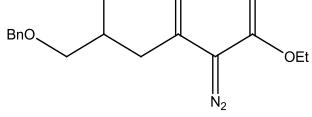
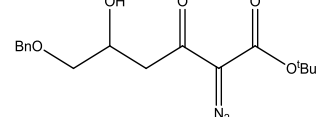
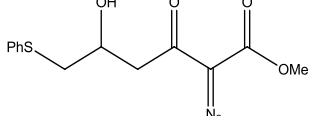
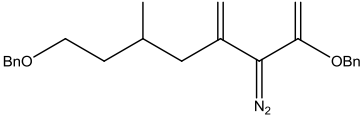
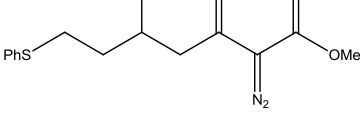
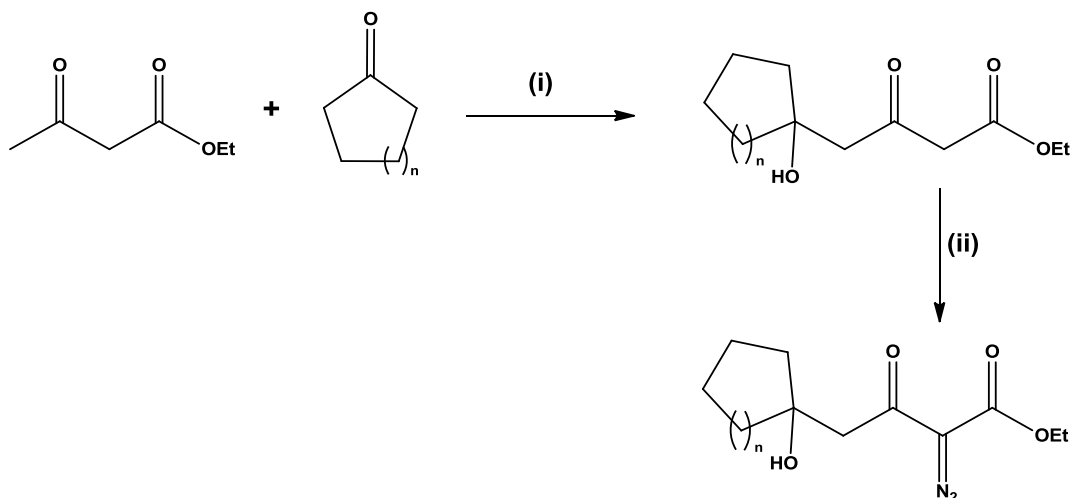
Aldol Product	Lewis acid	Yield (%)
 38	PhBCl ₂	49
	MeAlCl ₂	20
 50	MeAlCl ₂	16
 51	PhBCl ₂	65
 52	PhBCl ₂	45
	MeAlCl ₂	21
 48	PhBCl ₂	65
	MeAlCl ₂	23
 53	PhBCl ₂	18
 54	PhBCl ₂	11
 55	PhBCl ₂	37

Table 2.6.1 Table of aldol addition products **38, 48, 50 – 55**.

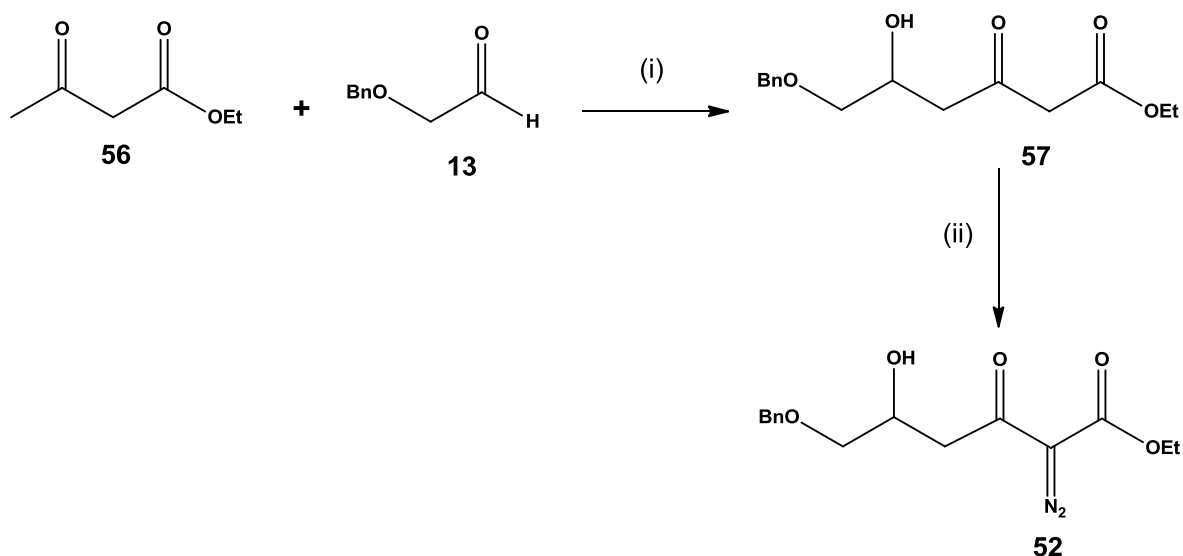
Due to the disappointing results obtained with the Lewis acid approach, an alternative approach was also attempted. This approach involved deprotonation of the α -diazo- β -keto ester with a base of appropriate strength to form an enolate. Followed by addition of an aldehyde to give the desired aldol addition product. Direct deprotonation of the α -diazo- β -keto ester with bases such as DABCO,²¹ LDA, BuLi, MeLi, NEt₃, ⁱPr₂NEt, DBU and TMG among others was investigated. These deprotonations were tried at both room temperature and at -40 °C. All of the attempted reactions involved either decomposition of the diazo moiety, in the case of strong bases such as butyl lithium, or recovery of the α -diazo- β -keto ester when mild bases were utilised. This was accompanied with recovery of the 2-benzyoxyacetaldehyde **12** or with evidence for aldehyde decomposition.

Another alternative, and potentially more economical route to the aldol product was investigated. This involved reaction of 2-(benzyloxy)acetaldehyde **12** with ethyl acetoacetate to create an aldol addition product which could undergo diazo transfer. Jones and co-workers²³ previously reported the reaction of ethyl acetoacetate with a cycloalkanones in the presence of lithium diisopropylamide (2 eq), creating the dianionic species of the ethyl acetoacetate (**Scheme 2.6.3**). The first equivalent deprotonates one of the methylene protons between the ketone and the ester followed by removal of the C4 proton.



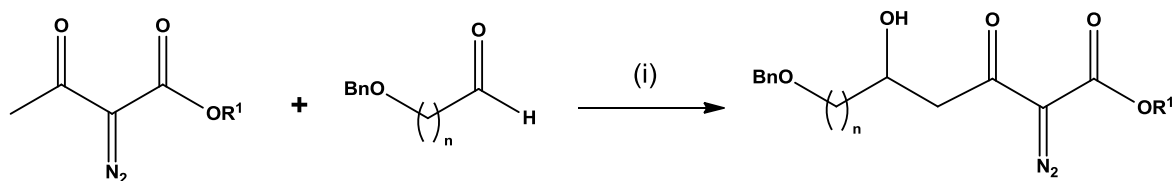
Scheme 2.6.3 Reagents: (i) 2 eq LDA (ii) TsN₃.

The procedure of Jones and co-workers²² was adapted for use with 2-(benzyloxy)acetaldehyde (**Scheme 2.6.4**). Lithium di-*isopropyl*amide was generated from the reaction of butyl lithium with anhydrous di-*isopropyl*amide. This was done at -40 °C and left to stir for 1 h to ensure the reaction had gone to completion. The mixture was cooled to -78 °C and ethyl acetoacetate **56** was added to the stirred solution of LDA at -40 °C resulting in the formation of the dianionic species. 2-(Benzyloxy)acetaldehyde **12** was then added dropwise to this solution. Following work-up, T.L.C. indicated that there were several products formed. This could have been due to various cross reactions such as the dianion of ethyl acetoacetate deprotonating 2-(benzyloxy)acetaldehyde **12**. This in turn could have led to various side products being formed *via* the aldehyde self condensation pathway.



Scheme 2.6.4 Reagents: (i) LDA, THF (ii) K₂CO₃, TsN₃, acetonitrile

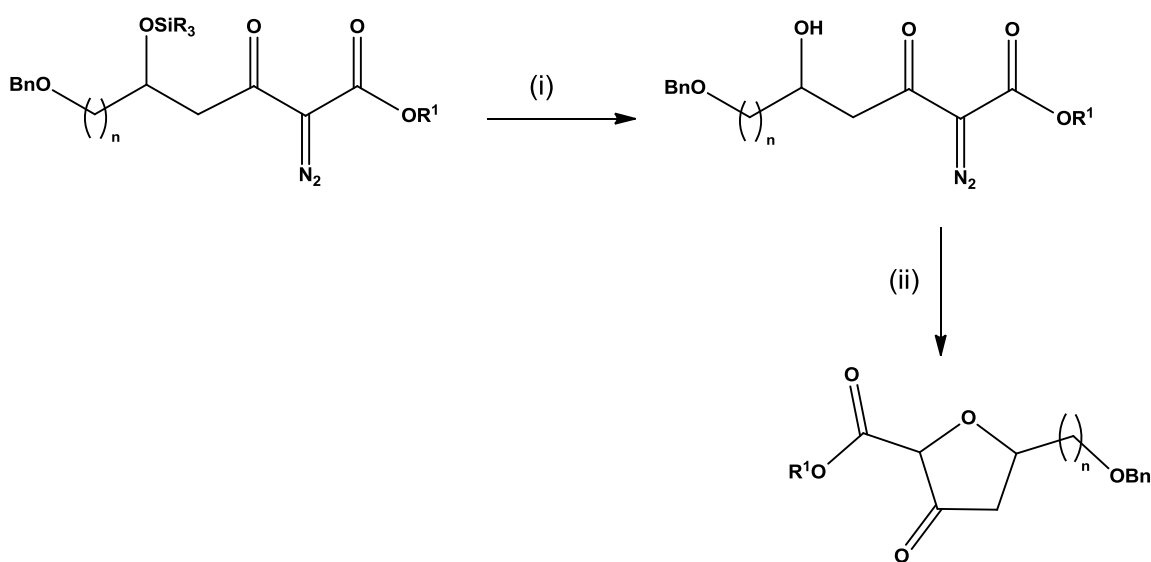
Jones and co-workers²² had reported a 55% yield for this reaction, however, in our hands a yield of only 22% was achieved. Future work may involve investigation of reverse addition along with other addition techniques for this particular reaction. Diazo transfer to ethyl 6-benzyloxy-5-hydroxy-3-oxohexanoate **57** using potassium carbonate (2 eq), as the base, led to a poor yield of 19%. This low yield could be attributed to the presence of a variety of acidic sites on the molecule affording the potential for other reaction pathways. The residual starting material, ethyl 6-benzyloxy-5-hydroxy-3-oxohexanoate **57**, was recovered by column chromatography.



Scheme 2.6.5, Reagents: (i) Lewis acid, NEt_3 , DCM, -78°C

Up to this point, the approach of directly synthesising the aldol addition product was low yielding or involved chemistry which was not economical at a scale which would produce gram quantities of the desired 3(2*H*)-furanone. We proceeded with investigating the previously discussed Mukaiyama aldol addition.

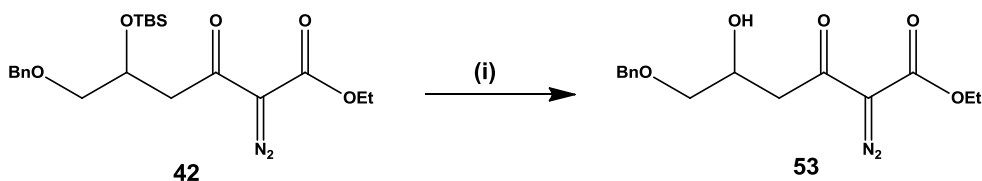
The deprotection of TBS silyloxy ether was examined firstly, as these TBS derivatives were the first to be synthesised during this work. Doyle and co-workers¹¹ did not deprotect the secondary TBS protected alcohol, but instead chose to cyclise the protected alcohol to afford highly functionalised cyclobutanoates (**Scheme 2.4.1**). However we decided to deprotect the silyl protected alcohol to yield the secondary alcohol which can be cyclised to yield 3(2*H*)-furanones (**Scheme 2.6.6**). Various methods were therefore trialled in an effort to cleave the TBS group.



Scheme 2.6.6, Reagents: (i) source of fluoride, (ii) $\text{Rh}_2(\text{OAc})_4$.

The cleavage of the TBS group proved to be more difficult than originally envisaged. TBS protected secondary alcohols are more stable than TES protected alcohols, but not as stable as their TIPS protected analogues. Literature precedent suggested that exposure to TBAF would afford the secondary alcohol. The secondary TBS ether **42** was treated with TBAF (1.5 eq) in THF at -10, 0, 22 and 40 °C. The equivalents of TBAF were increased to 5 and 10 eq. Reaction times were varied between 15 mins, 1 h and 4 h. After 15 mins reaction time, only starting material was recovered. After 1 hr starting material and an unidentifiable side product was observed by ¹H NMR. This side-product did not correspond to the desired product or starting material. At elevated temperatures this unidentified product became more evident, to a level of 7% as estimated by NMR analysis. After 3 days at 40 °C, complete decomposition of the Mukaiyama addition product was observed. Various other sources of fluoride were used in an attempt to cleave the silyl group, such as potassium fluoride, TBAF silica, silver fluoride, boron trifluoride, pyridium hydrofluoride and sodium fluoride. In all cases only starting material was recovered. THF, methanol and hexane were used as solvents to screen these reactions in a bid to cleave the TBS silyl group (**Scheme 2.6.6**). Weak organic acids were also trialled as a means to cleave the silyloxy group, such as *p*-toluenesulfonic acid and acetic acid but again without success.

Some success was achieved when cleavage was attempted with TBAF premixed with boron(III) trifluoride diethyletherate (2 eq) in THF. Further additions of TBAF (10 eq) were necessary to drive the reaction to completion (**Scheme 2.6.7**). Sekine and co-workers²³ have utilised this method to desilylate O-TBS-thymidine. The authors commented that two complexes, depending on the equivalents of TBAF and boron trifluoride diethyletherate, could exist which would lead to the cleavage of the silyloxy bond, complex A (Bu₄NF, BF₃.Et₂O) and complex B (Bu₄NF, 2BF₃.Et₂O). It was thought that a B-F-B linkage was a possible component which promoted the desilylation. Small scale reactions (one gram or less), showed quantitative yields for desilylation, however, scale up above one gram resulted in a considerable drop in yield. The addition of extra equivalents of TBAF and boron trifluoride diethyletherate were added to push the reaction to completion.

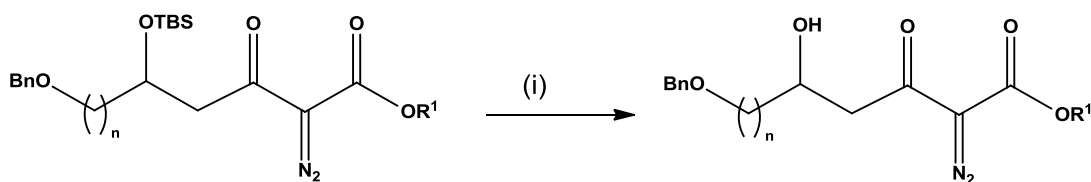


Scheme 2.6.7 Reagents: (i) BF₃.OEt₂, TBAF, THF.

Addition of TBAF and boron(III) trifluoride diethyletherate created a dark brown solution. The course of the reaction was monitored by TLC and NMR. NMR analysis showed TBAF (1 eq) and BF₃ (2 eq) resulted in 50% conversion. It was a further equivalent of each reagent was necessary to drive the reaction to completion. Scale up of the reaction following this procedure failed to quantitatively desilylate the TBS derivatised Mukaiyama aldol addition product **42**.

Variations of this procedure, which included substituting acetic acid for boron trifluoride diethyletherate resulted in only slight desilylation, of approximation 14%.

In a paper published by Scott and co-workers,²⁴ desilylation of multisilylated nucleosides were achieved when a mixture of THF : water : trifluoroacetic acid (4 : 1 : 1) was utilised. The authors used THF as a co-solvent as it leads to increased solubility of the substrates. This in turned increased the 5'-desilylation aswell as depyrimidination and depurination which are associated with acidic hydrolysis of nucleosides. This procedure was utilised in our laboratory by Maguire and co-workers²⁵ for the TBS deprotection of nucleoside analogues while in this work it was adapted for the desilylation of Mukaiyama addition products **37**, **40-44**.



Scheme 2.6.8 Reagents: (i) trifluoroacetic acid, water, THF, (4 : 1 : 1).

The TBS Mukaiyama addition product was dissolved in THF and cooled to 0 °C. Trifluoroacetic acid and water were premixed and the resulting solution was added dropwise to the silyloxy ether; a colour change from dark yellow to light yellow was

observed. The reaction mixture was stirred for 4 h at 0 °C followed by TLC analysis (**Figure 2.6.3**). After 4 h, the reaction was neutralised *via* addition of saturated aqueous Na₂CO₃ solution. Work-up and purification by flash chromatography afforded two fractions. The first of which, with an R_f of 0.85, corresponds to unreacted TBS ether. The second fraction being the desired secondary alcohol with an R_f of 0.15. This alcohol was isolated as a viscous oil.

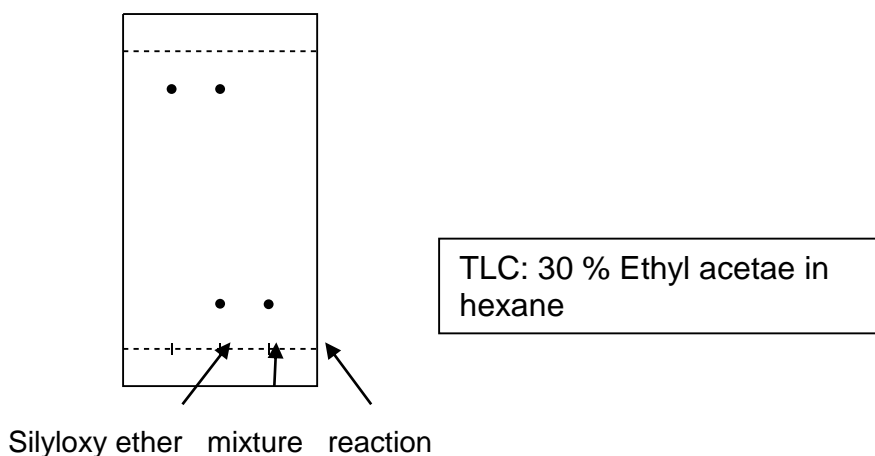


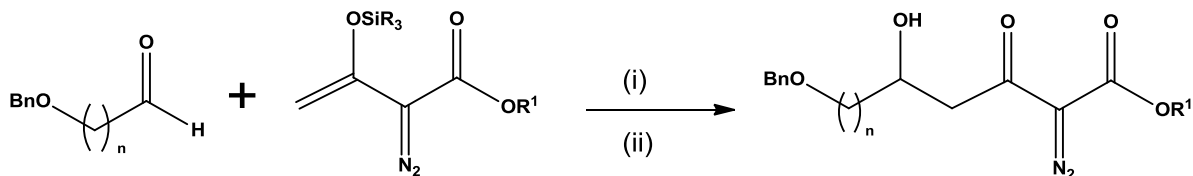
Figure 2.6.3 TLC of starting material (silyl ether, line 1) and the reaction mixture after 4 hr (line 3).

The same procedure was also applied to TES derivatives of the Mukaiyama aldol addition products. TES derivatives are more prone to hydrolysis than TBS analogues. To produce gram quantities of the 3(2*H*)-furanone, further investigation was required to establish which of our compounds underwent desilylation easily. [Quantitative desilylation of the TES derivatives of the Mukaiyama addition product was achieved, as expected, while following the procedure utilised for the desilylation of the TBS silyl ethers.]

An article authored by Doyle and co-workers²⁶ reported a one-pot Mukaiyama-type Michael addition and desilylation reaction, facilitated by *in situ* solvent replacement. This procedure used 4M HCl to cleave the TBDMS ether quantitatively. Attempted hydrolysis of the TBS and TES silyl groups with 4M HCl led to significant decomposition of the diazo moiety, however, partial deprotection with 1M HCl was achieved. The yields of the desired products obtained were between 19 and 22%. This procedure involved addition of 1M HCl to a stirring solution of TBDMS and TES ethers at 0 °C. The reactions were then stirred for 4 h. However it was found that increasing the concentration of the

hydrochloric acid to 2M resulted partial hydrolysis however some decomposition was observed.

The procedures which were seen to give the best yields were ultimately combined to afford a one-pot procedure for synthesising aldol addition product in moderate yields. This involved reacting the silyl enol ether with the appropriate aldehyde in the presence of the zinc(II) triflate, having DCM as the solvent. The reaction was monitored by IR and NMR sampling. Upon completion of the Mukaiyama addition, the reaction was concentrated *in vacuo* and solvent replaced with THF. A 1 : 1 mixture of trifluoroacetic acid : water was added *via* an addition funnel to afford the aldol addition product in moderate yield of 53 - 69% **scheme 2.6.9**.



Scheme 2.6.9 *Reagents:* (i) Zn(II)OTf₂, DCM, (ii) trifluoroacetic acid, water, THF, (4 : 1 : 1).

NMR analysis of 6-benzyloxy-2-diazo-5-hydroxy-3-oxohexanoic acid methyl ester **38** identified two ABX systems present in the molecule, the C4 and C6 protons which are diastereotopic in nature. The protons on the C6 carbon are more downfield (3.5 ppm) than the protons on the C4 carbon (3.10 ppm), this is due the protons on the C6 carbon being in closer proximity to oxygen of the benzyloxy ether when compared to the oxygen of the carbonyl group. The proton of the C5 carbon is significantly deshielded due to the hydroxyl group (**Figure 2.6.4**).

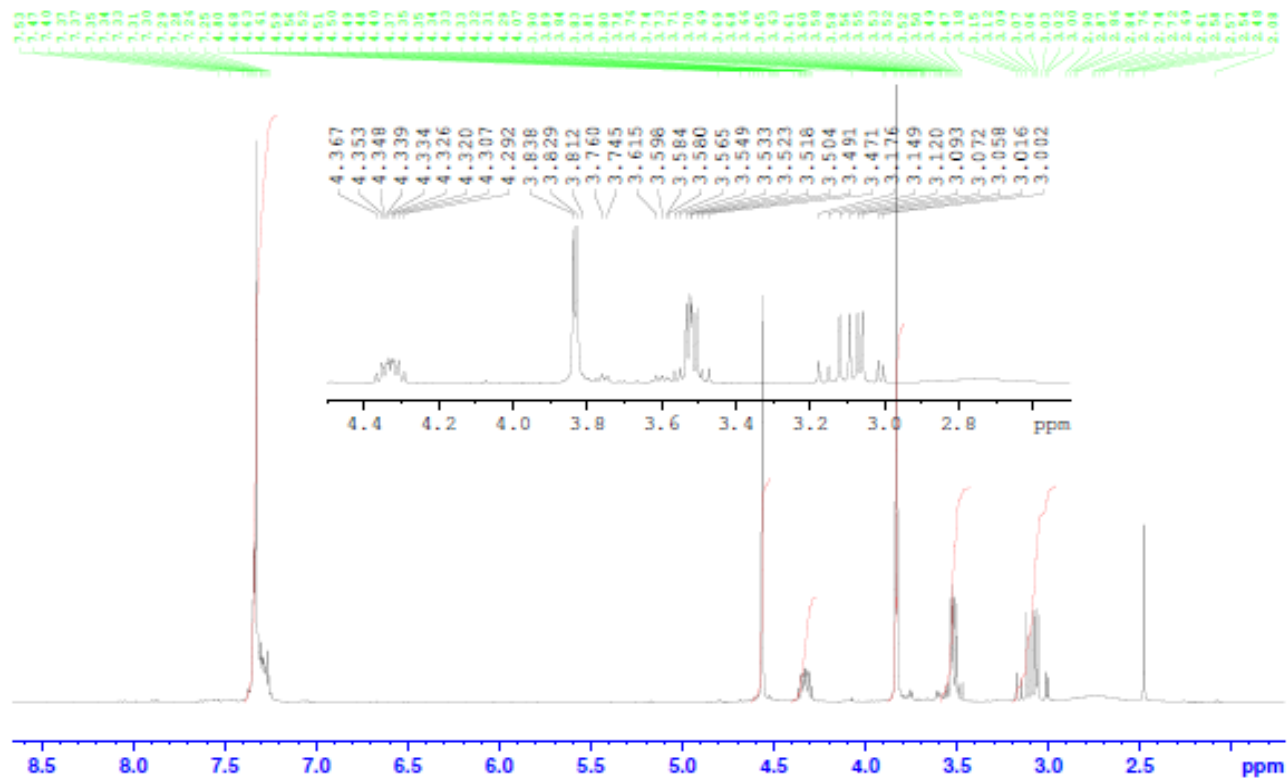


Figure 2.6.4 ¹H NMR of 6-benzyloxy-2-diazo-5-hydroxy-3-oxohexanoic acid methyl ester **38**.

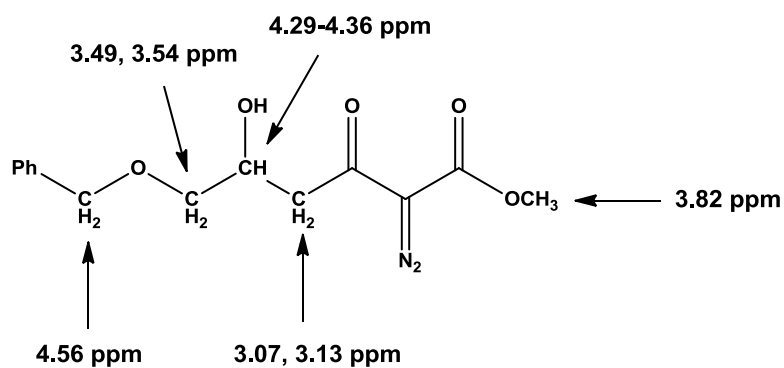


Figure 2.6.5 δH of selected resonances observed in the ¹H NMR spectrum of **38**.

For 7-benzyloxy-2-diazo-5-hydroxy-3-oxoheptanoic acid methyl ester **50**, there are three pairs of diastereotopic protons present in the molecule, the C4, C5 and C7 protons. The C4 protons display a doublet multiplicity although each of the C4 protons would be expected to appear as doublet of doublets. This is most likely due to a coincidental overlap of signal, leading to a breakdown of the first order approximation of splitting, giving an apparent doublet. The C6 protons are upfield due to the lack of deshielding groups in close proximity. They are observed as a multiplet due to further splitting from the C7 protons. The protons attached to the C7 carbon are shifted downfield due to the deshielding nature of the oxygen of the benzyloxy ether (**Figure 2.6.6**).

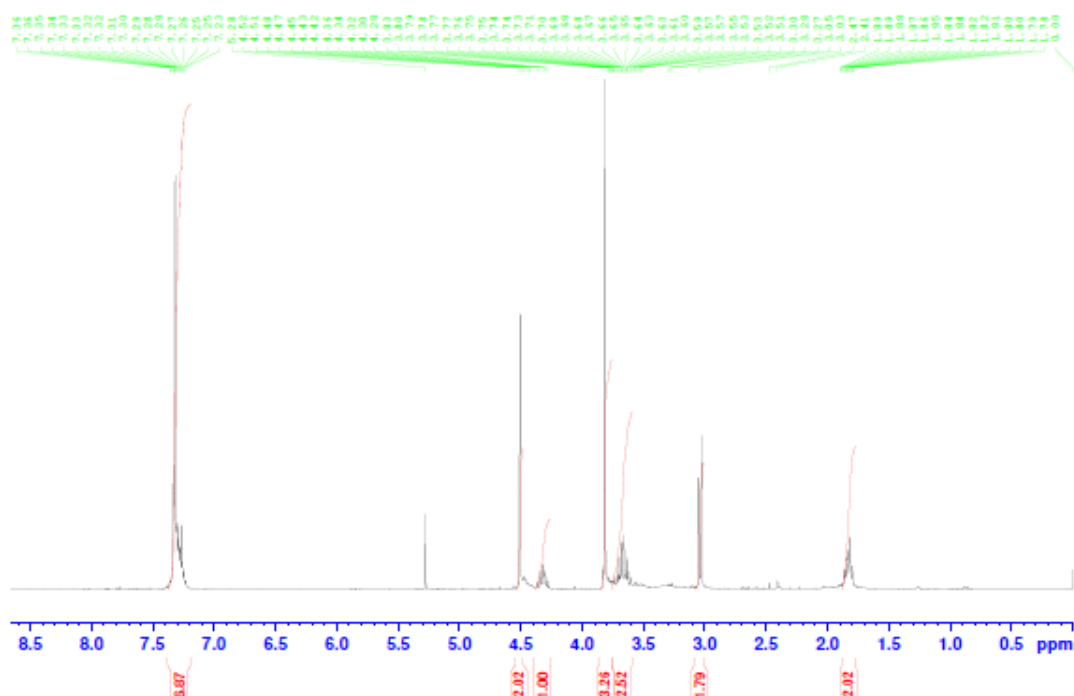


Figure 2.6.6 ^1H NMR of 7-benzyloxy-2-diazo-5-hydroxy-3-oxoheptanoic acid methyl ester **50**.

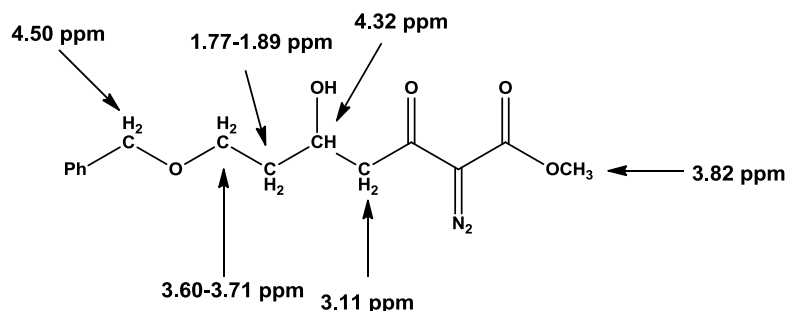


Figure 2.6.7 δH of selected resonances observed in the ^1H NMR spectrum of **50**.

In the ^1H NMR spectrum of 6-benzenesulfonyl-2-diazo-5-hydroxy-3-oxohexanoic acid methyl ester **54**, the protons attached to the C4 and C6 carbons overlap to form a multiplet.

In the mass spectra of the various desilylated aldol addition products loss of the diazo moiety is observed. This is due to the labile nature of the functional group and the decomposition often associated with mass spectrometry conditions. The LC of the mass spectrometer uses 0.1% formic acid as eluent, which could trigger decomposition of the diazo functional group when a high voltage is applied. This would lead to a loss of $m/z = 28$ [the mass of nitrogen (N_2)].

2.7 Rh(II) Mediated Cyclisations

Diazo chemistry has been studied since the late 19th century and diazo compounds remain the most widely utilised carbene precursors in organic synthesis. Diazo compounds possess a 1,3-dipolar structure (**Figure 2.7.1**). Diazo compounds are decomposed to carbenes in the presence of transition metal catalysts. The stability of the diazo group is very much dependent on the substituents present at the diazo carbon. The diazo 1,3-dipole can be resonance stabilised by electron withdrawing substituents on the carbon. Thermal generation of the carbene is preferred for synthetic purposes as photochemical methods produce intermediates with much higher energy. This often leads to side reactions due to the formation of triplet carbenes [**Figure 2.7.2 (b)**] which are higher in energy than their singlet counterparts. Thus, triplet carbenes are more reactive and less selective in their reactivity **Figure 2.7.2**.

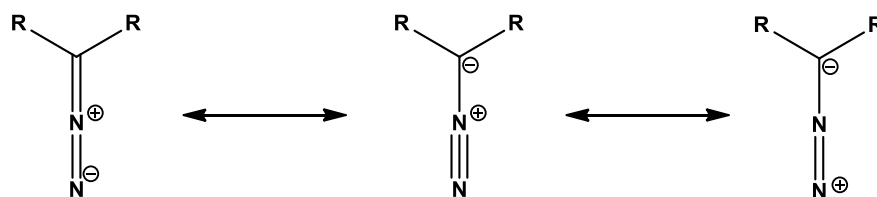


Figure 2.7.1 1,3-dipolar structure of diazo moiety.

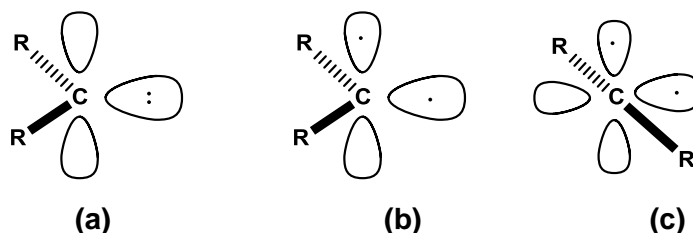


Figure 2.7.2 the singlet carbene (a) and the triplet carbene (b) and (c).

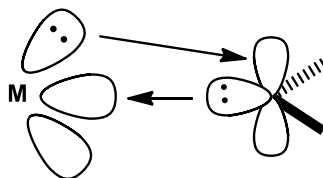
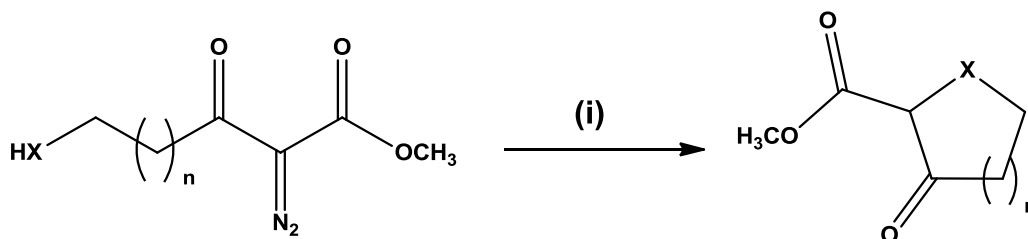


Figure 2.7.3 δ -type donating group of the methylene filling empty d-orbital and π -electron back bonding observed in carbenoids

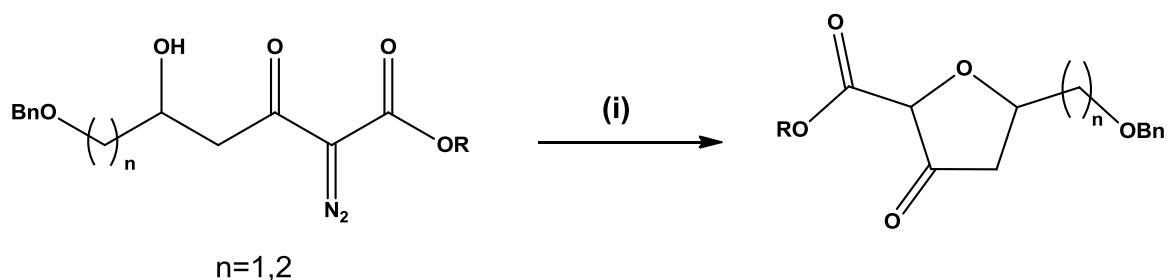
Thermal decomposition of the diazo functionality carried out in the presence of transition metals, such as copper and rhodium, generates intermediates which are not free carbenes but are transition metals complexes. These complexes are often referred to as metallocarbenes or carbenoids ($M = CR_2$) and contain a formal carbon metal double bond. Rhodium carbenoids are Fischer type carbenoids where chemical bonding is based on δ -type electron donation of the methylene filled lone pair orbital to an empty d-orbital of the metal. As well as π -electron back bonding to the empty p-orbital on the carbene carbon (**Figure 2.7.3**).²⁷ The transition metal carbenes possess the same electronic deficient nature as free carbenes and undergo similar reactions.



Scheme 2.7.1, Reagents: (i) $Rh_2(OAc)_4$, benzene.

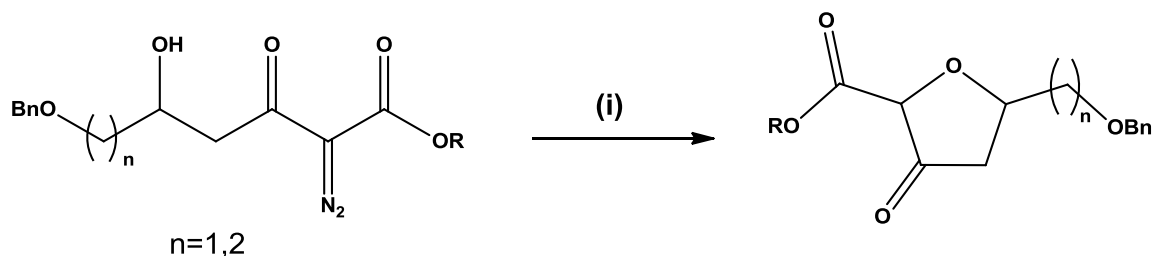
Cyclisation of the aldol adduct using the method described by Moyer and co-workers,²⁸ produced the 4,5-dihydro-3(2H)-furanones in quantitative yield (**Scheme 2.7.1**). All diazo decomposition reactions were carried out in a mixture of benzene and DCM. The apparatus was thoroughly dried so that no carbene insertion into water was possible. Water could also chelate to rhodium acetate, rendering the catalyst inert. Benzene was added to the flame dried round bottom flask, followed by a catalytic amount of rhodium acetate, (1 mol%). The mixture was heated to reflux for 3 h. The heating of the suspension for a number of hours allowed for degassing of the solvent to occur. The aldol addition product was dissolved in doubly distilled DCM and added dropwise at a rate of approximately of one drop per second to the suspended catalyst. It was important to add the diazo-β-keto ester slowly and at very low concentrations to limit any side reactions which may take place. Evolution of nitrogen gas was observed during the course of the reaction. The reaction was monitored by IR analysis, which showed disappearance of the diazo stretch at $2134 - 2145\text{ cm}^{-1}$ as well as shifts in the ketone and ester carbonyl stretches from 1713 and 1637 cm^{-1} to 1767 and 1739 cm^{-1} respectively. Reaction completion was monitored by IR analysis, upon complete

disappearance of the diazo peak, the reaction mixture was filtered through a bed of Celite® and concentrated. The concentrated crude reaction mixture was sufficiently pure to be carried through to subsequent reactions. The 3(2*H*)-furanone products isolated following cyclisation could not be purified further by column chromatography due to decomposition of the 3(2*H*)-furanone moiety.



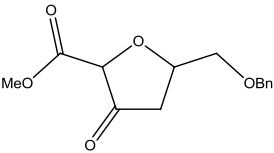
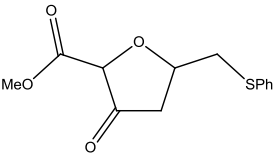
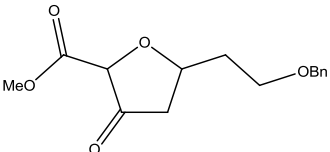
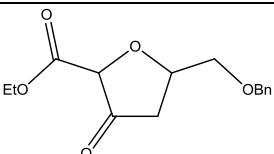
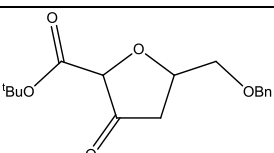
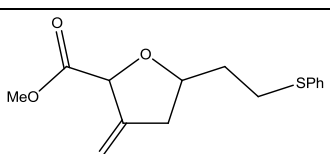
Scheme 2.7.2, Reagents: $\text{Rh}_2(\text{OAc})_4$, DCM, benzene, reflux.

Replacement of benzene with less toxic solvents was also investigated. Reactions carried out in DCM did not result in the formation of product with only starting material recovered. The procedure for cyclisation carried out by Jones and co-workers²² using toluene as solvent, was applied to this work with success with the isolation of the desired product. In addition to the desired product, side products were also observed in this reaction. Other solvents such as chloroform, hexane, THF and diethylether were also investigated, however, none of these solvents resulted in product formation, with only 1,2-dichloroethane affording the desired product. It did so in comparable yield to that of the benzene DCM mixture. High boiling solvents such as 1,2-dichloroethane seemed to be required for cyclisation to the 3(2*H*)-furanone to occur.



Scheme 2.7.3, Reagents: $\text{Rh}_2(\text{OAc})_4$, 1,2-dichloroethane, reflux.

The cyclisation proceeded by generation of a rhodium stabilised carbene (carbenoid) *via* loss of N₂. The carbene then inserted into the O-H bond of the alcohol group, resulting in the formation of a 5-membered ring. The tetrahydrofuran product was not purified by column chromatography due to degradation of the 3(2*H*)-furanone moiety. ¹H NMR analysis indicated that the compound was sufficiently pure to use in subsequent reactions.

3(2H)-Furanone	Solvent	d.r.*	Yield# (%)
 58	Benzene/DCM	2:1	89
	1,2-dichloroethane	1.8:1	86
 59	1,2-dichloroethane	1.3:1	74
 60	Benzene/DCM	1.2:1	83
 61	Benzene/DCM	^	92
 62	Benzene/DCM	3:2	93
 63	Benzene/DCM	1.1:1	83

*d.e. determined by NMR, diastereoisomers showed 2 distinct signal for esters.

#crude yield

^d.e. could not be determined as ester signals overlapped

Table 2.7.1 Table of *Rh(II)* cyclised 3(2H)-furanones.

In the ^1H NMR spectrum of compound **58**, the C4 protons are observed as the most upfield signal appearing at 2.2 - 2.7 ppm. This is an ABX system, however, since there are two diastereoisomers present the signals are doubled. Both *syn* and *anti* diastereoisomers contribute to the doubling of signals and as a result the C2 and C5 proton signals overlap making assignment of each single diastereoisomer difficult. In addition to the observed C2 and C5 proton signal overlap, the benzylic protons also overlap with the C2 and C5 signals. The IR spectrum shows two carbonyl signals, at 1743 cm^{-1} which is associated with the ester functional group and 1769 cm^{-1} which is associated with ketone moiety of the 3(2*H*)-furanone heterocycle (**Figure 2.7.4**).

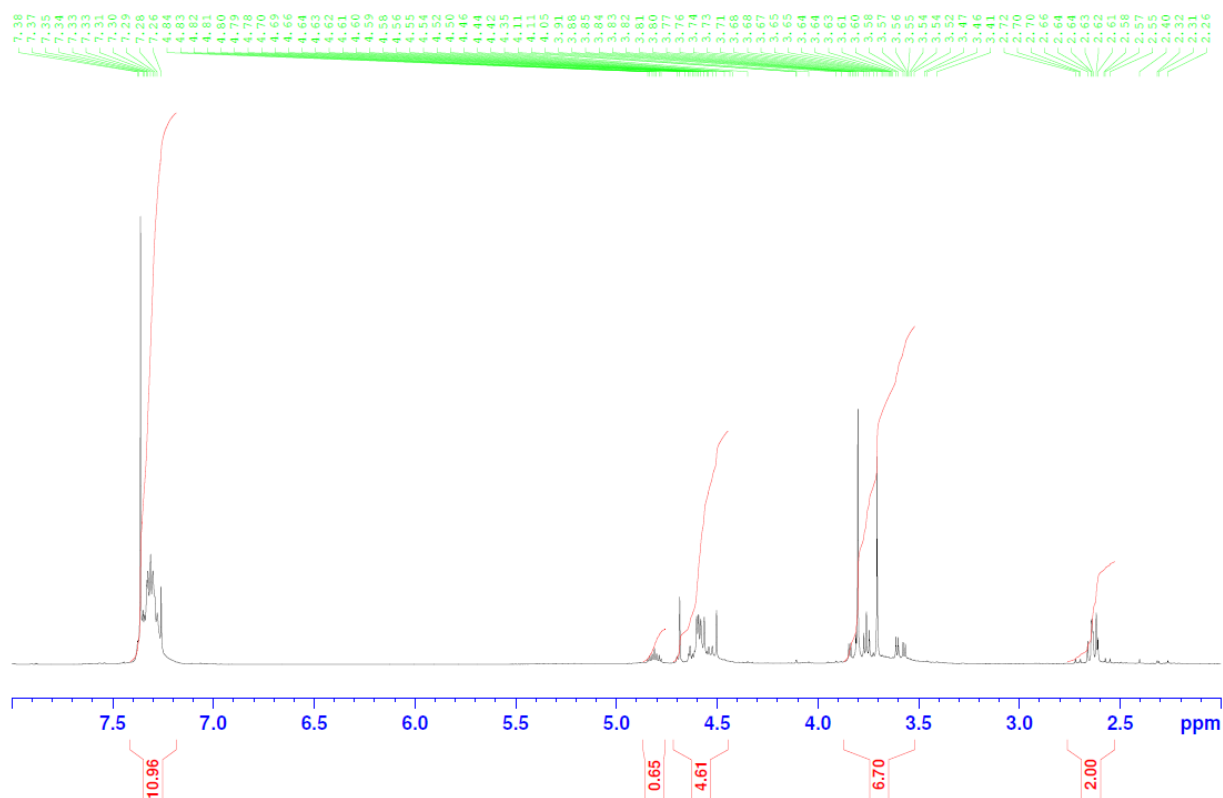


Figure 2.7.4 ^1H NMR of (\pm)-5-Benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid methyl ester **58**.

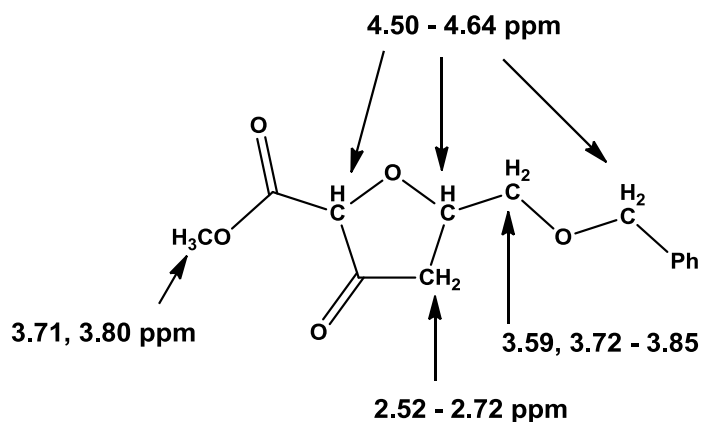


Figure 2.7.5 δH of selected resonances observed in the ^1H NMR spectrum of **58**.

The homologue of **60** ($n=2$) also shows doubling of its signals for the *syn* and *anti* diastereoisomers. The C2, C5 and the benzylic protons are shifted downfield due to the surrounding electron withdrawing groups present, such as the carbonyl and the ether oxygens (**Figure 2.7.5**). The protons adjacent to the benzylic ether appear downfield (3.6 ppm) due to the electronegative oxygen.

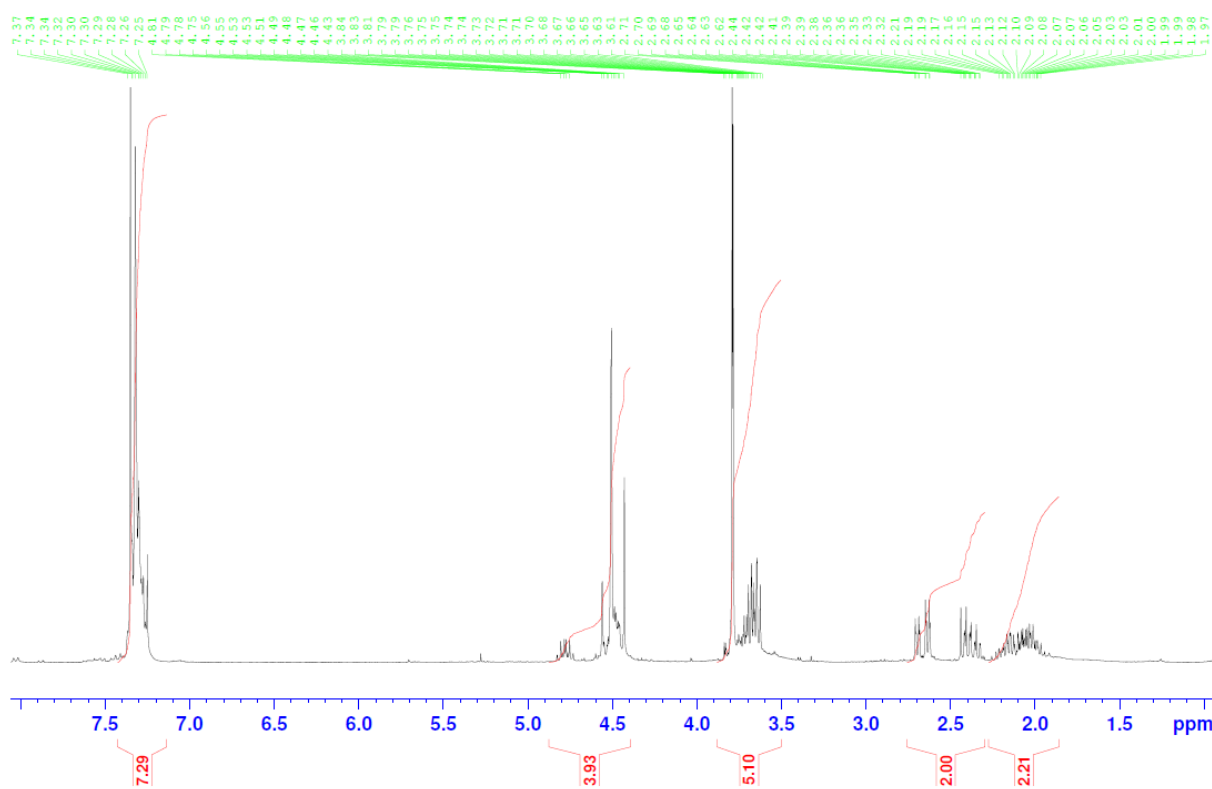


Figure 2.7.6 ^1H NMR of (\pm)-5-Benzyloxyethyl-3-Oxotetrahydrofuran-2-Carboxylic Acid Methyl Ester **60**.

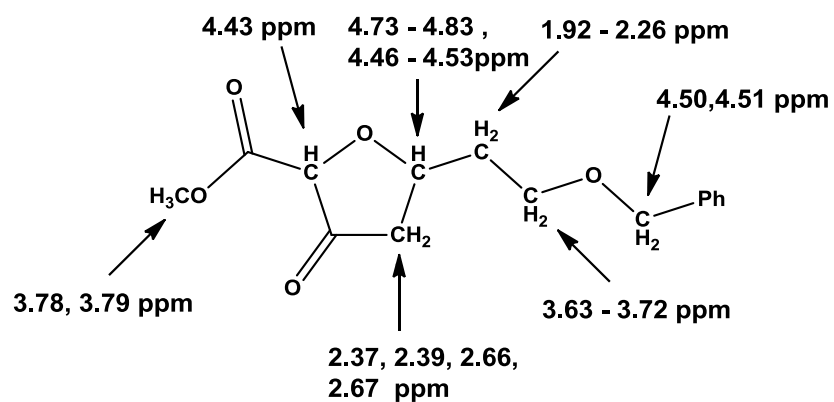
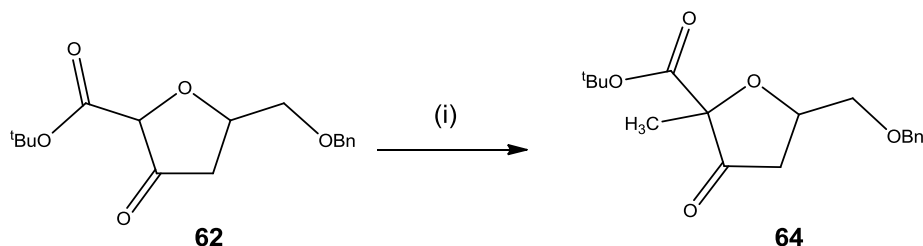


Figure 2.7.7 δH of selected resonances observed in the 1H NMR spectrum of **60**.

Both high resolution mass spectrum and nominal mass spectrum showed the ion of the parent molecule, 279 (M+H)⁺. A daughter ion showing the loss of the benzyl group (-91 Da) is evident in the nominal mass spectrum.

2.8 Methylation Reactions at the 2-Position of 4,5-Dihydro-3(2H)-furanones

The synthesis of muscarine and its analogues, requires the installation of a methyl group at the 2-position. The proton at the 2-position is relatively acidic, with a pK_a of approximately 8 to 9. Lambe¹⁹ had little success when attempting methylations at the 2-position, despite using various bases at a variety of temperatures. Lambe found that treatment of the (\pm)-5-benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid *tert*-butyl ester **62** with LiHDMS (1.3 eq) and methyl iodide (1.3 eq) in THF, with heating in a microwave for 15 mins at reflux afforded (\pm)-5-benzyloxymethyl-2-methyl-3-oxotetrahydrofuran-2-carboxylic acid *tert*-butyl ester **64** in 42% yield (**Scheme 2.8.1**). This initial reaction was carried out at small scale (less than 100 mg), however, scale-up to 550 mg gave a diminished yield of 11% for the combined set of diastereoisomers. Upon addition of the LiHDMS solution to the solution of (\pm)-5-benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid *tert*-butyl ester **64** in anhydrous THF, a deep red/burgundy colour was observed. This colour change is indicative of an anion being generated.



Scheme 2.8.1 Reagents: (i) LiHDMS, methyl iodide, THF

Attempts to improve the yields of the methylation reaction were considered necessary as this step could lead to a bottleneck in the synthesis. Various procedures were investigated for the installation of the methyl group at the 2-position. A variety of bases including potassium carbonate, sodium carbonate, potassium hydrogen carbonate and pyridine were tried in various solvents. These solvents included THF, DMSO, toluene and acetonitrile. The temperature of the reaction was varied between 25 °C and reflux. Dissappointingly none of these reaction variations resulted in the formation of product. Calter and co-workers¹⁰ had utilised potassium carbonate as the base and benzyl bromide as the alkylating reagent. Only three bases; DBU, TMG and potassium hydride gave the desired product in our hands. We found that when using potassium hydride, 18-crown-6 was a necessary additive as its absence leads to diminished yields. It is possible

that the anion, generated from the 3(2*H*)-furanone, undergoes resonance delocalisation and the negative charge resides on the oxygen of the ketone and on the ester oxygens of the 3(2*H*)-furanone (**Figure 2.8.1**). This would allow chelation of the metal cation through both the carbonyl group of the ester and the enolate anion of the ketone. The anion generated was quite stable and failed to undergo substitution reactions with methyl iodide. In this instance, 18-Crown-6 sequesters the potassium cation and renders the anion of the β -keto ester more nucleophilic and hence prone to methylation.

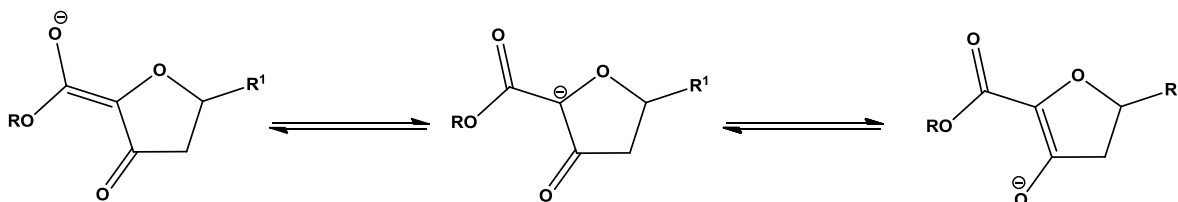
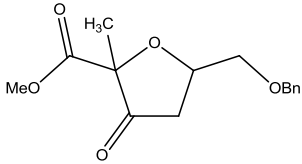
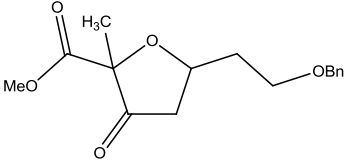
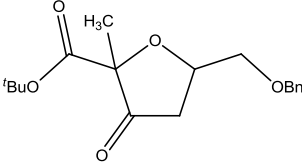


Figure 2.8.1 Resonance delocalisation of the negative charge on 3(2*H*)-furanone.

Upon addition of either potassium hydride, TMG or DBU to the β -keto ester of the cyclised 3(2*H*)-furanone in solution with either THF or DCM, a red/burgundy colour along with a minor exotherm was observed. Methyl iodide was then added dropwise to the reaction solution. Increases in yield for this reaction was achieved by adjusting the stoichiometry of the methyl iodide and screening of bases (DBU, TMG and potassium hydride) in the presence of 18-crown-6. Results identified DBU as the base of choice. These results also revealed that DBU (1.5 eq) and methyl iodide (4 eq) gave the best yields for this methylation. Reaction monitoring, carried out by ^1H NMR analysis showed a slight shift of the methyl protons of the methyl ester upfield from 3.7 to 3.6 ppm, which corresponded with the disappearance of methyl iodide from the reaction mixture. The reaction was quenched *via* the addition of 10% aqueous HCl. Following work-up and column chromatography, two sets of diastereoisomers were isolated as separate fractions. The 2-methylated 3(2*H*)-furanones were isolated in low yields. This yield could be attributed to the reduced nucleophilicity of the stabilised anion generated from the 3(2*H*)-furanone. Choice of base also had a minor impact on the d.r. of (\pm)-5-benzoyloxymethyl-2-methyl-3-oxo tetrahydrofuran-2-carboxylic acid methyl ester **65**. DBU afforded the highest d.r. which was determined from the crude ^1H NMR spectra of the reaction mixture (**Table 2.8.1**).

2-alkylated 3(2 <i>H</i>)-furanone Product	Base	d.r.*	Isolated Yield (%)
 65	DBU	2:1	39
	KH (with 18-crown-6)	17:10	24
	TMG	23:12	35
 66	DBU	5:2	17
 64	DBU	37:20	57

*d.r. determined from crude ¹H NMR of reaction.

Table 2.8.1 Table of 3(2*H*)-furanone methylation.

The two diastereoisomers which resulted from methylation of (±)-5-benzyloxymethyl-2-methyl-3-oxotetrahydrofuran-2-carboxylic acid methyl ester **65** were separable by column chromatography. The first fraction to elute was found to be one of the diastereoisomers of **65** where C2 methyl was *syn* to the C5 proton. This stereochemistry was determined by both NOE difference and NOESY experiments. In the NOE difference experiment, the C5 proton was irradiated and a weak enhancement of the signals associated with the methyl group attached to the C2 carbon was observed (**Figure 2.8.2**). In the corresponding NOESY experiment, a cross peak for both the methyl group and the C5 proton was observed. Also a crosspeak was observed for the more upfield of the C4 protons and the C5 proton which suggests that a *syn* conformation exists between these two protons.

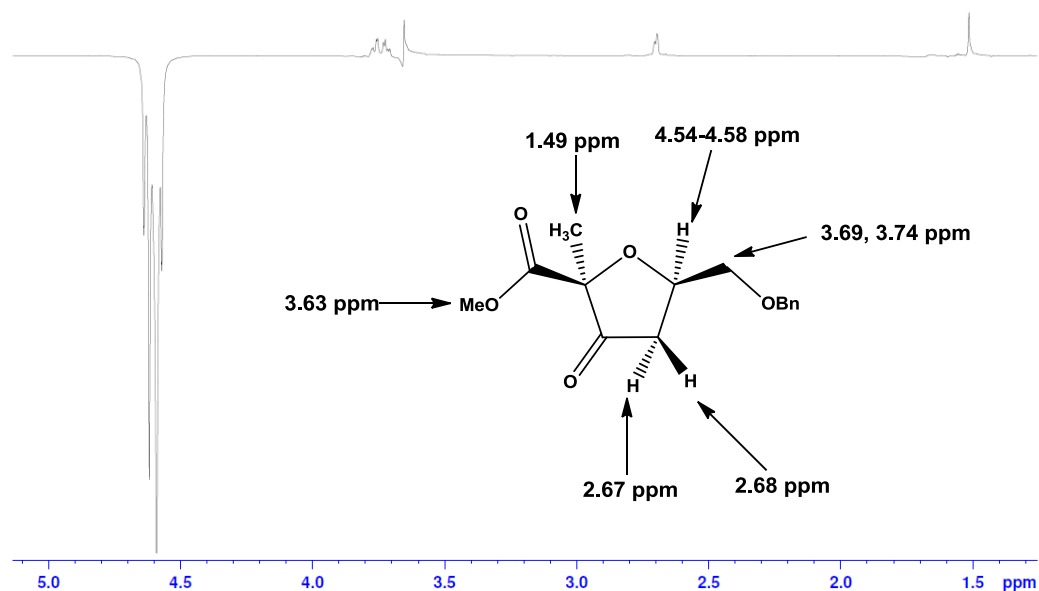


Figure 2.8.2 NOE difference spectrum associated with **65**. The C₅ proton is irradiated (δ_H 4.54-4.58 ppm).

The *syn* diastereoisomer showed that the C4 protons had less of a traditional ABX system. Near coalescence of the C4 signals results in each of the protons appearing as a doublet, as opposed to the expected doublet of doublets. The ¹H NMR spectrum also shows overlapping of the signal of the C5 proton and the benzylic protons. The benzyloxymethyl protons appear as an ABX system (**Figure 2.8.3**).

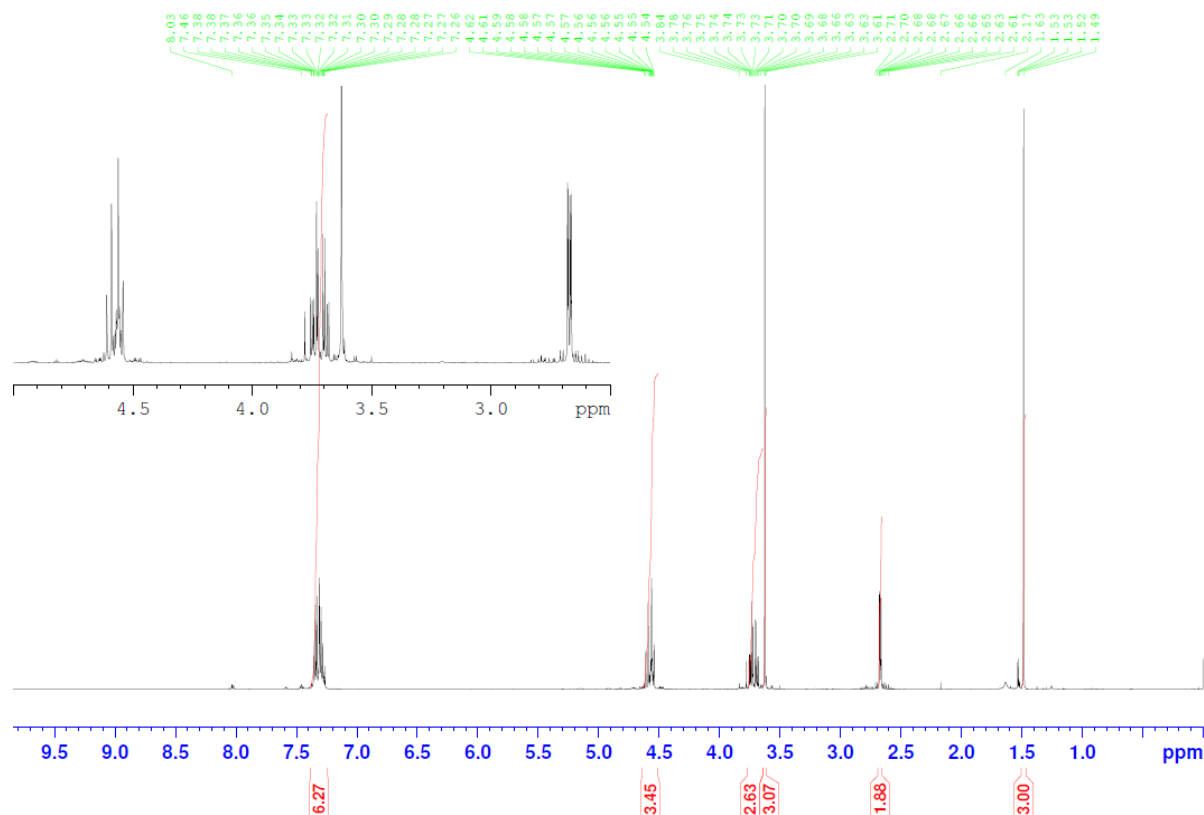


Figure 2.8.3. ^1H NMR of syn-(\pm)-5-benzyloxymethyl-2-methyl-3-oxotetrahydrofuran-2-carboxylic acid methyl ester **65**.

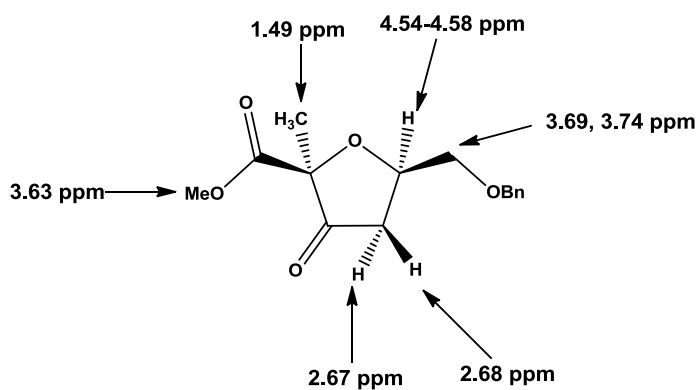


Figure 2.8.4 δH of selected resonances observed in the ^1H NMR spectrum of syn-**65**.

The most upfield of the signals is the methyl group which is attached to the C2 carbon. This methyl group does not couple to any protons, resulting in a singlet.

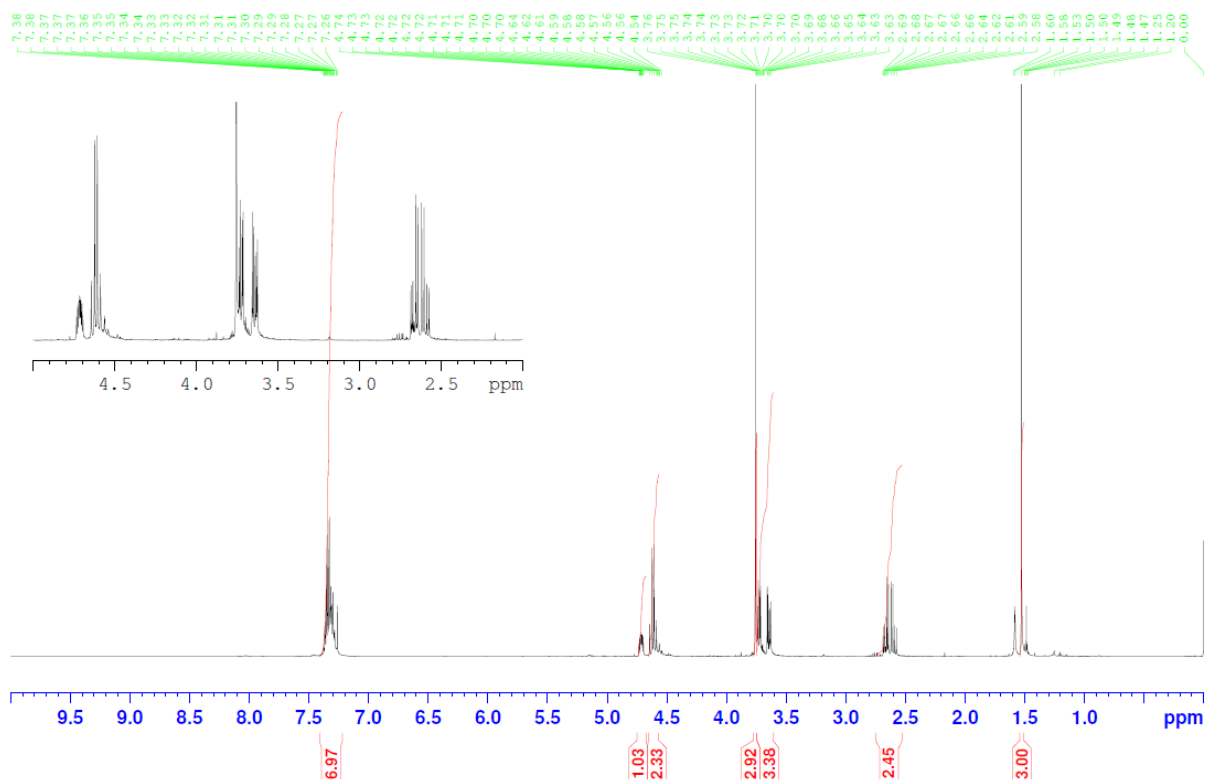


Figure 2.8.5 ^1H NMR of anti-(\pm)-5-benzyloxymethyl-2-methyl-3-oxotetrahydrofuran-2-carboxylic acid methyl ester **65**.

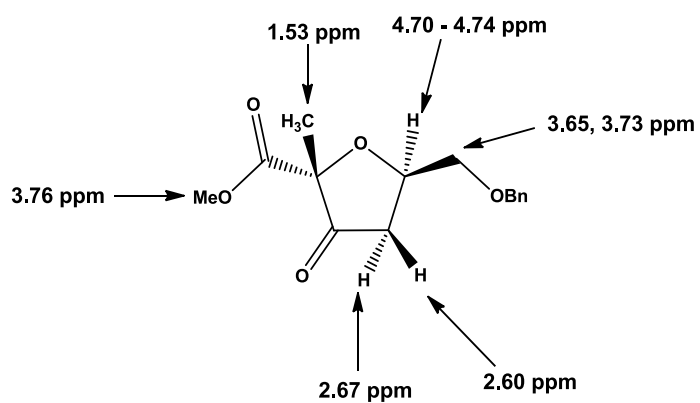
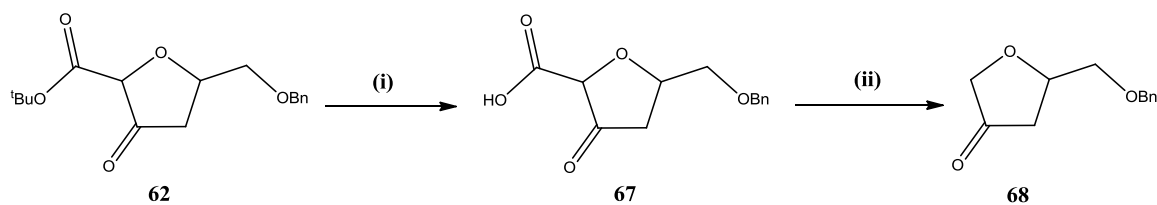


Figure 2.8.6 δH of selected resonances observed in the ^1H NMR spectrum of anti-**65**.

In the ^1H NMR spectrum of the *anti* diastereoisomer, the two ABX systems are quite recognisable. The C4 protons and the protons attached to the benzyloxymethyl group show a distinctive pattern with characteristic roofing. The proton attached to the C5 carbon appears most downfield of all the protons, excluding the aromatic resonances. This downfield shift is due to the electron-withdrawing effect of the furanone ether moiety. NOE difference experiments confirms the *anti* nature of the stereochemistry. Irradiation of the methyl group attached to the C2 carbon shows no enhancement of any other signal, while irradiation of the C5 proton shows enhancement of only one of the ABX protons on the C4 carbon which suggests that both protons are relatively *syn* to each other and correspondingly close in space (**Figure 2.8.5**).

2.9 Hydrolysis of Alkyl Ester at the 2-Position of the 4,5-Dihydro-3(2H)-furanone

Originally, Calter and co-workers¹⁰ used a *tert*-butyl group as the alkyl ester of choice. *tert*-Butyl esters are very stable under a wide range of conditions, for both basic and acidic media. Literature precedent suggested cleavage of this ester was feasible with trifluoroacetic acid. Calter and co-workers treated various substituted 3(2H)-furanones with trifluoroacetic acid and recovered the desired carboxylic acid in a quantitative yield. Repetition of this procedure in neat trifluoroacetic acid, as part of our work afforded a high mass transfer of (±)-5-benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid **67** and subsequent decarboxylation affording (±)-5-benzyloxymethyl-3(2H)-furanone **68** in low yield. Lambe had found previously that a 1 : 1 mixture of trifluoroacetic acid and DCM at 0 °C for 4 h gave a high mass transfer of the crude acid mixture, however, again decarboxylation afforded (±)-5-benzyloxymethyl-3(2H)-furanone **68** in a low yield. Repetition of this procedure during this work afforded a mass transfer of 75% of (±)-5-benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid **67** and a low yield of the (±)-5-benzyloxymethyl-3(2H)-furanone **68** (<6%) following decarboxylation. The ¹H NMR spectrum of the hydrolysed product, (±)-5-benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid **67**, showed evidence to support hydrolysis of the *tert*-butyl ester due to the disappearance of the two 9H *tert*-butyl singlets observed for the diastereoisomers.



Scheme 2.9.1 Reagents: (i) Trifluoroacetic acid, (ii) reflux.

The carboxylic acid was carried through to the decarboxylation step without further purification. Hydrolysis of the *tert*-butyl ester was not possible under basic conditions using either lithium or sodium hydroxide. Hydrolysis was also attempted using various Lewis acids, such as zinc(II) bromide, aluminium(III) trichloride, zinc(II) chloride and titanium(IV) tetrachloride amongst others. Degradation or recovery of starting materials was evident for all of these attempted reactions.

An investigation into the low yield of the decarboxylation was subsequently carried out. Following base extraction of the crude TFA/DCM reaction mixture, only a small amount of the (\pm)-5-benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid **67** was extracted, approximately 7%. The compound extracted conformed to the spectrometric properties of the acid as reported by O'Donovan¹⁸ and Lambe.¹⁹

Alternative ester groups were investigated in an effort to identify one which may be cleaved quantitatively or in high yield to give the desired acid. Methyl, ethyl and benzyl alkyl esters of (\pm)-5-benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid were synthesised. Attempted cleavage of the methyl and ethyl esters under basic conditions was carried out to give the appropriate carboxylic acid. Jones and co-workers,²² in their synthesis of spirocyclic 3(2*H*)-furanones reported the hydrolysis of ethyl alkyl ester, in the presence of lithium hydroxide. This was followed by acidification with 50% sulphuric acid to afford the hydrolysed and decarboxylated 3(2*H*)-furanone. A slightly modified version of this protocol involving heating the basic solution and varying the equivalents of the lithium hydroxide present in the reaction was tried. However, all attempts were unsuccessful. Several hydroxide nucleophiles, such as sodium hydroxide, barium hydroxide and potassium hydroxide were also substituted for lithium hydroxide without improvement. Alternative acids were used in place of sulphuric acid, such as phosphoric acid, hydrochloric acid and acetic acid, however decomposition and no recovery of starting material was observed. The α -proton of the β -keto ester is relatively highly acidic and can be deprotonated easily; it was thought therefore that more than one equivalent of base would be needed to hydrolyse the ester. The charge created by deprotonation of the α -proton can be delocalised into either the ketone or the carbonyl group of the alkyl ester which reduces the electrophilicity of the ester group towards the hydroxide anion and hinders its hydrolysis. Decomposition of the 3(2*H*)-furanone could be attributed to treatment with either the very harshly basic or acidic media which were being employed.

Alternative oxygen anions were also investigated to discover if the 3(2*H*)-furanone could be formed. These reactions led to either recovery of starting material (ester) or decomposition. The conditions investigated included potassium superoxide with 18-crown-6 in refluxing benzene, Krapcho conditions (NaCl, water, DMSO and heat) and variations of these conditions. DMSO and pyridine were investigated as potential solvents while sodium iodide, sodium chloride and potassium chloride were used as nucleophiles during investigation of Krapcho conditions.

Acidic conditions were also investigated. Mild acidic conditions, such as treating the methyl and ethyl alkyl esters with *p*-toluenesulfonic acid, acetic acid and formic acid at room temperature and at elevated temperature, for example 50 °C, led to recovery of starting material with some degradation. Mineral acids such as phosphoric acid, sulphuric acid and hydrochloric acid were also investigated. 1M HCl in THF at reflux for 6 h gave the desired compound in 19% yield. The crude ¹H NMR spectrum showed formation of (±)-5-benzyloxymethyl-3(2*H*)-furanone **68**. The distinctive C2-H doublet of doublets, due to the C2 AB system present at 4 ppm, was observed.

Further optimisation of the reaction led to finalised conditions of 6 M HCl heated in a microwave at 150 watts for 6 mins would afford the (±)-5-benzyloxymethyl-3(2*H*)-furanone **68** in high yield. These reaction conditions resulted in a one-pot saponification and decarboxylation. The alkyl ester was dissolved in 1,4-dioxane followed by the addition of 6M HCl to a round bottom flask prior to heating in the microwave. When the reaction mixture was left in solution with 6M HCl for a prolonged period of time either a significant amount of debenzylation was observed due to the harsh acidic conditions. The reaction was heated for exactly 6 mins, as this ensured complete hydrolysis and decarboxylation. However, if heated for a period longer than 6 mins, a reduction in yield was observed. Following irradiation in the microwave, the reaction was rapidly cooled and the acidic solution was neutralised with saturated sodium carbonate solution. Failure to achieve neutralisation of the acidic solution quickly resulted in a significant drop in yield. If the reaction was carried out in THF as the solvent, a reduction in the yield was also observed, along with an impurity which co-eluted with (±)-5-benzyloxymethyl-3(2*H*)-furanone **68**. The impurity shows two multiplets at 3.6 ppm and at 4.3 ppm in the corresponding ¹H NMR spectrum. Exchanging 1,4-dioxane for THF eliminated this impurity.

When the reaction was heated thermally, in an oil bath, a diminished yield and a significant amount of benzyl alcohol was obtained. This was due to cleavage of the benzyl ether. When formed, benzyl alcohol co-eluted with (±)-5-benzyloxymethyl-3(2*H*)-furanone **68**. The hydrolysis of the benzyl ether was due to the reaction time involved to ensure complete hydrolysis of the alkyl ester. The same protocol aforementioned was extended to (±)-5-benzyloxymethyl-2-methyl-3(2*H*)-furanone **70** and (±)-5-benzyloxyethyl-3(2*H*)-furanone **69** resulting in moderate to high yields.

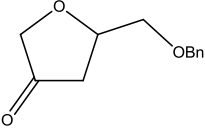
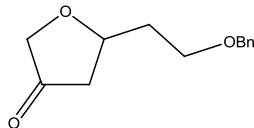
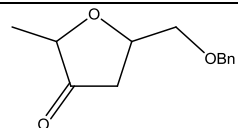
3(2H)-Furanone	Yield (%)	C4-H	$\nu/\text{cm}^{-1}(\text{C}=\text{O})$
 68	68	2.43,2.52	1760
 69	72	2.23,2.54	1760
 70	58	2.34-2.62	1759

Table 2.9.1 Yields and key spectroscopic properties of 3(2H)-furanones prepared by “one-pot hydrolysis and decarboxylation reactions.”

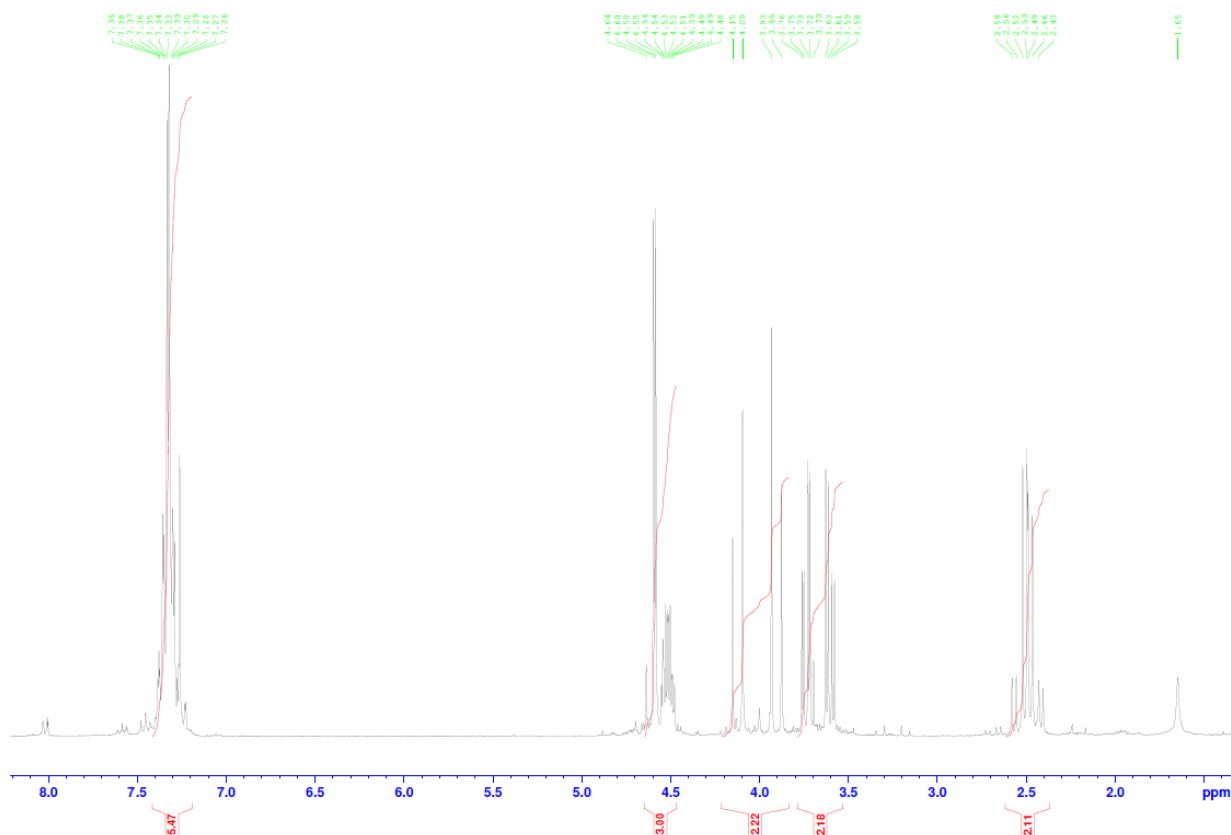


Figure 2.9.1 ^1H NMR of (±)-5-benzyloxymethyl-3(2H)-furanone.

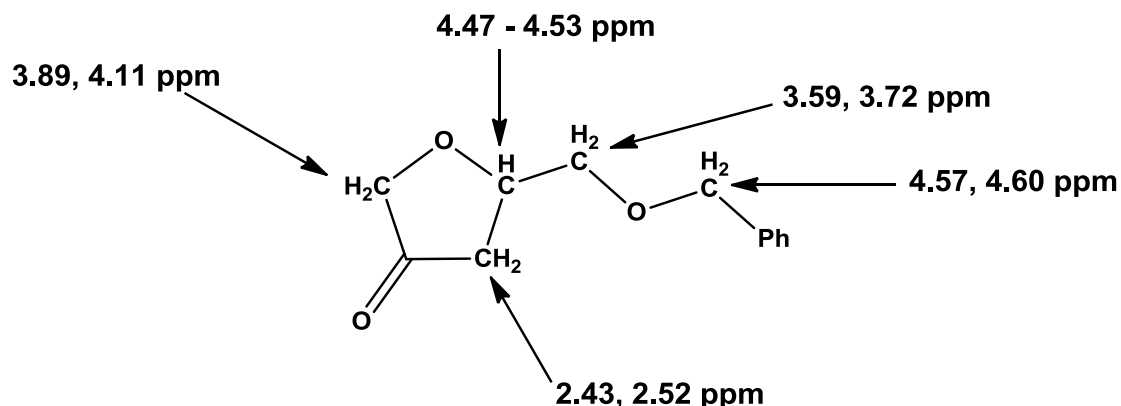


Figure 2.9.2 δH of selected resonances observed in the 1H NMR spectrum of **68**.

The proton spectrum associated with (±)-5-benzyloxymethyl-3(2*H*)-furanone **68** shows numerous ABX and AB spin systems. This is due to the various diastereotopic protons due to the conformational folding of the molecule. The AB spin system associated with the C2 protons at 3.89 ppm and 4.11 ppm are considerably deshielded due to the adjacent carbonyl group and the ring ether moiety. The C2 protons display a large coupling constant of 16 Hz. Each of these protons, which displays a doublet confirm the formation of the compound.

The C4 protons display an ABX system. Each of the protons display a doublet of doublets. Each proton shows germinal coupling and coupling to the C5 proton. Each of the benzyloxy ether (BnOCH₂) protons display a doublet of doublets for similar reasons (**Figure 2.9.1**). The 1H NMR spectra of (±)-5-benzyloxymethyl-3(2*H*)-furanone **68** and (±)-5-benzyloxyethyl-3(2*H*)-furanone **69**, displayed a similar spectrum with only one key difference, a multiplet at 1.91 - 1.21 ppm observed for the benzyloxyethyl protons (BnOCH₂CH₂). The IR spectrum displays only one carbonyl stretch, which occurs at 1760 cm⁻¹. The chemical shift of the carbonyl carbon of the 3(2*H*)-furanones was observed at 214 ppm in the corresponding ^{13}C NMR spectrum. All 3(2*H*)-furanones were verified by high resolution mass spectrum on the molecular ion peak.

For (±)-5-benzyloxymethyl-2-methyl-3(2*H*)-furanone **70**, the methyl group attached to the C2 carbon displays a doublet in the 1H NMR spectrum, due to coupling which occurs from the C2 proton. Due to the presence of two diastereoisomers, two sets of doublets were observed and these were integrated to give the diastereoisomeric ratio.

The C2 proton appears considerably downfield at 4.3 and 4.6 ppm due to the electron withdrawing effect of the C3 ketone and the ether functionality. COSY analysis confirmed the chemical shift of these signals and their assignment due to their coupling of the methyl group C2. NOE analysis of the diastereoisomeric mixture identified the *syn* isomer as the major diastereoisomer. Irradiation of the methyl group at 1.26 ppm gave an enhancement at 4.37 ppm, however the methyl group belonged to the minor diastereoisomer. When the methyl group at 1.32 ppm were irradiated no enhancement of the C5 proton was observed. The ^1H NMR spectrum of (\pm)-5-benzyloxymethyl-2-methyl-3(2*H*)-furanone **72** appears in **Figure 2.9.3**.

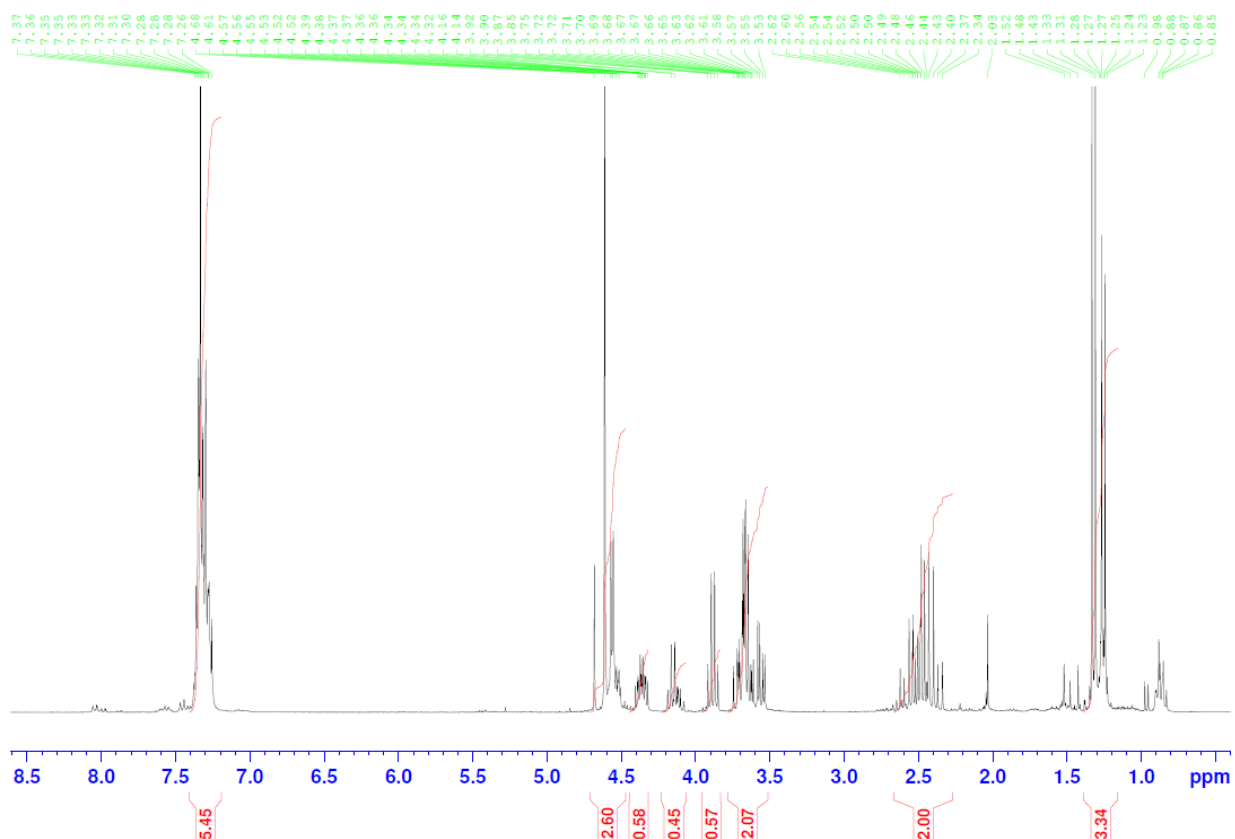


Figure 2.9.3 ^1H NMR of (\pm)-5-benzyloxymethyl-2-methyl-3(2*H*)-furanone.

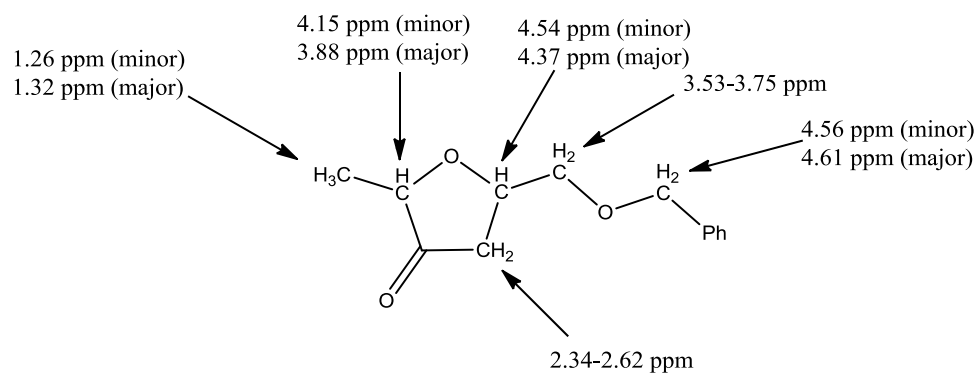
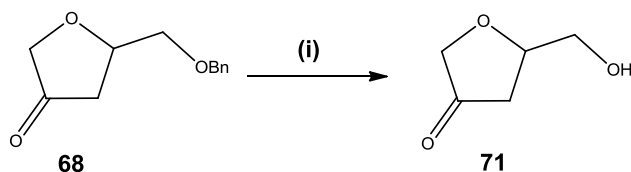


Figure 2.9.4 δH of selected resonances observed in the 1H NMR spectrum of **70**.

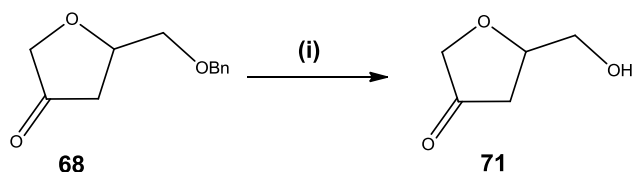
2.10 Derivatisations of Alkyl Chain at the 5-Position of the 4,5-Dihydro-3(2H)-furanone

Replacement of the benzyloxy ether functionality with various isosters of the quaternary ammonium group were carried out in order to create various analogues of desmethylnuscarine. Hydrogenolysis of the benzyloxy ether group was investigated by O'Donovan¹⁸ and Lambe¹⁹ using hydrogen gas with palladium on carbon as the catalyst. O'Donovan generated hydrogen from the reaction of sodium borohydride with HCl. The hydrogenolysis was carried out by bubbling hydrogen through the reaction which contained (±)-5-benzyloxymethyl-3(2H)-furanone **68** and 200% w/w catalyst loading of 10% Pd-C **Scheme 2.10.1**. However, for scale-up purposes and because of the number of reactions required, this protocol was not deemed feasible. Initial trial reactions were carried on (±)-5-benzyloxymethyl-3(2H)-furanone **68** where a number of loadings of up to 50% w/w Pd-C catalyst at an atmospheric pressure of hydrogen were investigated. However, none of these reactions showed formation of the desired alcohol **71**.



Scheme 2.10.1 Reagents: (i) H₂, Pd-C, ethanol.

The reactions were then carried out under varying pressures, up to 45 psi, while the catalyst loading was kept at 20% w/w of 10% Pd-C. The hydrogen pressure increased in 5 psi increments. At 10 psi, some debenzoylation was observed. It was observed that 30 psi and 35 psi proved to be the optimum pressure for maximum conversion to (±)-5-hydroxymethyl-3(2H)-furanone **71**. However, a large amount of (±)-5-benzyloxymethyl-3(2H)-furanone **68** was still present while an alkyl impurity was also observed in the crude ¹H NMR spectrum. The ratio of starting material to the product was 1.7 : 2.1. This protocol did not prove practical in the synthesis of (±)-5-hydroxymethyl-3(2H)-furanone **71** due to the large quantities required. Other catalysts were investigated and palladium hydroxide, Pd(OH)₂, proved to be a far superior catalyst to any others investigated. Cleavage of the benzyloxy ether group using Pd(OH)₂ as a catalyst allowed full conversion of the (±)-5-benzyloxymethyl-3(2H)-furanone **68** to (±)-5-hydroxymethyl-3(2H)-furanone **71** without impurity formation **Scheme 2.10.2**.



Scheme 2.10.2 Reagents: (i) H₂, 30 psi, Pd(OH)₂, ethanol.

Completion of the reaction was confirmed by ¹H NMR analysis, with disappearance of the phenyl and benzylic protons from the revalent spectra. No difference in reactivity was observed when the catalyst loading was increased from 20 - 30%. The reaction was completed in under 4 h and crude ¹H NMR analysis suggested that no further purification was necessary. Initially, the yield of the reaction was between 45 - 50%, however, addition of celite® to the reaction mixture and sonication for 15 mins prior to filtration through a bed of celite® increased the yield. This could be attributed to (±)-5-hydroxymethyl-3(2*H*)-furanone **71** chelating to the palladium and the use of celite® as a post reaction additive serving to attenuate this chelation. The product was isolated as a clear oil. The same protocol was extended to the hydrogenolysis of (±)-5-benzyloxyethyl-3(2*H*)-furanone **69** and for the hydrogenolysis of the 3-hydroxytetrahydrofurans.

3(2 <i>H</i>)-Furanone	Yield (%)	(C=O) ν/cm^{-1}
 71	72	1759
 72	61	1759

Table 2.10.1 Yields and key spectroscopic data for 5-hydroxyalkyl-3(2*H*)-furanones.

The IR spectra of both (\pm)-5-hydroxymethyl-3(2*H*)-furanone **71** and (\pm)-5-hydroxyethyl-3(2*H*)-furanone **72** had peaks corresponding to the ketone of the 3(2*H*)-furanone, at 1759 cm^{-1} and the alcohol, at 3423 cm^{-1} . Peaks corresponding to a monosubstituted phenyl ring were absent from the spectra. The ^1H NMR spectrum, of compound **71**, contains an AB system, the C2 protons (at 3.93 and 4.13 ppm), which is due to the diastereotopic nature of the C2 protons making them both chemically and magnetically inequivalent.

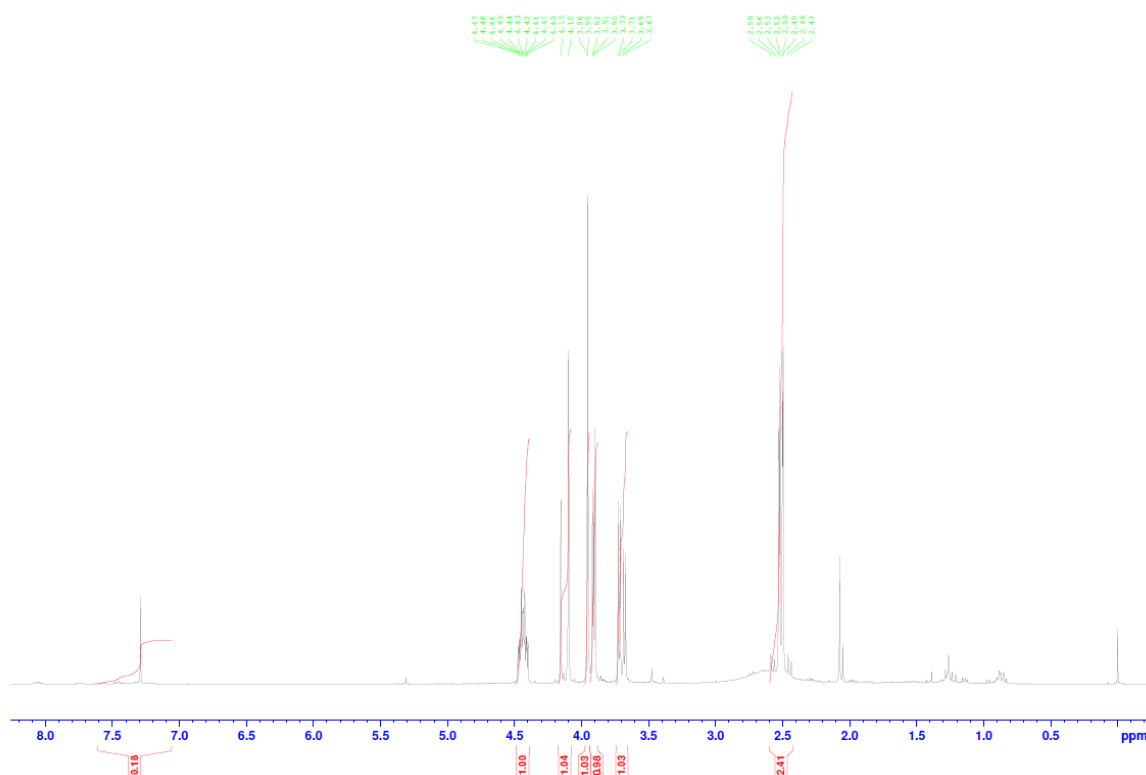


Figure 2.10.1 ^1H NMR of (\pm)-5-hydroxymethyl-3(2*H*)-furanone **71**.

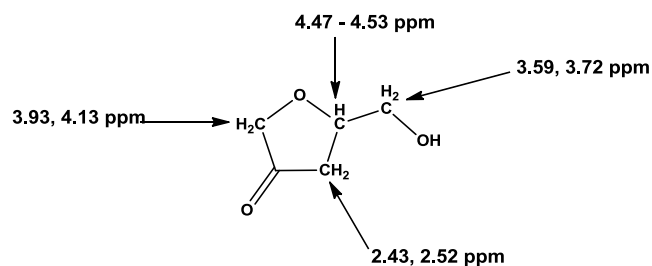
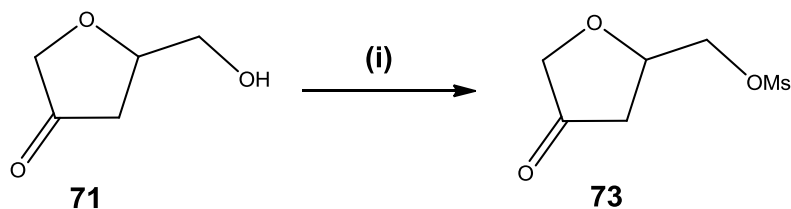


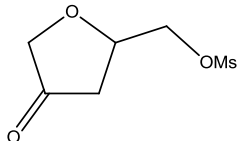
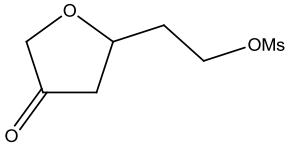
Figure 2.10.2 δH of selected resonances observed in the ^1H NMR spectrum of **71**.

The primary alcohol of (±)-5-hydroxymethyl-3(2*H*)-furanone **71** must undergo chemical transformation to afford the precursor to the desired desmethylnuscarine and its various analogues. To achieve this, the primary alcohol was mesylated with mesyl chloride in the presence of triethylamine using DCM as solvent, affording a mesylate which could be subsequently converted to the desired derivative. Triethylamine and the required 5-hydroxyalkyl-3(2*H*)-furanone were dissolved in DCM and cooled to 0 °C. Mesyl chloride was then added dropwise *via* syringe. Following addition of the mesyl chloride, the reaction was allowed to warm slowly to room temperature and stirred for 2 h, after which time TLC analysis indicated complete consumption of starting material. Crude ¹H NMR analysis indicated no further purification was necessary, and the product was carried through to the next reaction.

Mesylation of either (±)-5-hydroxymethyl-3(2*H*)-furanone **71** or (±)-5-hydroxyethyl-3(2*H*)-furanone **72** was carried out in DCM using mesyl chloride (1.3 eq) and triethylamine (1.3 eq) at 0 °C and stirred for 2 h. The reaction work-up was carried out using mild acidic conditions and the subsequent compound was used without further purification. Completion of the reaction was monitored by ¹H NMR analysis. The IR showed the absence of an OH functional group stretch at 3300 to 3500 cm⁻¹.



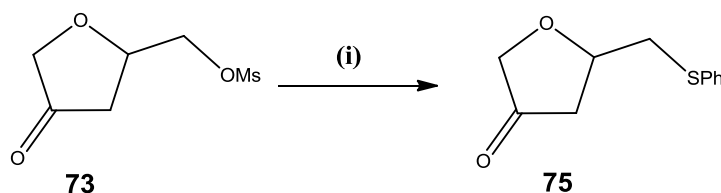
Scheme 2.10.3 Reagents: (i) MsCl, NEt₃, DCM, 0 °C.

3(2 <i>H</i>)-Furanone	Yield (%)*
 73	83
 74	79

*yields are for unpurified compounds.

Table 2.10.2 Yields for mesylated 5-hydroxyalkyl-3(2*H*)-furanones.

Replacement of the mesylate with a sulphide group was achieved using a nucleophilic substitution reaction. Thiophenol was treated with sodium hydride to afford the thiophenolate anion while the appropriate mesylate was dissolved in THF and added dropwise to the thiophenolate suspension. The reaction mixture was then heated to reflux overnight (**Scheme 2.10.4**). Following work-up, flash column chromatography was used to isolate the sulphide, **75** and **76** in moderate yield. A considerable quantity of diphenyldisulfide was also recovered due to the oxidation of thiophenol to diphenyldisulfide during the course of the reaction. 17% of product was isolated following stirring the reaction at room temperature, however, heating the reaction to reflux gave a 49% isolated yield. This reaction protocol was applied to the synthesis of (±)-5-benzenesulfenylmethyl-4,5-dihydrofuran-3(2*H*)-one **75** and (±)-5-(2-benzene sulfenylethyl)-4,5-dihydrofuran-3(2*H*)-one **76**.



Scheme 2.10.4 Reagent: (i) PhSNa, THF, reflux.

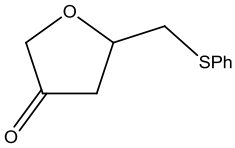
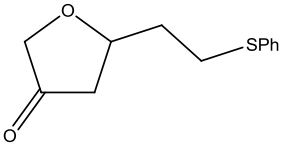
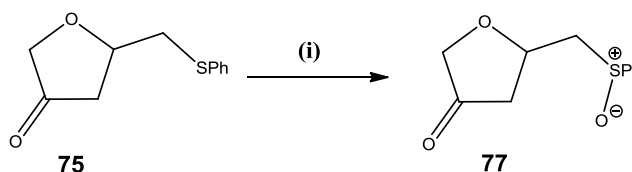
3(2 <i>H</i>)-Furanone	Yield (%)
 <p>75</p>	49
 <p>76</p>	68

Table 2.10.3 Yields for 5-(thiophenyl)-alkylated-3(2*H*)-furanones.

The ^1H NMR spectra associated with (\pm)-5-benzenesulfenylmethyl-4,5-dihydrofuran-3(2*H*)-one **75** and (\pm)-5-(2-benzenesulfenylethyl)-4,5-dihydrofuran-3(2*H*)-one **76** were similar to that of (\pm)-5-benzoyloxymethyl-3(2*H*)-furanone **68** and (\pm)-5-benzoyloxyethyl-3(2*H*)-furanone **69** respectively. Both sets of spectra had ABX systems corresponding to the C4 proton and PhSCH_2 protons as well as AB systems corresponding to C2 protons. These systems have already been discussed in **Section 2.9**.

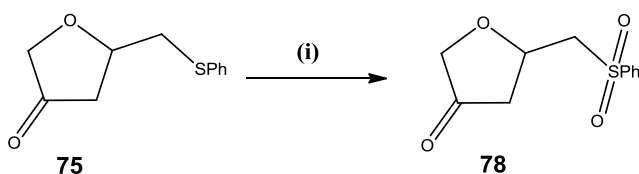
Different analogues of desmethylnuscarine including isosters such as the sulfoxide and sulfone were synthesised by oxidation of sulfide. Efficient oxidation of (\pm)-5-benzenesulfenylmethyl-3(2*H*)-one **75** to the corresponding (\pm)-5-benzenesulfinylmethyl-3(2*H*)-furanone **77** was achieved when using Oxone[®] (0.7 eq) was used as the oxidant (**Scheme 2.10.5**).



Scheme 2.10.5 Reagents: (i) Oxone[®] (0.7 eq), water, methanol.

Other reagents such as *m*-CPBA, acetic acid / hydrogen peroxide mixture and magnesium monoperoxyphthalate, all gave unidentifiable decomposition products.

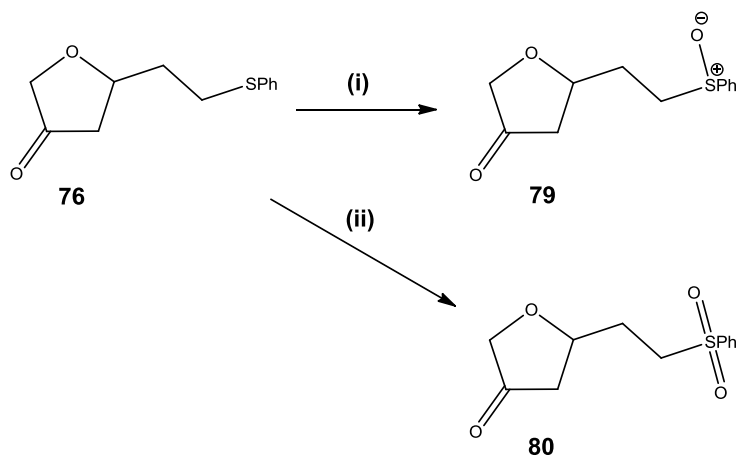
Oxone (0.7 eq) was dissolved in water and added dropwise to a methanolic solution of (\pm)-5-benzenesulfenylmethyl-3(2*H*)-furanone and stirred for 90 mins. The reaction was monitored by TLC analysis. Upon completion, the methanol was evaporated *in vacuo* and the reaction was partitioned across DCM and the aqueous layer was extracted twice. The desired product was isolated by flash column chromatography in moderate yield. The moderate yield could be attributed to the partial solubility of the products **77** and **79** in water. The sulfone was synthesised using the same protocol as for the synthesis of the sulfoxide, for the synthesis of the (\pm)-5-benzenesulfonylmethyl-3(2*H*)-furanone **80**, Oxone[®] (1.5 eq) were utilised (**Scheme 2.10.6**). The reaction was monitored by TLC analysis and the methanol was evaporated *in vacuo* when the reaction was deemed complete. The product **78** was again extracted with DCM and isolated by flash column chromatography.



Scheme 2.10.6 Reagents: (i) Oxone[®] (2 eq), methanol, water.

For synthesis of the sulfoxide and sulfone homologues of (\pm)-5-benzene sulfenylethyl-3(2*H*)-furanone **76**, a different protocol was adopted. To synthesise the sulfoxide of (\pm)-5-(2-benzenesulfenylethyl)-3(2*H*)-furanone **76**, *m*-CPBA with a potency of 77% was used as the oxidant. When *m*-CPBA (1 eq) was used, starting material; the sulfoxide and the sulfone, were recovered in a ratio of 0.4 : 1.1 : 0.6 following column chromatography. Increasing the equivalents of *m*-CPBA only increased the yield of the sulfone, while it was found that the isolated yield of the sulfoxide had decreased. As a result of this investigation, it was deemed *m*-CPBA would be a sufficient oxidant to convert (\pm)-5-(2-benzenesulfenylethyl)-3(2*H*)-furanone **78** to the sulfone, when the equivalents of *m*-CPBA were increased to push the oxidation to completion. It was found that hydrogen peroxide in acetic acid gave exclusively (\pm)-5-(2-phenylsulfinylethyl)-3(2*H*)-furanone **79** with no trace of the sulfone side product being observed. Hydrogen peroxide oxidises the acetic acid to peracetic acid and this in turn oxidises the sulfide to the sulfoxide. (\pm)-5-(2-Phenylsulfenylethyl)-3(2*H*)-furanone **76** was dissolved in acetic acid and hydrogen peroxide (1.5 eq) was then added dropwise to the reaction which was

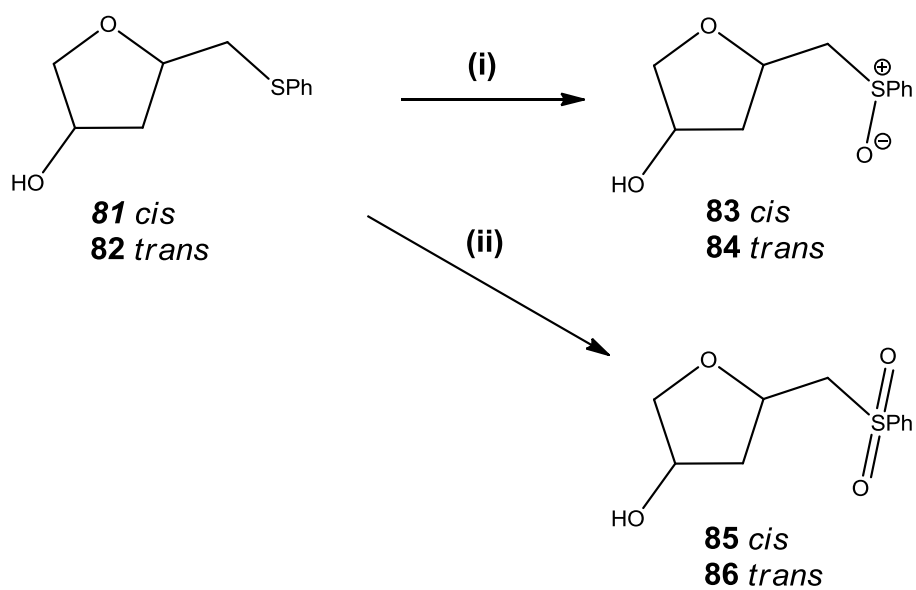
monitored by TLC. The reaction was deemed completed after 90 mins. The pH was then adjusted to 7 with saturated sodium bicarbonate and the product was extracted with DCM. The product was isolated by flash column chromatography in moderate yield. (**Scheme 2.10.7**).



Scheme 2.10.7 Reagents: (i) H_2O_2 , acetic acid, (ii) MCPBA.

For the synthesis of the sulfones **78** and **80**, *m*-CPBA (2.5 eq) at 77% potency was used as the oxidant. *m*-CPBA was added portion-wise to a stirring solution of (±)-5-(2-phenylsulfenylethyl)-3(2*H*)-furanone **76**. The reaction was monitored by TLC, and upon completion, the reaction was diluted with DCM and the organic layer was washed with 5% sodium sulphite solution to reduce any residual *m*-CPBA. The organic layer then was washed with sodium bicarbonate solution to remove the *meta*-chlorobenzoic acid. Flash column chromatography, using 40% ethyl acetate in hexane, isolated the product in moderate yield.

For 3-hydroxytetrahydrofurans, oxidation to the corresponding sulfoxides was carried out utilising the same protocol as for the oxidation of (±)-5-benzenesulfenylmethyl-3(2*H*)-furanone **75** to the corresponding (±)-5-benzenesulfinylmethyl-3(2*H*)-furanone **77**. Both *syn* and *anti* diastereoisomers of (±)-5-benzenesulfenylmethyl-3-hydroxytetrahydrofurans were oxidised to the corresponding (±)-5-benzenesulfinylmethyl-3-hydroxytetrahydrofurans using Oxone[®] (0.7 eq). While full oxidation to the corresponding (±)-5-benzene sulfonylmethyl-3-hydroxytetrahydrofurans was achieved using Oxone[®] (2 eq) (**Scheme 2.10.8**).



Scheme 2.10.8 Reagents: (i) Oxone (0.7 eq), methanol, water, (ii) Oxone (2 eq), water, methanol.

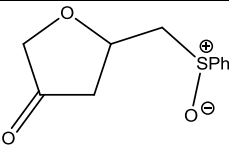
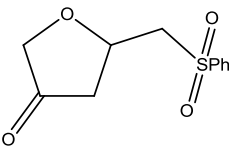
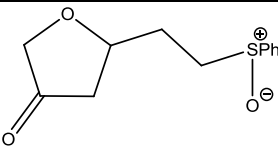
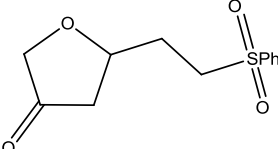
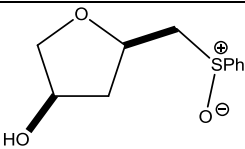
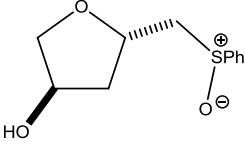
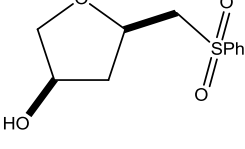
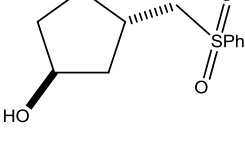
Oxidised 3(2H)-Furanone	Yield (%)	Oxidant	$\nu/\text{cm}^{-1}(\text{C}=\text{O})$
 77	39	Oxone [®] (0.7 eq)	1759
 78	56	Oxone [®] (2 eq)	1759
 79	58	H ₂ O ₂ , acetic acid	1758
 80	51	<i>m</i> -CPBA	1760
 83	67	Oxone [®] (0.7 eq)	-
 84	72	Oxone [®] (0.7 eq)	-
 85	76	Oxone [®] (2 eq)	-
 86	72	Oxone [®] (2 eq)	-

Table 2.10.4 Yields and key spectroscopic data for oxidised sulphur derivatives of 3(2H)-furanones and 3-hydroxytetrahydrofurans.

The ^1H NMR spectrum associated with (\pm) -5-(2-phenylsulfinylmethyl)-3(2H)-furanone **77** contains doubling of signals. This is due to the mixture of diastereoisomers present in the mixture. The extra chiral centre is due to the sulfoxide in the molecule (Figure 2.10.1). The sulfoxide moiety is a chiral centre, much like an asymmetric carbon; this results in the doubling of signals. Both the ^1H NMR spectra of (\pm) -5-(2-phenylsulfinylmethyl)-3(2H)-furanone **77** and (\pm) -5-(2-phenyl sulfonylmethyl)-3(2H)-furanone **78** are similar to (\pm) -5-benzyloxy-3(2H)-furanone **68** as all of these compounds contain the 3(2H)-furanone moiety.



Figure 2.10.1 A pair of enantiomeric sulfoxides

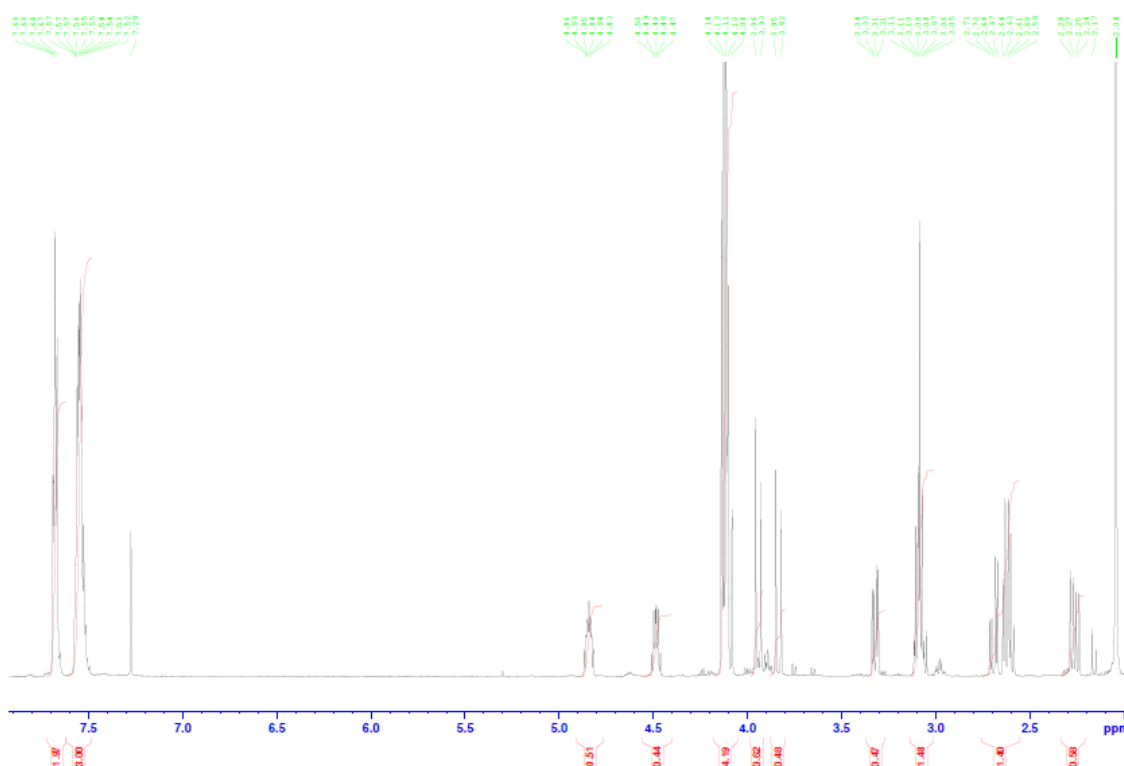


Figure 2.10.3 ^1H NMR of (\pm) -5-(2-phenylsulfinylmethyl)-3(2H)-furanone **77**.

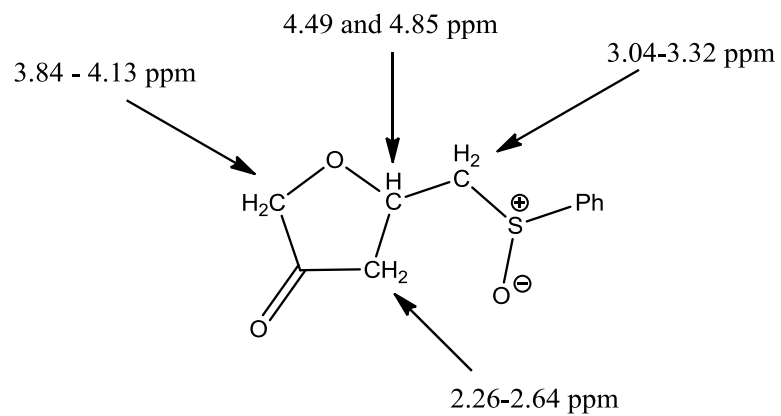


Figure 2.10.4 δ H of selected resonances observed in the 1 H NMR spectrum of **77**.

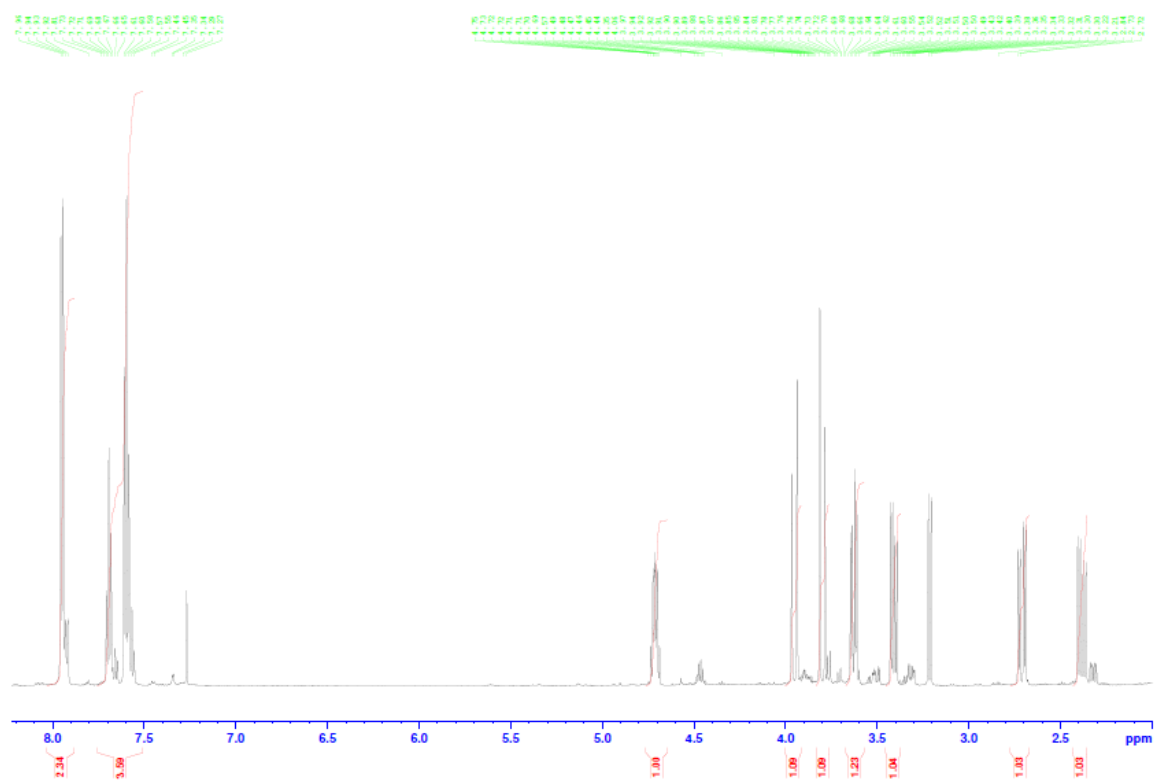


Figure 2.10.5 1 H NMR of (\pm)-5-(2-phenylsulfonylmethyl)-3(2H)-furanone **78**.

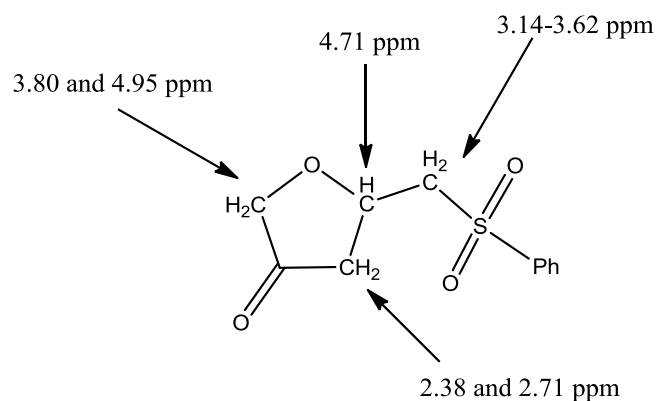
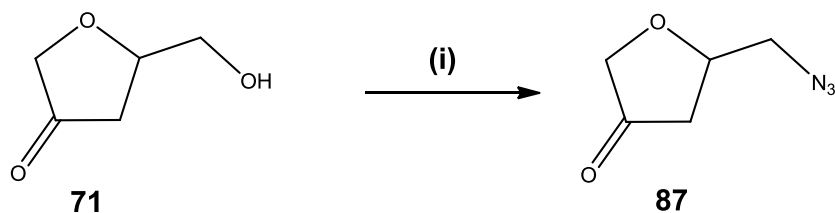


Figure 2.10.6 δH of selected resonances observed in the ^1H NMR spectrum of **78**.

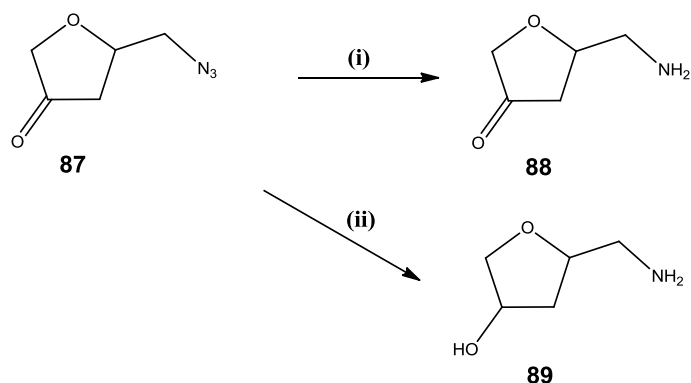
In the synthesis of the alkyl azide desmethylnuscarine analogue, two routes were used. In one route, the alcohol was transformed to the alkyl iodide using the Appel reaction. This reaction involved treating the alcohol with triphenylphosphine, imidazole and iodine (1.3 eq) in acetonitrile to afford the alkyl iodide. This alkyl iodide was not isolated but was carried through to the next stage in a “one pot” reaction. After 2 h, sodium azide and 15-crown-5 were added to the reaction, which was then heated to 60 °C overnight. 15-crown-5 was used to sequester the sodium from the azide and hence make it more nucleophilic. For the duration of the reaction the apparatus was covered with aluminium foil, to prevent photo degradation of the alkyl iodide. The reaction solution was extracted with DCM and washed with sodium thiosulfate solution to oxidise any residual iodine. Flash column chromatography was then used to isolate the product as a clear oil in low yield (**Scheme 2.10.9**).



Scheme 2.10.9 Reagents: (i) Imidazole, I_2 , Ph_3P , acetonitrile, 0 °C (ii) 15-crown-5, NaN_3 , 60 °C. or (i) MsCl , NEt_3 , DCM, 0 °C (ii) 15-crown-5, NaN_3 , acetonitrile, reflux.

In the alternative route, the alcohol was first converted to the mesylate using the same protocol implemented during the synthesis of **73**. IR analysis of the reaction indicated consumption of starting material after 2 h, due to the absence of the alcohol

functionality in the spectrum. Upon consumption of the starting material, 15-crown-5 and sodium azide were added to the reaction, which was then heated and allowed to reflux overnight. The reaction was washed with 10% w/v HCl and flash column chromatography isolated the desired azide product in moderate yield. The “one pot” reaction, involving methanesulfonyl chloride followed by addition of sodium azide, gave a far higher yield than the reaction which generated the alkyl iodide *in situ* (26% compared to 56%). Upon synthesis of the azide, attempted reduction of the azide to the corresponding amine was carried out using 5% palladium on carbon at 10 psi, however, only starting material was recovered. Attempted reduction of the azide was also carried out using lithium aluminium hydride, however an inseparable mixture of compounds was recovered (**Scheme 2.10.10**). IR analysis of the crude reaction mixture showed the absence of any amine or alcohol signals. Crude ^1H NMR analysis also showed the absence of the C4 proton in the 1.9 ppm to 2.5 ppm region, these protons would be recognisable by their distinctive pattern.



Scheme 2.10.10 Reagents: (i) H_2 , Pd-C, ethanol, (ii) LiAlH_4 , THF.

3(2H)-Furanone	Conditions	Yield (%)	(C-N=N=N) ν/cm^{-1}
 87	(i) Imidazole, I_2 , Ph_3P , (ii) 15-crown-5, NaN_3 .	26	2100
	(i) MsCl , NEt_3 , (ii) 15-crown-5, NaN_3 .	56	

Table 2.10.4 Yields and key spectroscopic data for 5-(2-azidoethyl)-3(2H)-furanones.

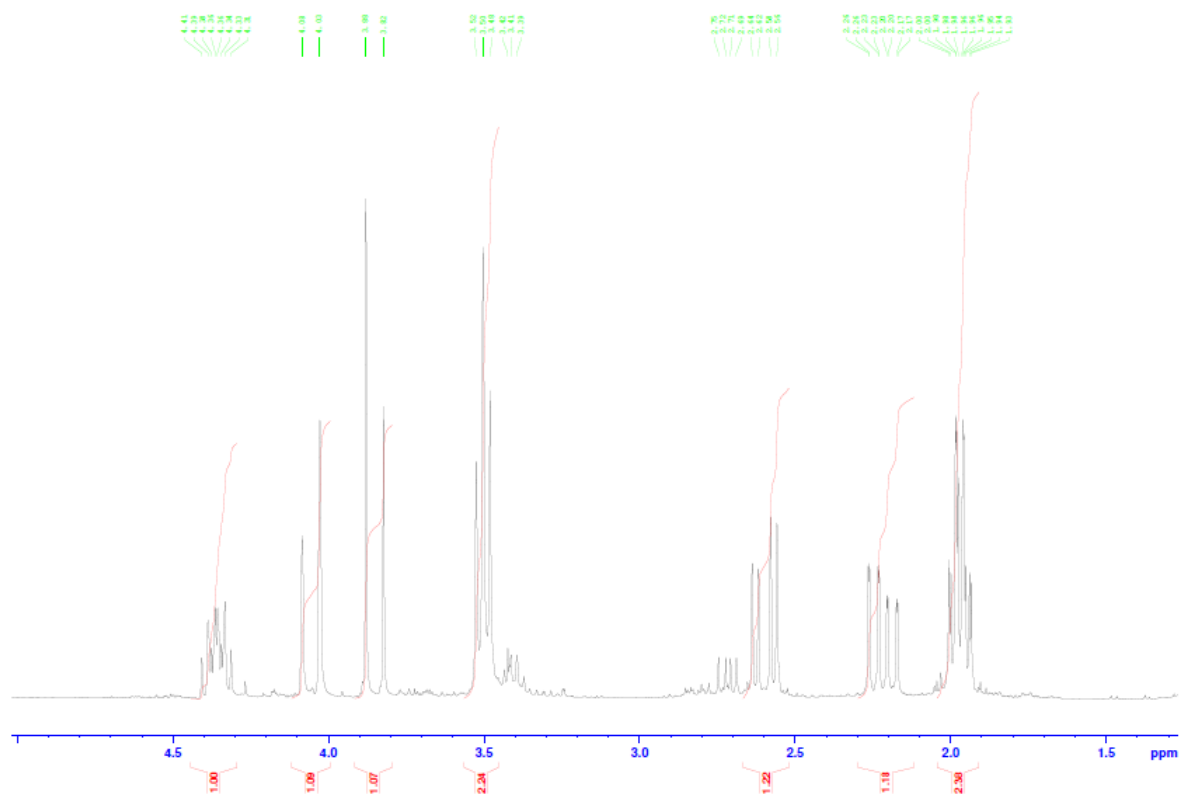


Figure 2.10.7 ^1H NMR of 5-(2-Azidoethyl)-3(2H)-furanone.

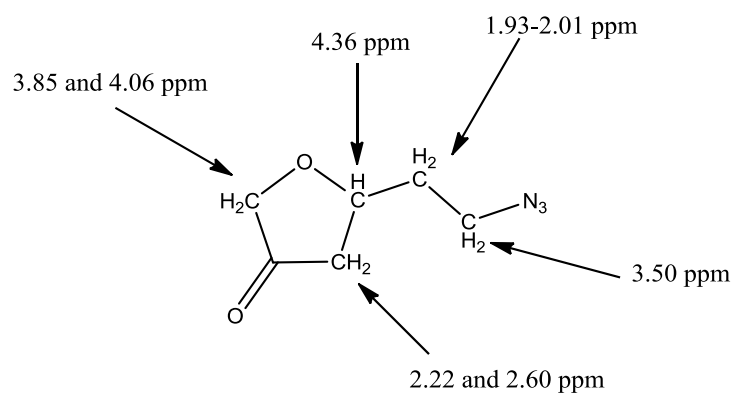
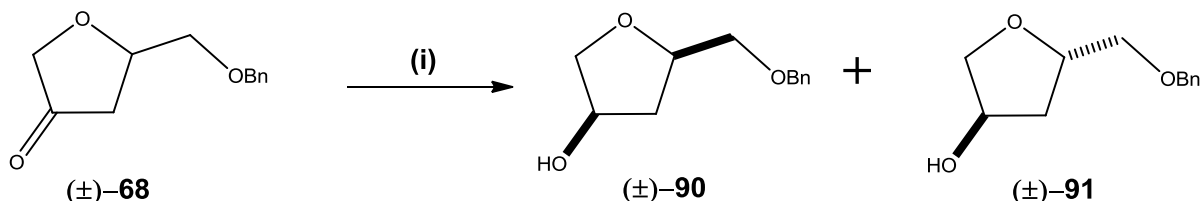


Figure 2.10.8 δH of selected resonances observed in the ^1H NMR spectrum of **87**.

2.11 Reduction of 4,5-Dihydro-3(2*H*)-furanones to 3-Hydroxytetrahydrofurans

Borohydride reductions of the 3(2*H*)-furanones afforded the racemic 3-hydroxytetrahydrofurans. Depending on the nature of the substituents on the 3(2*H*)-furanones, delivery of the hydride could be directed to afford diastereoisomerically enriched 3-hydroxytetrahydrofurans. Sodium borohydride reduction was carried out on (±)-5-benzyloxymethyl-3(2*H*)-furanone **68** by dissolving the same compound in methanol and cooling to 0 °C. Sodium borohydride suspended in water was added slowly to the reaction and the effervescence of hydrogen was observed. The reaction was monitored by TLC. Although (±)-5-benzyloxymethyl-3-hydroxytetrahydrofurans **90** and **91** both possess a phenyl ring, visualisation by UV (254 nm) was not possible, visualisation was achieved by ceric sulfate staining. The appearance of a spot lower on the TLC plate indicated the presence of a more polar alcohol, the 3-hydroxytetrahydrofuran.

The reaction was quenched by the addition of 10% HCl and work-up gave a crude reaction mixture. This reduction was high yielding and ¹H NMR analysis of the crude material revealed the presence of diastereoisomers in an 11 : 7 ratio. The diastereoisomers were separable by column chromatography using 10% to 30% ethyl acetate as the eluent. The *syn*-(±)-5-benzyloxymethyl-3-hydroxy-tetrahydrofuran **90**, eluted first appearing as a clear oil in 55% yield, followed by the *anti* isomer **91** which was isolated as a clear oil in 35% yield.



Scheme 2.11.1 Reagents: (i) NaBH₄, methanol, water.

Numerous ABX systems were observed in the ¹H NMR spectra of both the *syn* and *anti* isomers of 3-hydroxytetrahydrofurans. All CH₂ protons, on the C2, C4 and BnOCH₂ protons, give rise to ABX splitting patterns, coupling to either the C3 or C5 protons. The C3 and C5 protons are the most deshielded of the protons on 3-hydroxytetrahydrofuran rings. This deshielding is due to the proximity of the protons to either the oxygen of the ether or alcohol functionalities. The stereochemistry of the

protons in both the *syn* and *anti* systems were analysed by NOE difference and NOESY experiments. Due to the coincidental overlapping nature of the C3 and C5 protons in the *syn* diastereoisomer **90**, assignment of stereochemistry using these experiments was not feasible. However, NOE difference and NOESY experiments carried out on the *anti* diastereoisomer **91** of the 3-hydroxytetrahydrofuran identified the relative stereochemistry of the hydrogens. During NOE difference experiments, irradiation of the C3 or the C5 protons did not show enhancement of the other proton (C3 proton did not enhance C5 proton or vice versa). NOESY experiments carried out on the *anti* diastereoisomer **91** meanwhile showed cross peaks between the C5 proton and one of the C4 protons and cross peaks between C3 proton and one of the C2 protons and the other C4 proton.

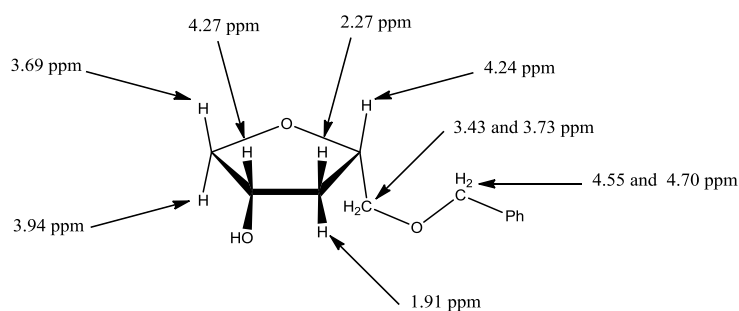


Figure 2.11.1 δH of selected resonances observed in the ^1H NMR spectrum of **90**.

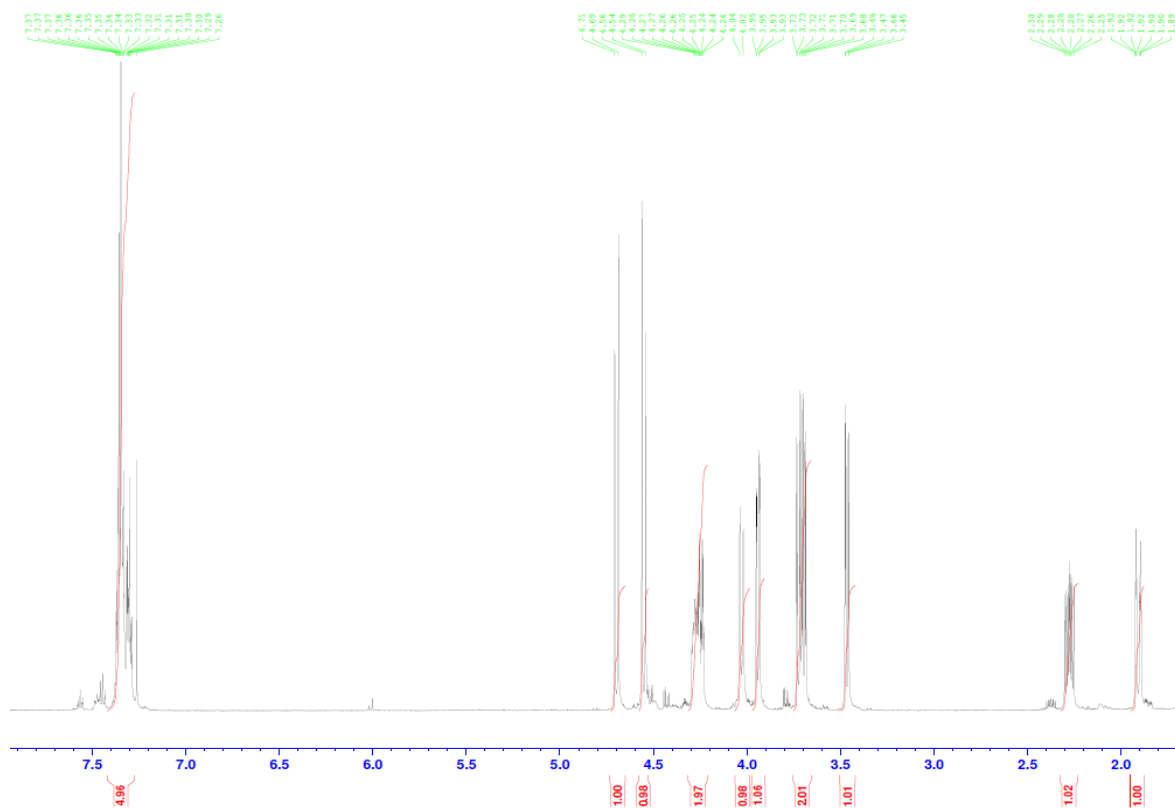


Figure 2.11.2 ^1H NMR of syn-(±)-5-benzylloxymethyl-3-hydroxytetrahydrofurans **90**.

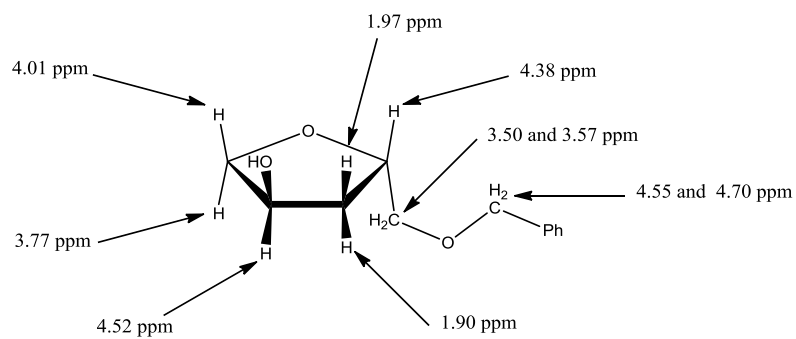


Figure 2.11.3 δH of selected resonances observed in the ^1H NMR spectrum of **91**.

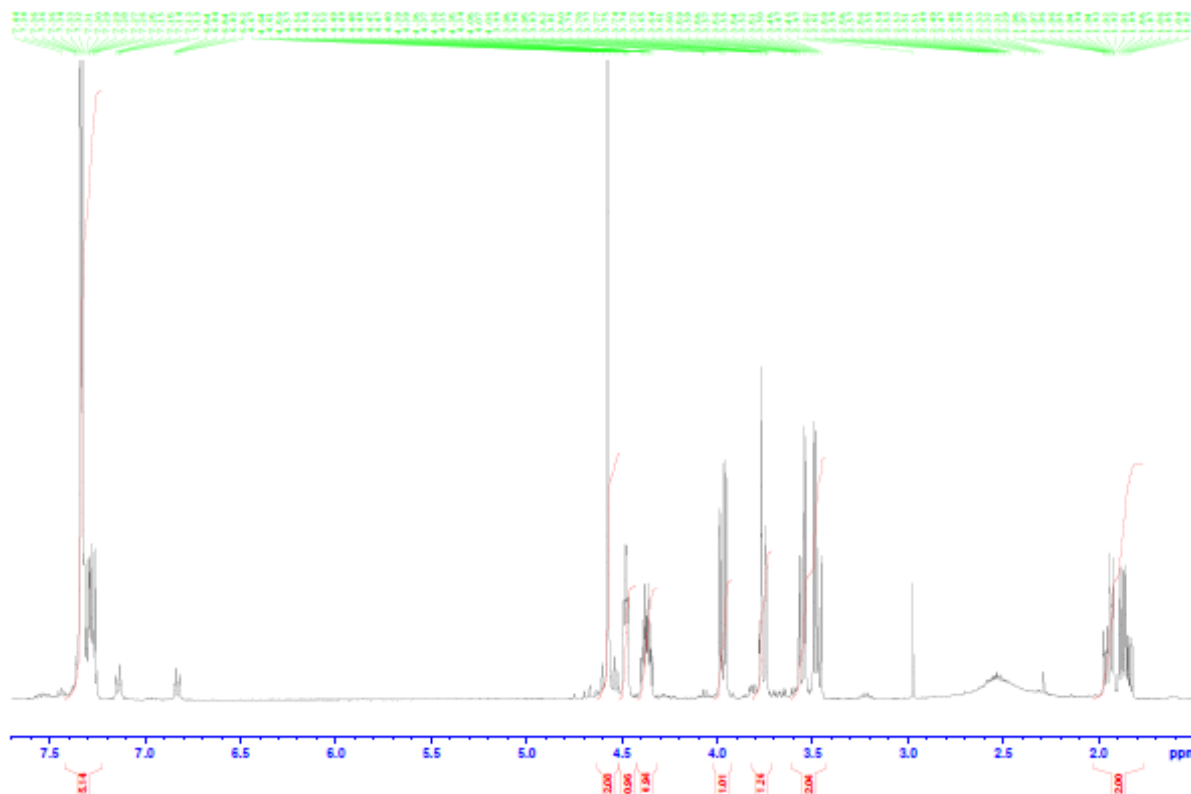
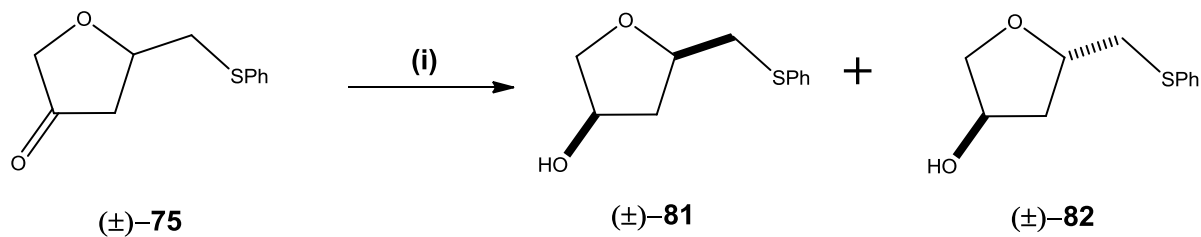


Figure 2.11.24 ^1H NMR of anti (\pm)-5-benzyloxymethyl-3-hydroxytetrahydrofurans **91**.

Both *syn* **81** and *anti* **82** (\pm)-3-hydroxy-5-(2-phenylsulfenylmethyl)-tetrahydrofurans were synthesised using the same aforementioned protocol. (\pm)-5-(2-Phenylsulfenylmethyl)-3(2*H*)-furanone **75** was dissolved in methanol with sodium borohydride added dropwise. The reaction was monitored as previously, with the same observations being recorded.

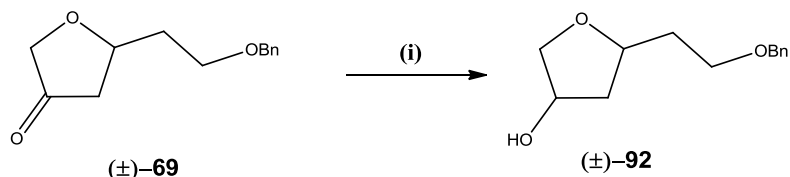
Flash column chromatography, using 10 to 30% ethyl acetate in hexane as eluent, allowed for the separation of the pair of diastereoisomers. The *syn* diastereoisomer **81** was isolated first as a clear oil in 42% yield followed by the *anti* diastereoisomer **82** which was isolated as a clear oil in 19% yield.



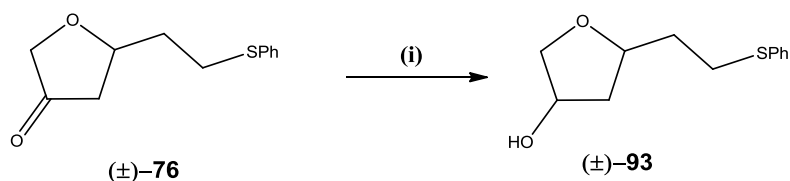
Scheme 2.11.2 Reagents: (i) NaBH_4 , methanol, water.

Similar protocols were used for the synthesis of both (\pm)-3-hydroxy-5-(2-benzyloxyethyl)tetrahydrofuran **92** and (\pm)-5-(2-benzenesulfonyl)ethyl)-3-hydroxy-tetrahydrofuran **93** with similar observations being recorded. ^1H NMR analysis of the crude reaction material showed a mixture of diastereoisomers, however, flash column chromatography using 10 to 30% ethyl acetate in hexane did not separate the individual compounds. Both the lengths of the silica column used in conjunction with different solvent mixtures as eluents were investigated in a bid to achieve separation. In this series of compounds, which extends to the sulfone analogues (\pm)-5-(2-benzenesulfinylethyl)-3-hydroxytetrahydrofuran **94**, none could be separated by chromatographic means.

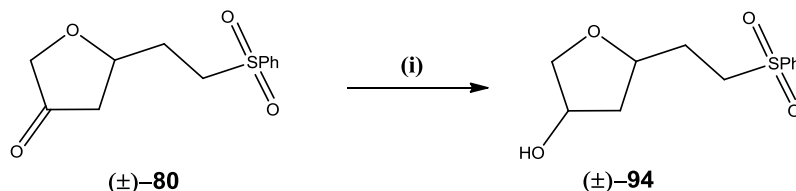
(\pm)-5-(2-Benzenesulfonyl)ethyl)-3(*2H*)-furanone **80** was reduced with lithium-tri-(*tert*-butoxy)-aluminium hydride, in a bid to stereochemically reduce the ketone to afford a diastereoisomerically enriched 3-hydroxytetrahydrofuran **94** (Scheme 2.11.4). However, purification of the 3-hydroxytetrahydrofuran product **89** by chromatography did not yield any diastereoisomeric enrichment.



Scheme 2.11.2 Reagents: (i) NaBH_4 . methanol, water.

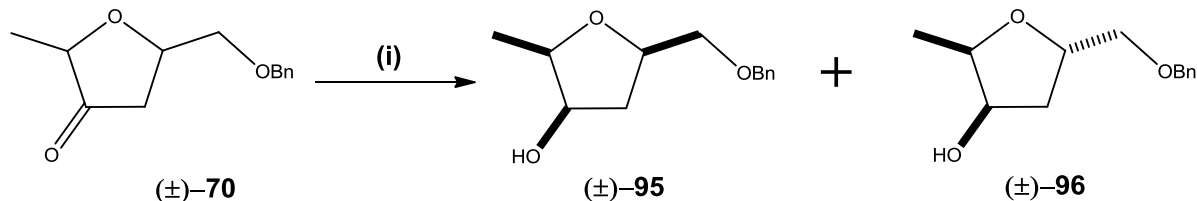


Scheme 2.11.3 Reagents: (i) NaBH_4 methanol, water.



Scheme 2.11.4 Reagents: (i) lithium-tri-(*tert*-butoxy)-aluminium hydride, THF.

Reduction of (±)-5-benzyloxymethyl-2-methyl-4,5-dihydro-3(2*H*)-furanone **70** to afford (±)-5-benzyloxymethyl-3-hydroxy-2-methyl-tetrahydrofuran was also carried out. In theory, four pairs of diastereoisomers are possible after the reduction of (±)-5-benzyloxymethyl-2-methyl-4,5-dihydro-3(2*H*)-furanone **70**, however, the possibility of complete separation of the diastereoisomeric mixture by chromatography seemed highly unlikely. As a result, a sterically hindered reducing agent was used to limit the number of diastereoisomers which could be formed. L-Selectride[®] was used as the reductant at -80 °C (**Scheme 2.11.5**). Upon purification of the crude reaction mixture, two diastereoisomers were isolated. The major diastereoisomer, which eluted first, was (±)-2*R**,3*R**,5*R**-5-benzyloxymethyl-3-hydroxy-2-methyltetrahydrofuran **95**, followed by the minor diastereoisomer (±)-2*R**,3*R**,5*S**-5-benzyloxymethyl-3-hydroxy-2-methyltetrahydrofuran **96**. Separation on a TLC plate was not evident, so ¹H NMR analysis of the individual test tubes was undertaken to determine their composition. There was a slight co-elution of both diastereoisomers. The ¹H NMR spectra of both diastereoisomers isolated from the reaction looked similar to the corresponding demethylated analogues.



Scheme 2.11.5 Reagents: (i) L-selectride, THF.

The stereochemistry of both diastereoisomers **95** and **96** was established through both NOE and NOESY experiments. It was found there were a number of ABX systems present in the ¹H NMR spectrum of (±)-2*R**,3*R**,5*R**-5-benzyloxymethyl-3-hydroxy-2-methyltetrahydrofuran **95** at the C4 and BnOCH₂ protons. In the NOESY experiment and NOE difference experiments, cross peaks and enhancements were observed for the C2 proton and the C3 proton, the C2, C3 and the C4 proton *anti* to the C₃ alcohol and a cross peak between the C5 proton and the C4 proton *anti* to the C₃, alcohol were all observed.

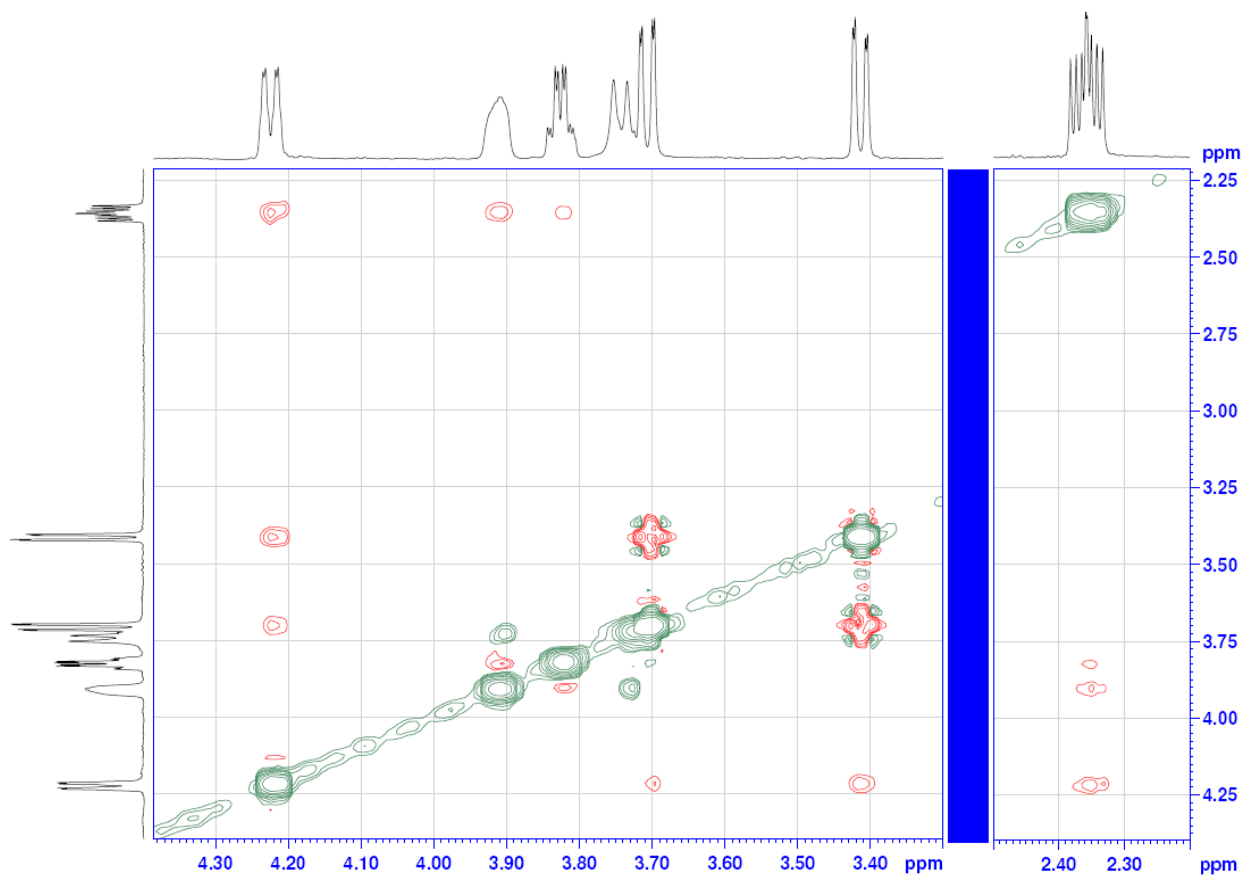
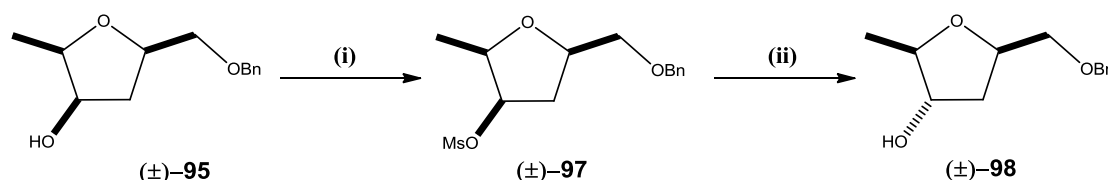


Figure 2.11.3 NOESY spectrum of (\pm) -2*R**,3*R**,5*R**-5-benzyloxymethyl-3-hydroxy-2-methyltetrahydrofuran **95**.

For (\pm) -2*R**,3*R**,5*S**-5-benzyloxymethyl-3-hydroxy-2-methyltetrahydrofuran **96**, the NOESY experiment showed cross peaks between the C2 and C3 protons, as well as between the C3 proton and C4 proton *anti* to the C3 hydroxyl. However, the C5 proton did show a crosspeak for a correlation with the proton *anti* to the C3 hydroxyl.

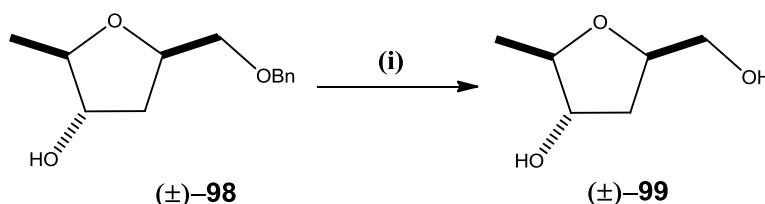
(\pm) -2*R**,3*R**,5*R**-5-(Benzyloxymethyl)-3-hydroxy-2-methyltetrahydrofuran **95** was mesylated in order to invert the stereochemistry at the 3-position of the 3-hydroxytetrahydrofuran ring. This was achieved using mesyl chloride with pyridine as both the solvent and base. Work-up of the reaction yielded the (\pm) -2*R**,3*R**,5*R**-5-(benzyloxymethyl)-3-methanesulfonyloxy-2-methyl-tetrahydrofuran **97** in sufficient purity to be used without further purification. S_N2 reaction conditions were expected to afford the inverted alcohol at the 3-position. O'Donovan¹⁸ had explored various methodologies to invert the stereochemistry at the 3-position, amongst which was the Mitsunobu

reaction, using 4-nitrobenzoic acid, however, most of these reactions did not prevail. O'Donovan found potassium superoxide, when used in conjunction with 18-crown-6 and with DMSO as solvent, showed the desired inversion of stereochemistry (**Scheme 2.11.6**). However, repetition of these conditions did not completely invert the alcohol, rather racemisation of the alcohol was observed. Purification by chromatography did not completely separate the unwanted diastereoisomer from the desired diastereoisomer, (\pm)-2*R**,3*S**,5*R**-5-benzyloxymethyl-3-hydroxy-2-methyltetrahydro furan **98**.



Scheme 2.11.6 Reagents: (i) mesyl chloride, pyridine, (ii) KO_2 , 18-crown-6, DMSO.

(\pm)-2*R**,3*S**,5*R**-5-Benzyloxymethyl-3-hydroxy-2-methyltetrahydrofuran **98** was subsequently debenzylated to afford (\pm)-2*R**,3*S**,5*R**-5-hydroxymethyl-3-hydroxy-2-methyltetrahydrofuran **99**. This was achieved using $\text{Pd}(\text{OH})_2$ (10% on carbon) at 35 psi. The reaction was monitored by TLC and ^1H NMR analysis of the crude reaction mixture, which showed the absence of the benzyl group. The reaction was filtered through celite® and washed with methanol to afford the diol in a low yield (**Scheme 2.11.7**). The reasons for this low yield were not established during the course of the work. The relative stereochemistry was confirmed by NOESY experiment. Cross peaks were observed between the C5 proton and one of the protons on the C4 carbon, while the other C4 proton showed a cross peak with the C3 proton. NOE difference experiments revealed the protons at the C2 and C5 protons have *syn* relative stereochemistry. The molecule had previously been synthesised by Boukouvalas and co-workers.³⁰



Scheme 2.11.7 Reagents: (i) H_2 , $\text{Pd}(\text{OH})_2$, 30 psi, ethanol.

2.12 Synthesis of Enantioenriched 3-Hydroxytetrahydrofurans

Microbial transformations and yeast mediated transformations in particular, have been used for many years in the production of bread, dairy products and alcoholic beverages.

Biotransformations can be carried out using either whole cells or isolated enzymes; both having several advantages.³⁰ Isolated enzymes are generally more specific for selected reactions, whereas undesired side reactions may occur when whole cells are used for the transformation. In addition, the simultaneous operation of *R*- and *S*-selective enzymes, which occur in whole cells, may result in low overall selectivity. Significantly larger amounts of biomass are also required for whole cell systems. This makes work-up and separation of the reaction product from the biomass difficult and time consuming. However, whole cell systems have been shown, in many cases, to be highly selective for a given reaction.^{31,32} In such cases, their lower cost makes whole cell systems an attractive alternative to isolated enzyme systems.

Biotransformations have been used for a range of applications in organic synthesis, including resolution of racemates,^{33,34} selective conversion of a specific functional group among several groups of similar reactivity^{35,36} and introduction of a chiral centre.³⁷ The enantioselectivity generated by biotransformations arises from the unique relationship between the 3-dimensional structure of the active site of an enzyme and the substrate molecule. A number of factors contribute to the binding of a substrate molecule, including size and its 3-dimensional structure, compared with that of the active site.³⁸ Enantioresolving transformations occur when predominantly one enantiomer of the substrate becomes bound within the active site and this binding facilitates the desired transformation. Therefore, enzymes utilise the single physical feature which distinguishes enantiomers from one another, (their 3-dimensional structure in space), to catalyse enantioselective transformations.

Baker's yeast (BY, *Saccharomyces cerevisiae*) has become the most popular microorganism for synthetic purposes and has been extensively reviewed. A small number of baker's yeast mediated asymmetric hydrolyses,³⁹⁻⁴² and oxidation⁴³ reactions have been reported, however, such reports are scarce, and the bulk of the literature on baker's yeast refers to the asymmetric reduction of carbonyl containing compounds. The reducing action of baker's yeast was first observed by Dumas in 1874.⁴⁴ He reported that

on addition of finely powdered sulphur to a suspension of fresh yeast in a sugar solution, hydrogen sulfide was liberated. MacLeod⁴⁵ and Hub⁴⁶ have conducted systematic investigations on the baker's yeast mediated asymmetric reduction of a series of ketones with varying substituents. The secondary alcohols obtained were mainly of *S*-configuration. Sterically hindered ketones (4-octanone, *tert*-butyl methyl ketone) were not reduced at all. These results followed Prelog's rules,⁴⁷ with reduction occurring by hydride ion transfer to the *Re* face of the prochiral ketone, to give the *S*-alcohol exclusively.

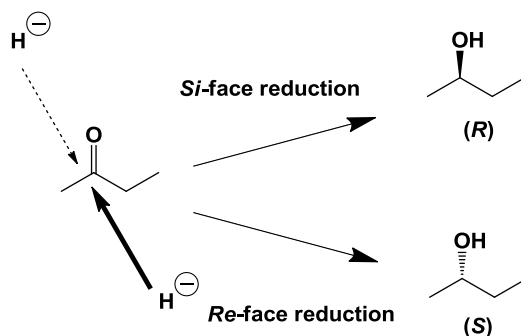
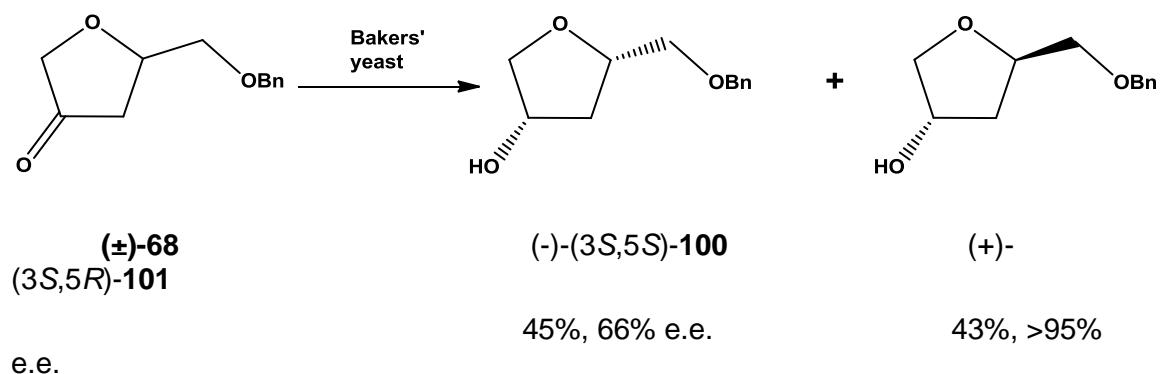


Figure 2.12.1

A number of analogues of 5-substituted 3(*2H*)-furanones were reduced using bakers' yeast as the reductant. The reaction conditions involved dissolving 100 mg of the prochiral ketone in DMSO. This solution was then added dropwise to a suspension of 10 g of bakers' yeast, 10 g sugar (table sugar) and a few drops of antifoam in 100 mL water. The reaction was shaken at 120 rpm for 24 h. Antifoam was essential as it prevents foaming of the suspension, and therefore loss of reaction media. The sugar used acted as the hydride source, and was oxidised by glucose dehydrogenase which reduces co-factors such as NAD/NADP to NADH/NADPH and in turn a reductase then reduces the prochiral ketone.

Yeast mediated reduction of 5-benzyloxymethyl-3(*2H*)-furanone **68** was undertaken to generate enantioenriched 3-hydroxytetrahydrofurans **100** and **101** (**Scheme 2.12.1**), which following subsequent chemical transformations afforded desmethylnuscarine and its stereoisomers. The yeast mediated reduction of (\pm)-5-benzyloxymethyl-3(*2H*)-furanone **68** under standard conditions proceeded in a satisfactory manner, however, the isolated yields of the diastereoisomeric alcohols, which were readily separated by wet flash column chromatography were moderate. A revision of the work-up was undertaken in a bid to improve the isolated yields.



Scheme 2.12.1

Ridley's method⁴⁸ required filtering of the suspension through Celite[®] and washing of the filter cake with water and ethyl acetate followed by sonication in ethyl acetate and further filtration of the reaction cake. However when we repeated this protocol it was found that yields were low. It was proposed the poor extraction process could be due to insufficient lysing of the bakers' yeast cell and it was deemed, therefore necessary to revise the work-up procedure to increase the yield of the 3-hydroxytetrahydrofuran. Variations of Ridley's work-up procedure were attempted, such as adding Celite[®] to the crude suspension and stirring for 30 mins to 1 h, sonicating the crude reaction mixture in Celite[®] as well as varying the amount of Celite[®] used. Alternative solvents were also investigated and it was found that THF was the solvent of choice for extraction of the 3-hydroxytetrahydrofuran. We found that THF when used as extraction solvent caused cell lysis to a noticeably higher extent than ethyl acetate. Consequently, higher yields were obtained for the extraction from bakers' yeast. Following extraction and concentration of the organic layers, column chromatography of the crude reaction mixture afforded $(-)\text{-(3S,5S)}$ -3-hydroxy-5-benzyloxymethyltetrahydrofuran **100**, as the first fraction in a moderate e.e. of 66% (**Figure 2.12.2**) and $(+)\text{-(3S,5R)}$ -3-hydroxy-5-benzyloxymethyltetrahydrofuran **101**, as the second fraction in high e.e of 94% (**Figure 2.12.3**). No (\pm) -5-benzyloxymethyl-3(2*H*)-furanone **68** was isolated from the reaction. However, the 3-hydroxytetrahydrofurans **100** and **101** formed as diastereoisomers. Optical rotation data was obtained and compared with data which was obtained from O'Donovan.⁸ O'Donovan oxidised the 3-hydroxytetrahydrofuran, $(-)\text{-(3S,5S)}$ -3-hydroxy-5-benzyl oxymethyl tetrahydrofuran **100** and $(+)\text{-(3S,5R)}$ -3-hydroxy-

5-benzyloxymethyl tetrahydrofuran **101**, using the Swern oxidation to the corresponding ketones. These corresponded to the enantiopure (+)-5-benzyloxymethyl-4,5-dihydro-3(2*H*)-furanone **68**. As expected, we observed the (*S*)-configuration for both isomers of the alcohol obtained by baker's yeast mediated reduction, based on the analytical data obtained during previous work by O'Donovan.

(-)-(3 <i>S</i> ,5 <i>S</i>)-3-hydroxy-5-benzyloxymethyltetrahydrofuran 100			(+)-(3 <i>S</i> ,5 <i>R</i>)-3-hydroxy-5-benzyloxymethyltetrahydrofuran 101		
Yield (%)	e.e. (%)	[α] _D (CHCl ₃)	Yield (%)	e.e. (%)	[α] _D (CHCl ₃)
45	66	-19.9	43	>95	+17.7

Table 2.12.1 Data for **100** and **101** obtained from baker's yeast reduction (revised conditions).

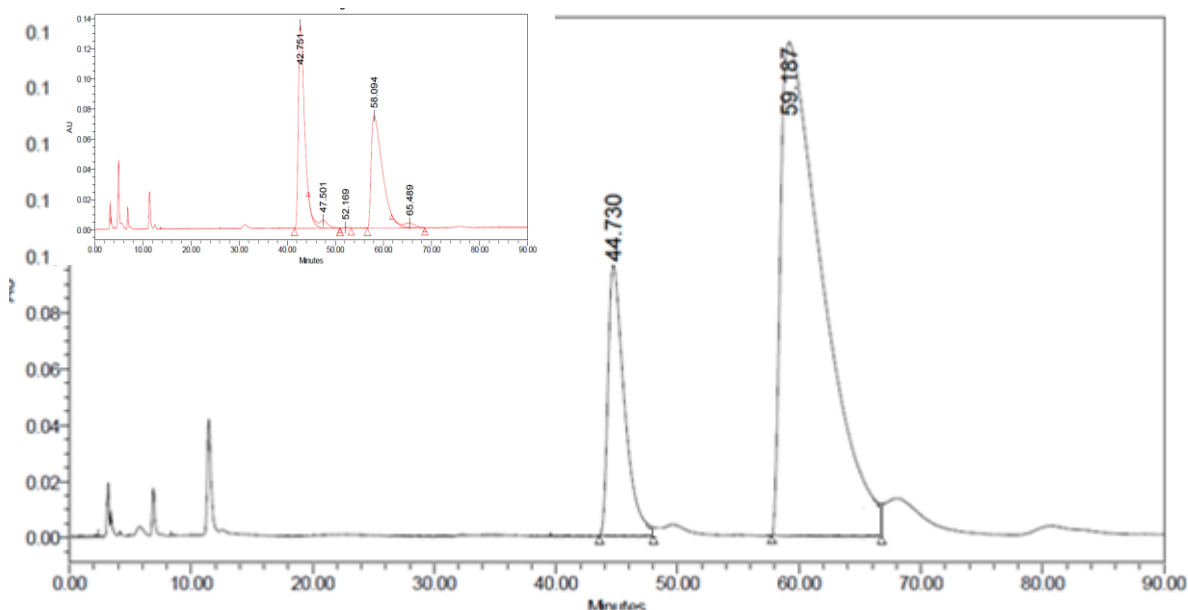


Figure 2.12.2 Chiral HPLC trace for compound **100** obtained using AS-H column, Insert: HPLC trace for racemic **100**.

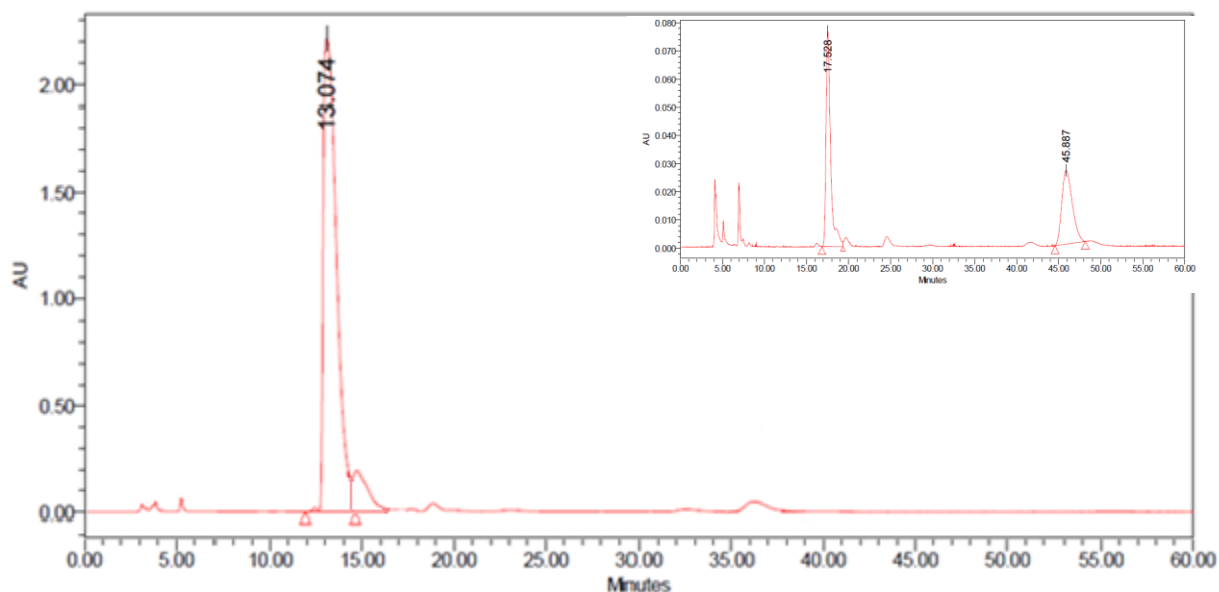
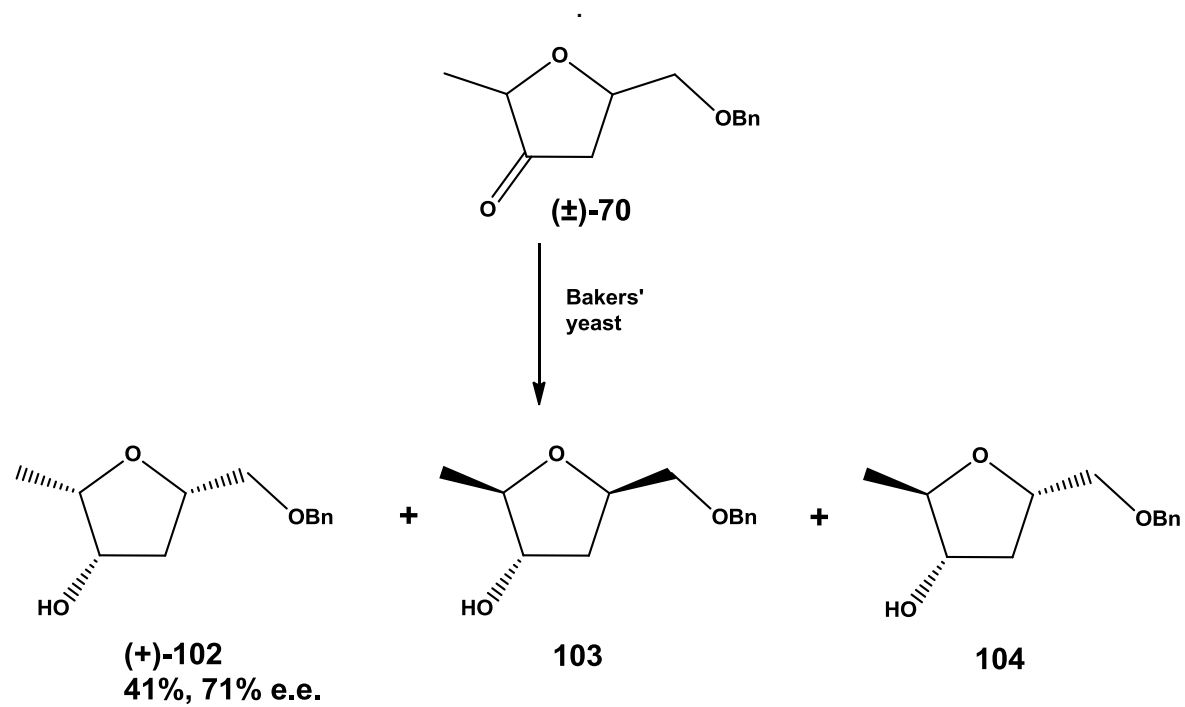


Figure 2.12.3 Chiral HPLC trace for compound **101** obtained using AS-H column, Insert: HPLC trace for racemic **101**.

(±)-5-Benzyloxymethyl-2-methyl-3(2*H*)-furanone **70** was reduced by bakers' yeast (**Scheme 2.12.2**). Initially it was unknown what products would be formed from this bioreduction. The reaction was examined after 24 h by TLC and it was found that starting material was not fully consumed and so the reaction time was extended. After 48 h, TLC showed consumption of the parent ketone (±)-**70**. The extraction was carried out under modified conditions, using THF as the solvent of choice for the extraction process. Wet flash chromatography afforded two fractions, which were analysed by concentrating individual test tubes. The first fraction contained (+)-(2*S*,3*S*,5*S*)-3-hydroxy-2-methyl-5-benzyloxymethyltetrahydrofuran (**+**)-**102**, while the second fraction was found to contain (+)-(2*R*,3*S*,5*R*)-3-hydroxy-2-methyl-5-benzyloxymethyltetrahydrofuran **103** and (+)-(2*R*,3*S*,5*S*)-3-hydroxy-2-methyl-5-benzyloxymethyltetrahydrofuran **104** which co-eluted. The relative stereochemistry was determined by NOESY and NOE difference NMR experiments. HPLC analysis of (+)-(2*S*,3*S*,5*S*)-3-hydroxy-2-methyl-5-benzyloxymethyltetrahydrofuran (**+**)-**102** showed a 71% e.e. **Figure 2.12.3**.



Scheme 2.12.2

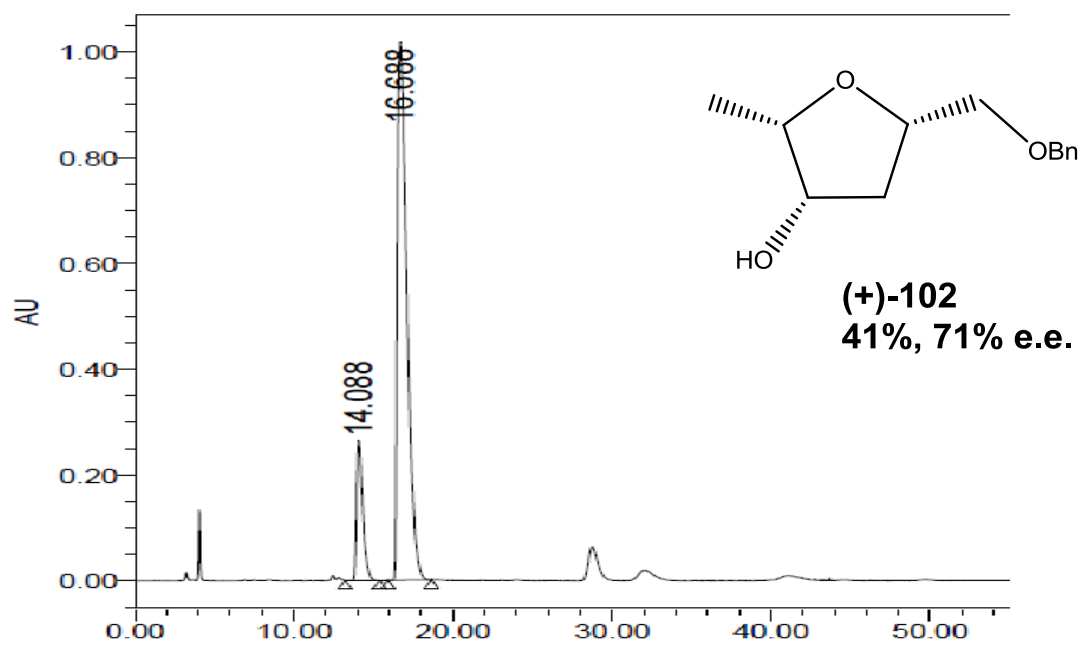


Figure 2.12.4 Chiral HPLC trace of compound **102** using AS-H column.

It was found that upon stopping the reaction after 24 h, the parent ketone, (\pm)-5-benzyloxymethyl-2-methyl-3(2*H*)-furanone (**\pm -70**), was isolated (36% recovery) along with the three aforementioned 3-hydroxytetrahydrofurans **102** – **104**. After 48 h no parent ketone was observed by TLC analysis and (+)-(2*S*,3*S*,5*S*)-3-hydroxy-2-methyl-5-benzyloxymethyltetrahydrofuran (**+102**) was isolated with no loss in e.e due to this longer bioreduction time employed. To assess keto-enol tautomerism *in situ*, (\pm)-5-benzyloxymethyl-2-methyl-3(2*H*)-furanone (**\pm -70**) was subjected to Ridley's conditions without bakers' yeast, after which crude analysis of (\pm)-5-benzyloxymethyl-2-methyl-4,5-dihydro-3(2*H*)-furanone (**\pm -70**) showed no change in the d.e. by ^1H NMR analysis. Chiral separation of **103** was attempted but not achieved due to the presence of **104** in the isolated sample.

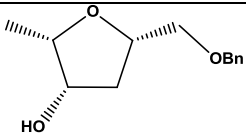
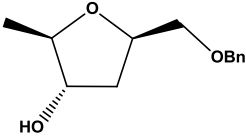
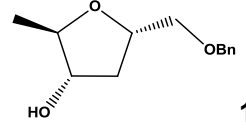
3-Hydroxy-2-methyl-5-benzyloxymethyltetrahydrofuran	Yield (%)	e.e. (%)	$[\alpha]_D$ (CHCl_3)
 102	41	71	+22.0
 103	14	-	-
 104	34	-	-

Table 2.12.1 Table of 3-Hydroxy-2-methyl-5-benzyloxymethyltetrahydrofurans and selected spectroscopic data.

2.13 Synthetic Approaches to Epimuscarine, Desmethylnuscarine and its analogues

The interesting pharmacological properties of naturally occurring (+)-(2*S*,3*R*,5*S*)-muscarine **105** and its stereoisomers have been of renewed interest in recent years. As a result, the synthesis of all stereoisomers of muscarine has been accomplished at this stage with the biological activity of these compounds tested. A number of analogues of muscarine have also been synthesised, including the 2-methylmuscarone **106** and 2-methylmuscarine **107** derivatives in racemic form (Figure 2.13.1).^{49,50}

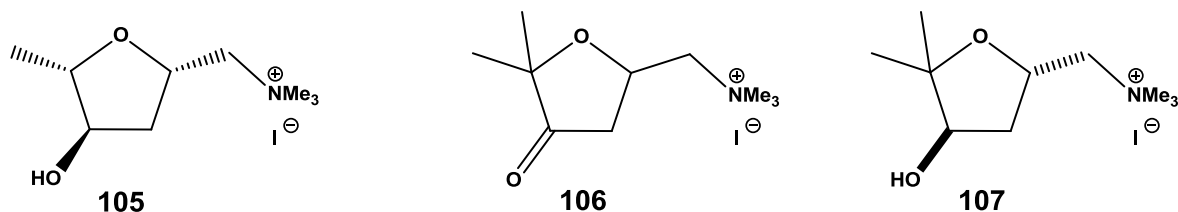
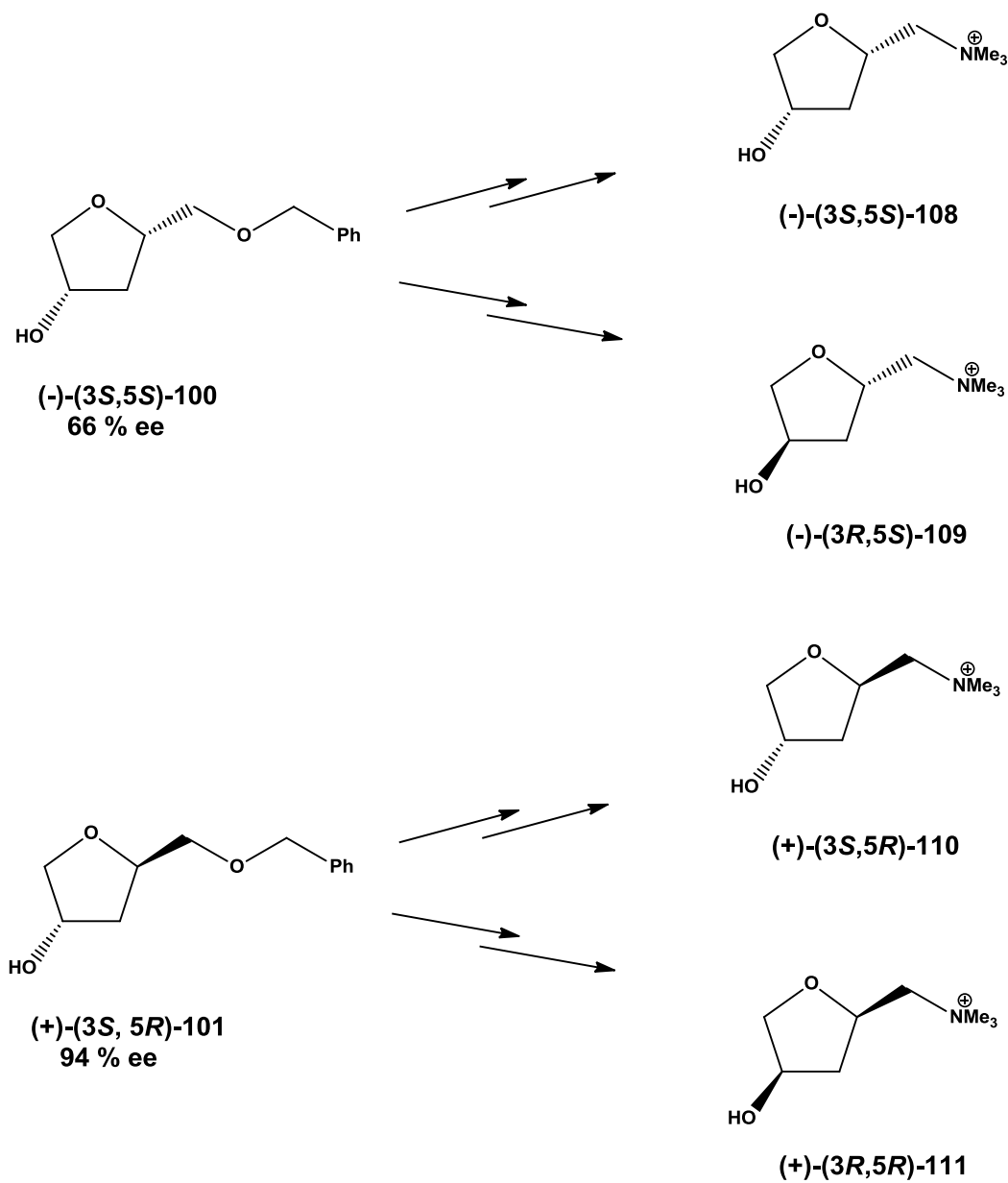


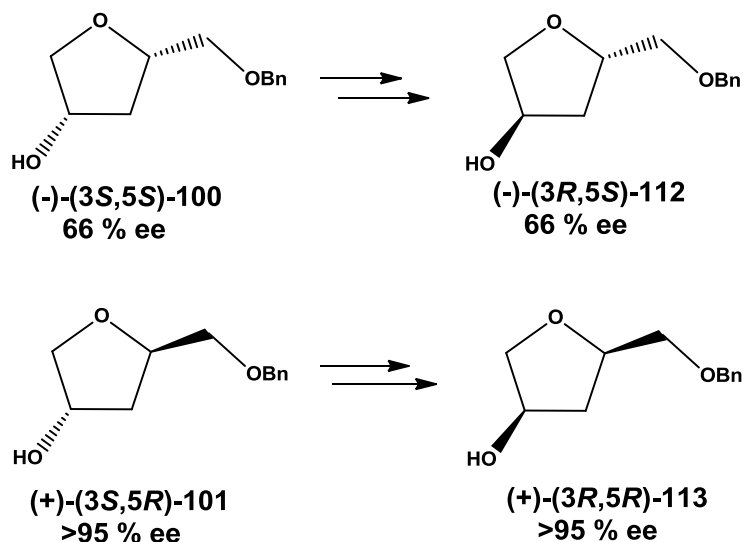
Figure 2.13.1

A number of synthetic routes to enantiomerically pure muscarine **105** and its analogues have already been discussed in the Introduction chapter (Section 1.6). The majority of these syntheses utilise enantiomerically pure starting materials derived from either naturally occurring carbohydrate derivatives such as glucose or mannose, lactic acid or amino acids as the source of chirality. For the synthesis of desmethylnuscarine and its analogues, it was envisaged that (±)-5-benzyloxymethyl-4,5-dihydro-3(2*H*)-furanone **68** would be utilised as a substrate for baker's yeast mediated reduction, with a view to gaining access to enantioenriched 5-benzyloxymethyl-3-hydroxytetrahydrofurans (-)-**100** and (+)-**101**. Subsequently further chemical transformations would then be employed to synthesise enantioenriched desmethylnuscarine. O'Donovan had found that bakers' yeast mediated reduction of (±)-5-benzyloxymethyl-4,5-dihydro-3(2*H*)-furanone **68** proceeded in an efficient manner to afford (-)-(3*S*,5*S*)-5-benzyloxymethyl-3-hydroxy tetrahydrofuran **100** and (+)-(3*S*,5*R*)-5-benzyloxymethyl-3-hydroxytetrahydrofuran **101**. These 3-hydroxytetrahydrofurans were separable by column chromatography and each present in a high enantioenriched state.

Following on from the initial investigations carried out by O'Donovan synthesis of all four stereoisomers of desmethylnuscarine was undertaken (**Scheme 2.13.1**)



Scheme 2.13.1

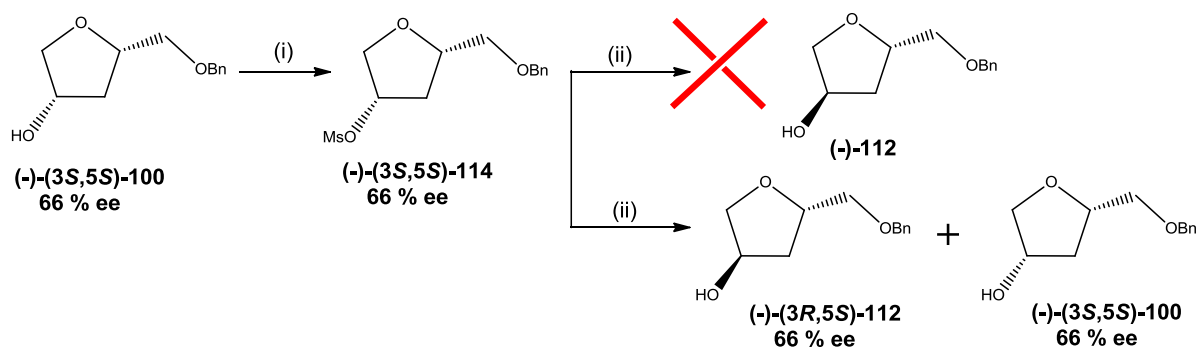


Scheme 2.13.2

The strategy initially focused on the synthesis of the all four diastereoisomers of 5-benzyloxymethyl-3-hydroxy-tetrahydrofurans. This would involve inverting the stereochemistry at the C3 position of enantioenriched tetrahydrofurans obtained from Bakers' yeast reductions (**Scheme 2.13.2**). Initial work carried out by O'Donovan indicated that inverting the stereochemistry at C3 would be troublesome. O'Donovan had investigated the inversion using Mitsunobu reaction conditions but enjoyed better success using potassium superoxide as a nucleophile. Upon repetition of this work similar results were achieved. Other synthetic protocols were also investigated, specifically, Mitsunobu conditions. Mitsunobu reaction conditions were investigated using both DIAZD and DEAZD with *p*-nitro-benzoic acid and acetic acid, as the nucleophile and the source of the oxygen. However, only starting material was recovered from these reactions. Further examination of the reaction conditions, including repetition of the Mitsunobu reaction at elevated temperatures proved unsuccessful.

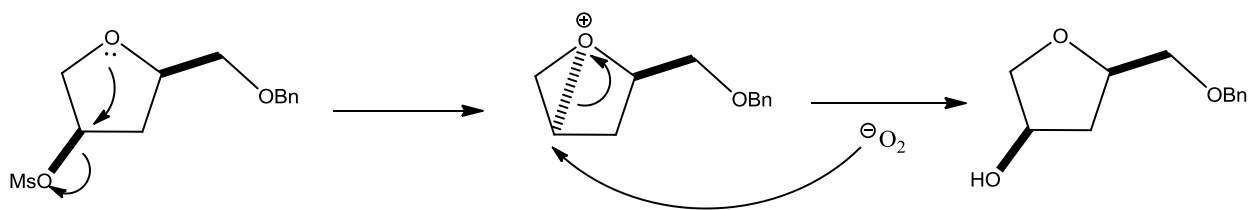
Inversion of the alcohol was ultimately achieved by mesylation of the C3 alcohol and subsequent displacement of the mesylate with potassium superoxide (**Scheme 2.13.3**). Mesylation of the diastereoisomers was carried out using either pyridine, as both the base and solvent or triethylamine in dichloromethane. Addition of the methanesulfonyl chloride was carried out dropwise, at a rate, which would not lead to displacement of the mesylate (**-**)-114 with the chloride anion. ^1H NMR analysis of the crude mesylate showed the reaction had gone to completion after 2 h. IR analysis of the

reaction material, meanwhile, showed the absence of an alcohol group. Upon ^1H NMR analysis, the crude mesylate reaction product was sufficiently pure to be used for the subsequent inversion. Examination of the signals surround the C4 protons did not show any impurity formation such as the 3-chloro-tetrahydrofuran. The reaction was carried out under anhydrous conditions as potassium superoxide reacts violently with water, to produce potassium hydroxide and oxygen. DMSO were freshly distilled and 18-crown-6 was dried over phosphorous pentoxide under high vacuum. Reaction conditions were optimised which involved carrying out the reaction under Schlenk conditions. After stirring the reaction overnight, analysis of the crude reaction material showed some epimerisation at the C3 carbon however, the diastereoisomers **(-)-100** and **(-)-112** were easily separable by column chromatography.

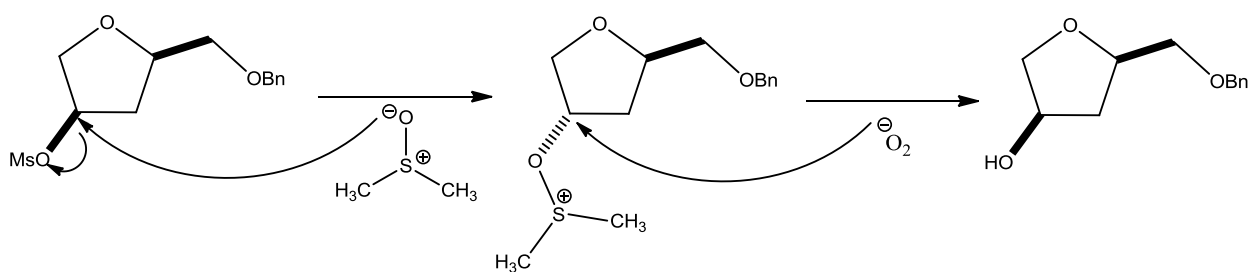


Scheme 2.13.3 Reagents: (i) MsCl, pyr or NEt_3 , (ii) 18-crown-6, KO_2 , DMSO.

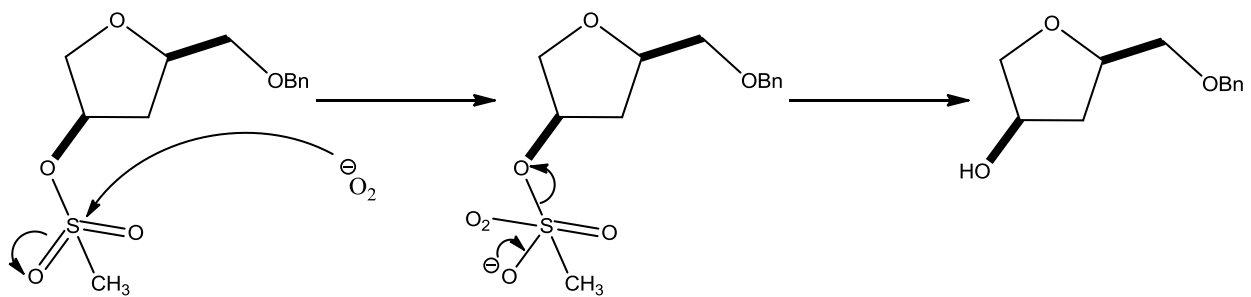
There are number of possible explanations for this epimerisation. One being be the possible displacement of the mesylate by the ether group in the tetrahydrofuran (**Scheme 2.13.4**), while displacement of the mesylate by DMSO followed by displacement of the DMSO adduct by potassium superoxide could be an alternative explanation (**Scheme 2.13.5**). Attack of the sulphur of the mesylate by the superoxide anion (**Scheme 2.13.6**) is also a possibility which is worthy of consideration.



Scheme 2.13.4



Scheme 2.13.5



Scheme 2.13.6

The enantiomeric alcohols displayed the expected opposite optical rotation. Furthermore, the HPLC traces confirmed the presence of the opposite enantiomers in both instances **Figure 2.13.2**. These results confirm inversion of **(-)-(3S,5S)-100** and **(+)-(3S,5R)-101** using potassium superoxide.

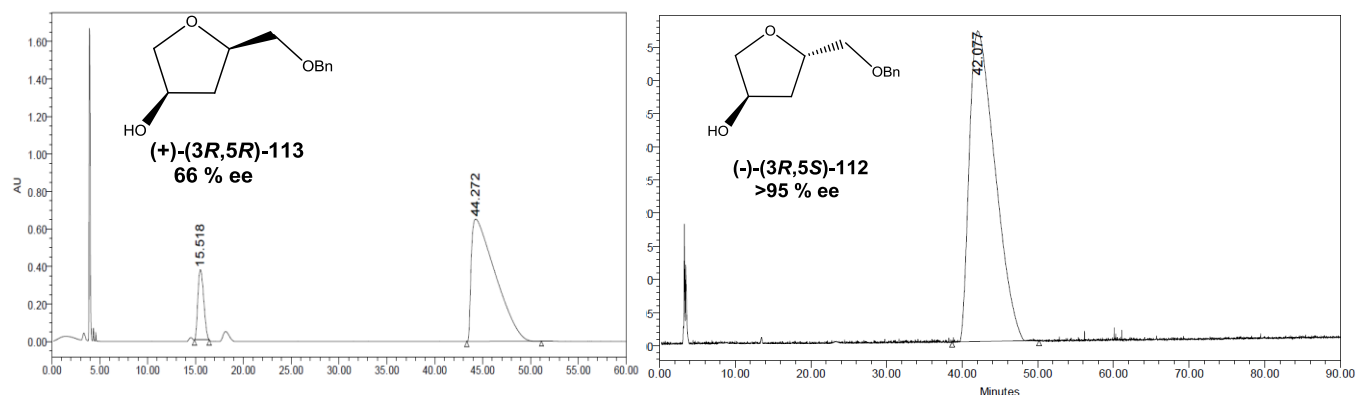


Figure 2.13.2 Chiral HPLC trace of Compounds **107** (LHS) and **108** (RHS).

(-)-(3R,5S)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran 112			(+)-(3R,5R)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran 113		
Yield (%)	e.e. (%)	[α] _D (CHCl ₃)	Yield (%)	e.e. (%)	[α] _D (CHCl ₃)
58	65	-2.75	48	>95	+37.8

Table 2.13.1 Isolated yield and selected spectroscopic data for compounds **112** and **113**.

Following successful inversion of stereochemistry at the C3 position, all four stereoisomers of 5-benzyloxymethyl-3-hydroxytetrahydrofuran were synthesised **(-)-100**, **(+)-101**, **(-)-112** and **(+)-113**. These molecules could then be converted to the stereoisomers of desmethylnuscarine **108** - **111**. All four stereoisomers were subjected to *O*-debenzylation to afford the diols **115** - **118**. The reactions were carried out in a Parr hydrogenation apparatus at 35 psi for 15 h. Reaction completion was monitored by ¹H NMR analysis. The reaction mixture was filtered through Celite® was washed with

methanol. It had been found that separation of the diol from the palladium could prove difficult. This was overcome by sonication of the palladium with Celite® and subsequent filtration which increased the crude yield of the reaction. The crude product was purified by column chromatography using 50% acetone in hexane. This procedure was utilised for the synthesis of all stereoisomers of 3-hydroxymethyl-5-hydroxytetrahydrofuran **115** - **118**. The yield for the reactions were moderate to good (**Table 2.13.2**).

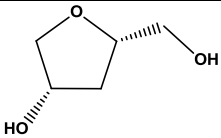
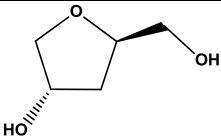
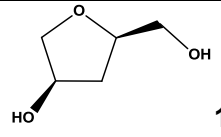
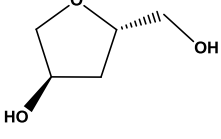
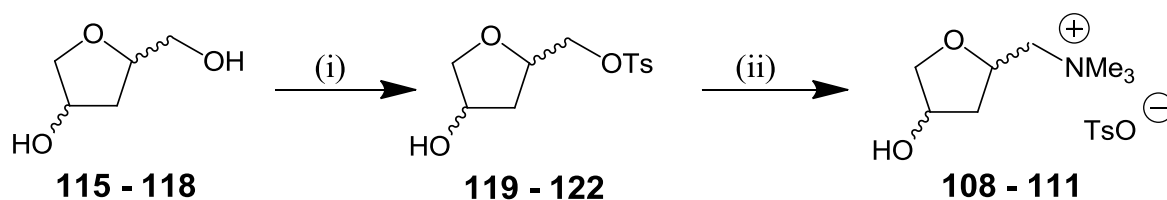
3-hydroxy-5-hydroxymethyltetrahydrofuran	Yield (%)	$[\alpha]_D$ (CHCl ₃)	e.e. (%)
 115	64%.	-18.20°	66
 116	68%.	+8.30	>95
 117	78%.	+25.15°	>95
 118	64%.	-2.45°	66

Table 2.13.2 *Isolated yield and selected spectroscopic data for compounds **110** – **113**.*

Following synthesis of the diols **115** – **118**, the primary alcohol were converted to a leaving group and displacement of the leaving group with trimethylamine was to be undertaken to form desmethylnuscarine. The chosen leaving group was the tosylate moiety. There is good literature precedent for the conversion of the alcohol to the trimethylammonium group using this approach.^{51,52}

During the course of this work, initial efforts to synthesise the monotosylate were unsuccessful, selective tosylation of the primary alcohol was successful using freshly distilled pyridine, as both base and solvent and *p*-toluenesulfonyl chloride (1 eq). *p*-Toluenesulfonyl chloride was added in one portion to a stirring solution of the appropriate 3-hydroxy-5-hydroxymethyltetrahydrofuran **115** - **118** in precooled pyridine (-20 °C). This temperature was held at -20 °C for 24 h, with the aid of a cryocooler and allowed to warm to +4 °C for 24 h and finally room temperature for a further 24 h. Upon reaction completion, 10% HCl was added and the mixture was extracted with dichloromethane three times. The temperature of the water bath for evaporation, of the dichloromethane extract, methanol and chloroform following product chromatography, was kept at a low temperature of approximately 20 °C to prevent decomposition. Initial reactions carried out, for which the temperature of the water bath was elevated, led to decomposition of the crude reaction product. The crude reaction product was purified using methanol in chloroform. Following chromatography, starting material and the desired monotosylate **119** - **122** were isolated. Analysis of the crude reaction product and fractions following purification showed no evidence of the regioisomer or the bis-tosylate. The monotosylates **119** - **122** were purified *via* column chromatography using gradient elution from 100% chloroform to 1% methanol in 99% chloroform.



Scheme 2.13.7 *Reagents:* (i) TsCl, Py, -20°C (ii) NMe₃ (20% solution in ethanol), 80°C.

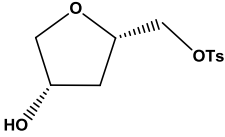
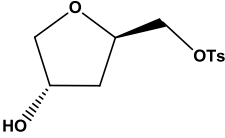
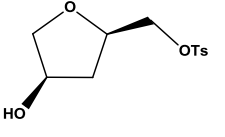
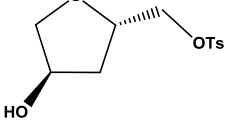
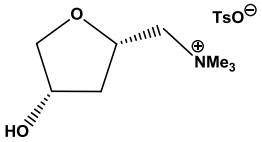
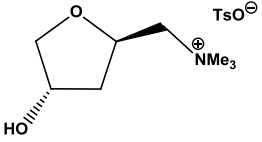
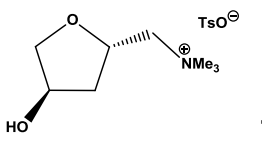
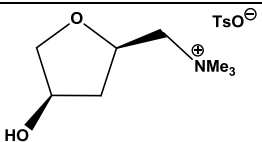
3-Hydroxy-5-hydroxymethyltetrahydrofuran-5-yl)methyl 4-methylbenzenesulfonate	Yield (%)	$[\alpha]_D$ (CHCl ₃)	e.e. (%)
 119	34	-9.30	66
 120	42	+22.30	>95
 121	46	+5.38	>95
 122	73	-25.25	66

Table 2.13.3 Isolated yield and selected spectroscopic data for counts **119 – 122**.

Conversion of the tosylates **119 - 122** to desmethylnuscarine and its analogies **108 - 111** was achieved by refluxing the appropriate tosylate in an ethanolic solution of trimethylamine. This involved heating the ethanolic trimethylamine in the presence of tosylate to 80 °C for 16 h in a sealed tube. The ethanol was evaporated and any water present removed by azeotropic distillation with toluene. The crude product was recovered as a viscous gel. Numerous attempts to crystallise or precipitate the product were attempted however this proved to be futile.

Desmethylnuscarine analogues	Yield (%) [*]	[α] _D (CHCl ₃)	e.e. (%)
 108	60	-11.25	66
 109	61	+7.20	>95
 110	51	-4.70	66
 111	48	+14.15	>95

^{*}isolated yields following azeotropic distillation.

Table 2.13.4 Yield and selected spectroscopic data for compounds **108** – **111**.

The ¹H NMR spectrum of compounds **(-)-108** and **(+)-111** showed a number of ABX systems centred at the C2, C4 and C6 (carbon adjacent to the tetra-alkylated ammonium group) carbons. The proton spectrum also displayed a broad singlet which corresponded to the methyl groups attached to the nitrogen. The ¹³C spectrum displayed a triplet (~70 ppm, *J*~ 3Hz) for the C6 carbon. The ¹H NMR of the *syn* diastereoisomers **(-)-108** and **(+)-111** is shown in **Figure 2.13.1** with relative stereochemistry was confirmed by NOESY experiment. The ¹H NMR of the *anti* diastereoisomers **(+)-109** and **(-)-110** is shown in **Figure 2.13.2** and relative stereochemistry again established by NOESY experiment.

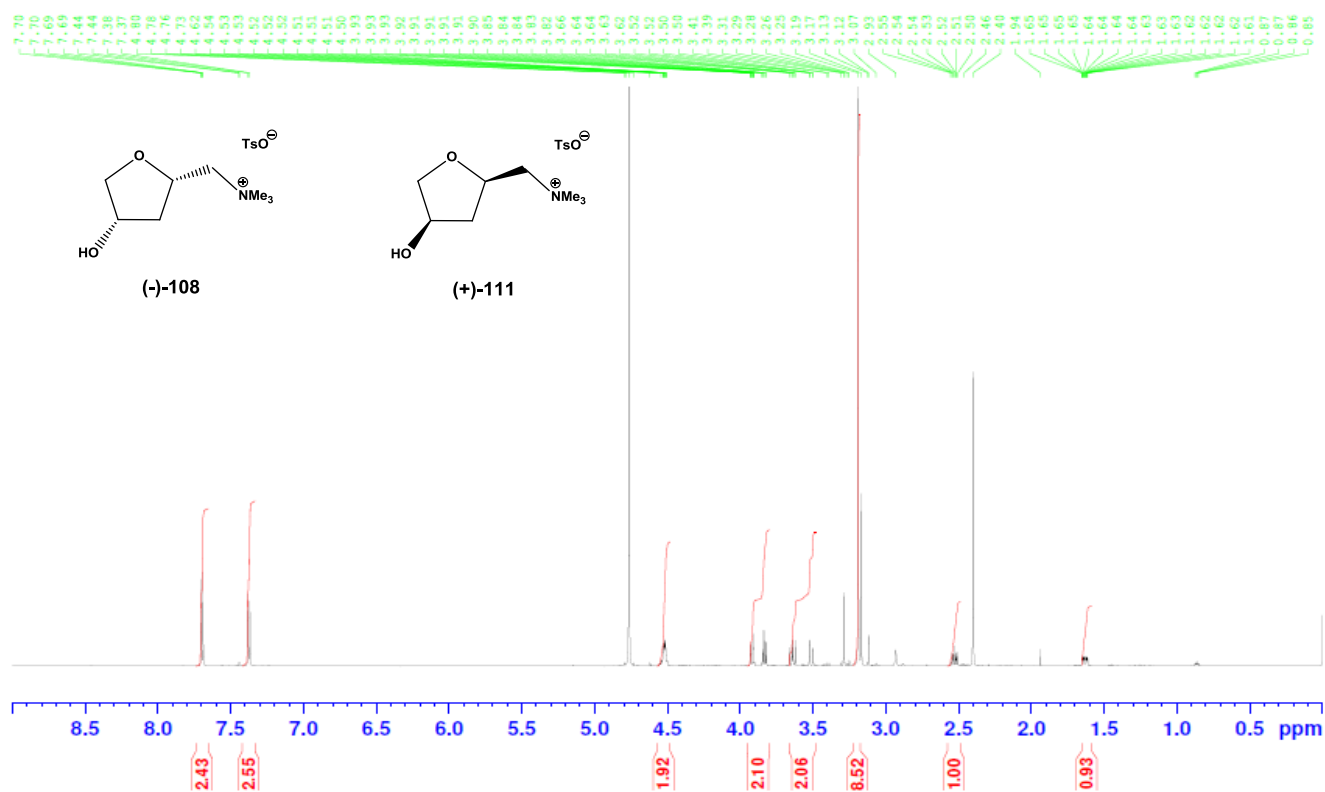


Figure 2.13.3 ¹H NMR of *(-)-(3S, 5S)-Desmethylepipimuscarine 108* and *(+)-(3R, 5R)-Desmethylallomuscarine 111*.

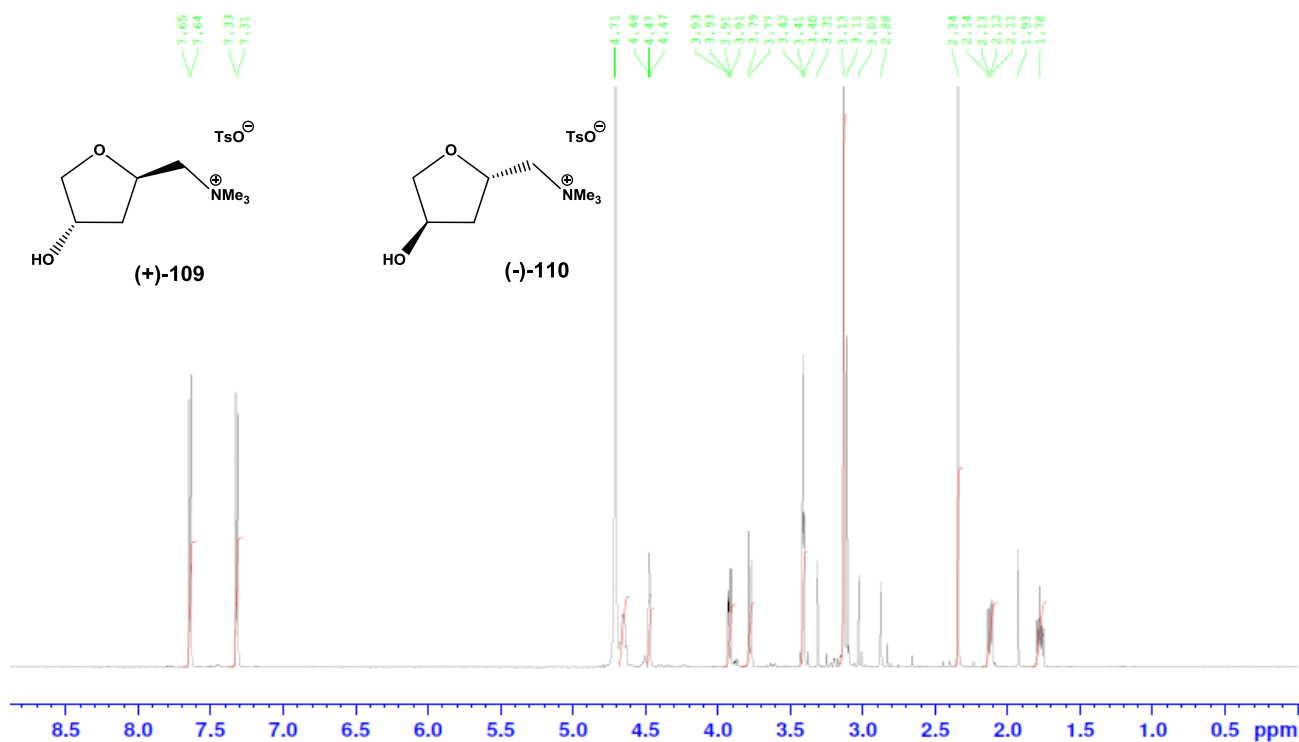
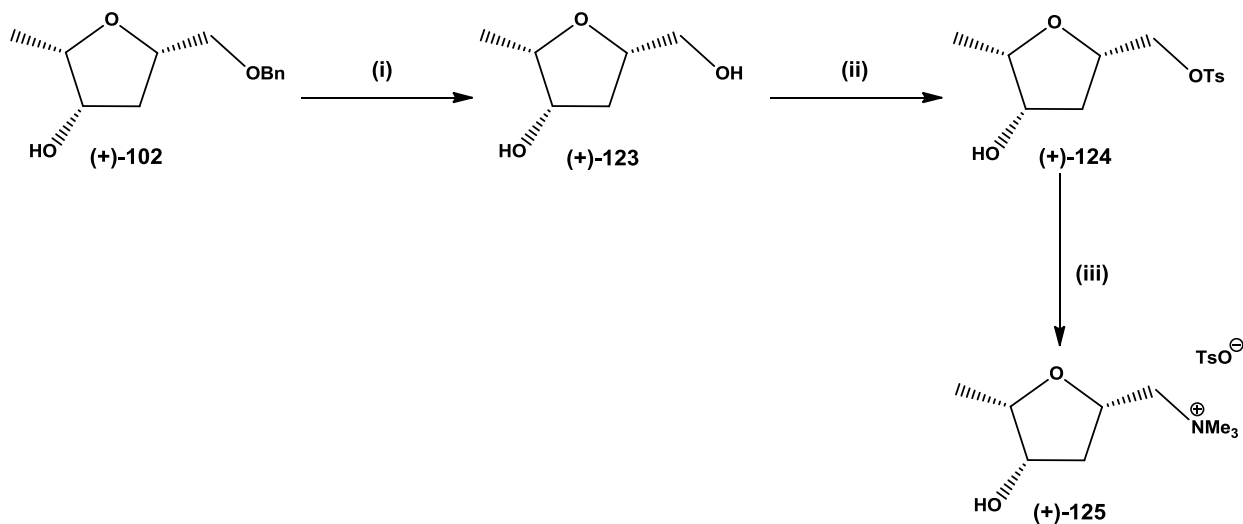


Figure 2.13.4 ^1H NMR of (+)-(3*S*,5*R*)-Desmethylepipiallomuscarine **109** and (-)-(3*R*,5*S*)-Desmethylepipiallomuscarine **110**.

Conversion of (+)-(2*S*,3*S*,5*S*)-3-hydroxy-2-methyl-5-benzyloxymethyl-tetrahydrofuran **102** to epimuscarine was undertaken, resulting in (+)-(2*S*,3*S*,5*S*)-3-hydroxy-2-methyl-5-benzyloxymethyltetrahydrofuran in an enantioenriched form from bakers' yeast reduction of the parent (\pm)-3(2*H*)-furanone **70**. The (+)-(2*S*,3*S*,5*S*)-3-hydroxy-2-methyl-5-benzyloxymethyltetrahydrofuran **102** was debenzylated at the 5-methoxy position using the same protocol for the debenzylation of desmethylepipiallomuscarine and its analogues. $\text{Pd}(\text{OH})_2$ was the catalyst of choice with methanol as the solvent and pressure of 35 psi used. The reaction was shaken in a Paar rocker flask for 16 h after which time TLC indicated no starting material was present. The reaction was filtered and the residue concentrated and purified *via* column chromatography using acetone and hexane as the mobile phase. Following debenzylation of (+)-**102**, (+)-(2*S*,3*S*,5*S*)-3-hydroxy-2-methyl-5-methoxytetrahydrofuran **123** was tosylated. Once again the same protocol which was utilised in the synthesis of **119-122** was employed, tosyl chloride was added to a stirring solution of (+)-**123** in pre-cooled pyridine. Over the course of three days the temperature of the reaction was warmed slowly to room temperature. This was to allow the more reactive primary alcohol to react exclusively. ^1H NMR revealed no trace formation of the

regioisomer. Purification of the mono tosylate **(+)-124** was achieved with gradient elution column chromatography using 100% chloroform to 1% methanol in chloroform and concentration in an ice-water bath to prevent degradation of the monotosylate **(+)-124**. Following synthesis, the monotosylate **(+)-124** was subjected to treatment with trimethylamine in ethanol overnight in a sealed tube and heated to 80 °C. Following work-up using toluene to azeotrope residual water, (+)-epi-muscarine **125** was recovered which was recrystallised from acetone and isolated as a white powder (**Scheme 2.13.8**). The ^1H NMR of epimuscarine is shown in **Figure 2.13.3** and relative stereochemistry was confirmed by NOESY experiment.



Scheme 2.13.8 Reagents: (i) H_2 , $\text{Pd}(\text{OH})_2$, ethanol, (ii) TsCl , Py , $-20\text{ }^\circ\text{C}$, (iii) NMe_3 (20% in ethanol solution), $80\text{ }^\circ\text{C}$.

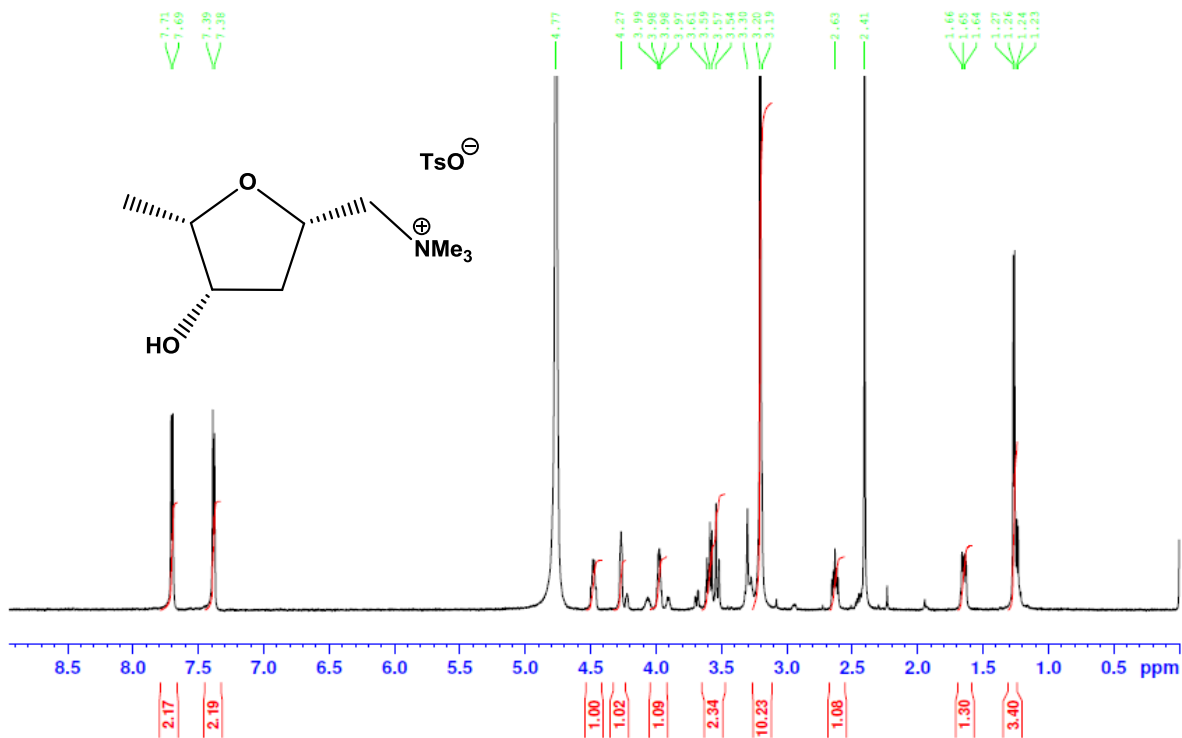
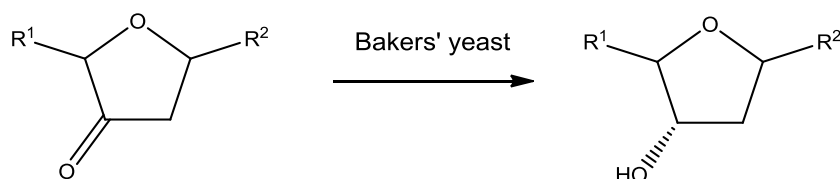


Figure 2.13.5 ^1H NMR of (+)-(2S,3S,5R)-Epimuscaine **125**.

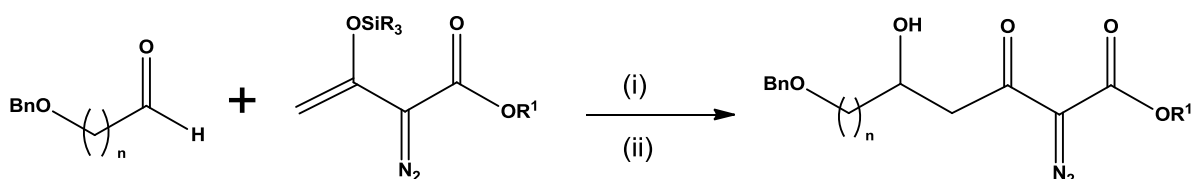
2.14 Concluding Remarks

The objective of the thesis was to develop a route to enantiopure 3-hydroxytetrahydrofurans *via* Bakers' yeast mediated bio-reduction of 3(2*H*)-furanones (**scheme 2.14.1**). Every effort was made to optimise each step to make the synthesis as efficient as possible.



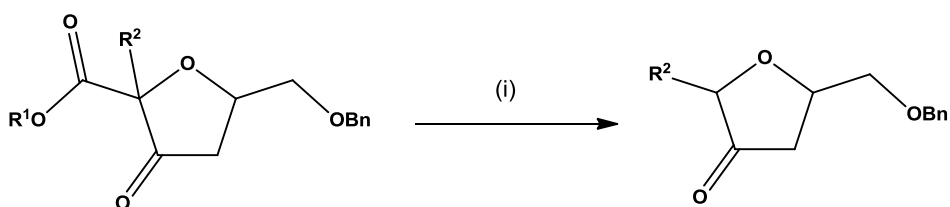
Scheme 2.14.1 *Bakers' yeast reduction of 3(2*H*)-furanone.*

Our route to the 3-hydroxytetrahydrofuran involved benzylation of either ethane-1,2-diol or propan-1,3-diol followed by Swern oxidation. In the first step of the synthesis, an advance in yield from 42% to 72% was achieved. The subsequent aldol addition proved problematic, however, through continued perserverance and investigation an enhanced route was developed *via* a catalytic Mukaiyama reaction followed by deprotection of the silyl ether. A similar catalytic reaction utilised by Doyle and co-workers¹¹ was applied and optimised for our synthesis. This led to an additional work which involved deprotection of the resulting silyl ether, which proved challenging. New conditions were developed for the deprotection of the silyl ether without degradation of the sensitive diazo functional group. A one-pot procedure was also developed following this investigation, which prevented decomposition of the diazo group **scheme 2.14.2**. This afforded yields of 53 – 61%. This methodology does not employ cryogenic conditions or harsh Lewis acids and allowed access to gram quantities of the aldol addition intermediate.



Scheme 2.14.2 *Reagents: (i) Zn(II)OTf₂, DCM, (ii) trifluoroacetic acid, water, THF, (4 : 1 : 1).*

Following formation of the 3(2*H*)-furanone by Rh(II) mediated diazo decomposition, we focussed on hydrolysis of the 3(2*H*)-furanone. Lambe¹⁹ had repeated conditions outlined by Calter⁹ which hydrolysed and decarboxylated a 3(2*H*)-furanone, however, had obtained extremely low yields, <6%. It was therefore necessary to develop new conditions which were capable of generating moderate to high yield for the hydrolysed and subsequent 3(2*H*)-furanone product. Following extensive screening and development, it was found exposure to a mixture of aqueous 6M HCl in 1,4-dioxane afforded products in a 58 – 72% yield. This was carried out in a microwave for 6 mins **scheme 2.14.3**.



Scheme 2.14.3 Reagents: (i) 6M HCl, 1,4-dioxane, 150 watts, 6 mins.

The next body of work focussed on the methylation of the 3(2*H*)-furanone. Some work had been carried by Lambe¹⁹ which again gave poor yields. Existing methodology (potassium carbonate, methyl iodide in acetonitrile) did not afford the desired products for unknown reasons. Screening of bases and optimisation afforded conditions in which a choice of three bases, KH in the presence of 18-crown-6, TMG and DBU afforded the alkylated product. It was found DBU and TMG afforded the best yields of 39% and 37% respectively for 3(2*H*)-furanone **65**. When 3(2*H*)-furanone **64** was treated with DBU, a yield of 57% was obtained. There was also diastereoselectively observed, NOE difference experiments confirmed relative stereochemistry.

Following successful development of methylation methodology, our attention turned to bakers' yeast mediated bioreduction of 3(2*H*)-furanones (**±**)-**68** and (**±**)-**70**. Development of the work-up procedure increase the yield from 63% to 88% following addition of celite[®] and THF to the reaction mixture. The resulting 3-hydroxytetrahydrofurans displayed e.e.'s of 66% e.e. for compound (**-**)-**100**, 94% e.e. for compound (**+**)-**101** and 71% e.e. for compound (**+**)-**102**. As bakers' yeast mediated reduction furnishes only the 3*S* alcohol, technology has advanced towards the use of metagenomics, enzyme evolution and protein expression. Current biocatalysis

technology allows access to the *R* alcohol by screening of recombinant libraries of carbonyl reductases. This would allow access to the *R* alcohol in high e.e. without the need for stereochemistry inversion.

Once access to the enantioenriched 3-hydroxytetrahydrofurans was achieved, the next step was to carry out a series of chemical transformation to afford the 3*R*-hydroxytetrahydrofurans. In order to achieve this, the stereochemistry at the 3-position had to be inverted, this was accomplished by mesylation and nucleophilic attack with potassium superoxide. All four stereoisomers of 3-hydroxytetrahydrofurans were debenzylated, tosylated and subsequently treated with ethanolic triethylamine to afford the four stereoisomers of desmethylnuscarine **108** to **111**. The same methodology was also applied for the synthesis of (+)-epinuscarine **125**.

This thesis discloses an efficient, robust, general synthetic route to substituted 3(2*H*)-furanones, including alkylation of 3(2*H*)-furanones at the 2-position. Epinuscarine was synthesised in a 10 step reaction sequence with an overall yield of 1.1%.

The successful synthesis of the stereoisomers of desmethylnuscarine was achieved, (+)-(3*R*,5*R*)-desmethylallomuscarine **110** and (-)-(3*R*,5*S*)-desmethyl nuscarine **111** in an 11 step reaction sequence with (-)-(3*S*,5*S*)-desmethylepi nuscarine **108** and (+)-(3*S*,5*R*)-desmethylepi allomuscarine **109** following a 9 step reaction sequence, all isolated 1 -2% yield.

A novel synthetic route to epinuscarine has been developed, as well as the first stereoselective synthesis of desmethylnuscarine and its stereoisomers. Due to the unfortunate low yields achieved in this future work could focus on the refinement of the later steps of the synthesis.

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3 Experimental

3.1 General procedures

Solvents were distilled prior to use, as follows; hexane was purified by fractional distillation and ethyl acetate was distilled from phosphorous pentoxide. DCM was distilled from phosphorous pentoxide; and when needed in an anhydrous state was redistilled from calcium hydride and stored over 4Å molecular sieves. THF was distilled from sodium in the presence of benzophenone. Pyridine was distilled from sodium hydroxide and was subsequently distilled from calcium hydride. Triethylamine was distilled from calcium hydride. DMSO was distilled from calcium hydride under reduced pressure and stored over 4Å molecular sieves.

Sodium hydride and potassium hydride were washed when used in a reaction by adding 60 mL of hexane for every 10 g of the hydride used. The hexane was removed and this wash procedure was repeated twice.

Hydrogenation reactions were carried out in a Parr rocking hydrogenator. Bulb-to-bulb distillations were carried out on an Aldrich kugelröhr apparatus and boiling points refer to the oven temperatures.

In the yeast reactions, sucrose obtained from Siucra granulated sugar was employed; the antifoam solution employed was antifoam 289, obtained from Aldrich. Ordinary tap water was used as solvent. Sigma Type II baker's yeast (BY; *Saccharomyces Cerevisiae*) was used.

Infrared (IR) spectra were recorded on either a Perkin-Elmer Paragon 1000 or a Perkin Elmer Spectrum FT-IR spectrometer. Liquid samples were examined as thin films between sodium chloride plates. Solid samples were dispersed in potassium bromide and recorded as pressed discs.

During bakers' yeast mediated reductions, temperature was maintained between 28 - 30 °C using either a Labortechnik ETS-D2 temperature probe or a Jubalo SW1 thermostated shaker. The sucrose employed was Siúcra® granulated sugar and the antifoam solution employed was Antifoam 289 (pfs) (Aldrich) mixed solution. Ordinary tap water was used as a solvent and was allowed to run for at least 5 min prior to use. Sigma Type II baker's yeast (*Saccharomyces cerevisiae*) was used.

NMR spectra were recorded on Bruker Avance 300 NMR, 400 NMR and 600 NMR instruments, the latter using a dual C-H cryoprobe. ¹H spectra were recorded at 300 MHz, 400 MHz and 600 MHz, while ¹³C spectra were recorded at 75 MHz, 100 MHz,

150 MHz respectively on these instruments. All spectra were recorded at 20 °C in deuterated chloroform (CDCl_3) using tetramethylsilane (TMS) as an internal standard unless otherwise stated. Chemical shifts (δ_{H} and δ_{C}) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in hertz. Splitting patterns in ^1H spectra are designated as s (singlet), bs (broad singlet), bd (broad doublet), bt (broad triplet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), ddt (doublet of doublet of triplets), ABq (AB quartet) and m (multiplet).

All organic solutions were dried using magnesium sulphate. Thin layer chromatography was performed on pre-coated silica gel (Merck HF_{254}) plates and compounds were visualised under ultraviolet light at 254 nm or stained with ceric sulfate stain. "Flash" column chromatography was performed using Aldrich silica gel 60 (typical ratio of silica : crude reaction mixture ~30 : 1 wt/wt). Bulb-to-bulb distillations were carried out on a Buchi GKR-50 Kugelröhr apparatus and the oven temperature is given as the boiling point of the compound at the recorded pressure. Low temperature reactions were cooled using a Labplant Cryocooler RP-100-CD and Jubalo FT902 Cryocooler.

Optical rotations were recorded on a Perkin Elmer 341 polarimeter at 20 °C using the sodium D line ($\lambda = 589 \text{ nm}$) in the solvent indicated. Samples were analysed in a 1 cm^3 dual walled glass walled cell of path length 10 cm. Sample temperature control was maintained using a Jubalo F25-MV immersion circulator. Results were processed on a Dell Optiplex GX260 PC using Bio Light POL Winlab software (version number 1.00.01). The units of $[\alpha]$ are recorded $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$.

Microwave reactions were carried out in a CEM Discoverer Labmate Sensitizer in conjugation with Chemdriver software (version number 3.5.0).

Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole LC-mass spectrometer in electrospray ionization mode (ESI) using 50% acetonitrile-water, containing 0.1% formic acid, as eluent; samples were made up in acetonitrile at a concentration of 1 mg/ml. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier Time of Flight LC-mass spectrometer in electrospray ionization (ESI) mode using 50% acetonitrile-water, containing 0.1% formic acid, as eluent; samples were made up in acetonitrile, also at a concentration of 1 mg/ml and then diluted further by the analyst

3.2 Experimental Procedures

3.2.1 Preparation of Reagents

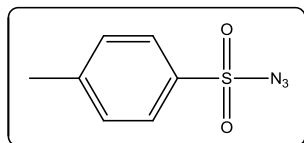
Lithium-tri-(*tert*-butoxy)-aluminium hydride¹



A flame dried, 100 mL round bottomed flask was charged with a suspension of lithium aluminium hydride (0.38 g, 10.13 mmol) in anhydrous diethylether (25 mL). Neat *tert*-butanol (3.00 g, 40.54 mmol) was added dropwise to this suspension, resulting in vigorous effervescence. The reaction mixture was stirred at room temperature for 1 h under a nitrogen atmosphere, after which the diethylether was removed under reduced pressure to give the title compound as a white solid.

Yield = 2.21 g, 89%.

p-Toluenesulfonyl azide²

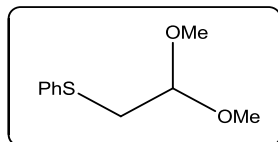


A solution of freshly recrystallised *p*-toluenesulfonyl chloride³ (11.97 g, 63 mmol) in acetone (32 mL) was added to a stirring solution of sodium azide (4.49 g, 69 mmol) in water (20 mL) and acetone (32 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The acetone was removed *in vacuo* (bath of rotary evaporatory was kept below 35 °C) and DCM (40 mL) was mixed with the remaining aqueous solution. The organic layer was separated and washed with water (2 × 25 mL). The organic layer was then dried and concentrated under reduced pressure to give the product as a clear oil, which solidified upon cooling below 0 °C.

Yield = 11.68 g, 93%.

ν_{max} (NaCl): 2132, 1595, 1372, 1169, 1086, 814, 747 cm^{-1} .

Benzenesulphenylacetaldehyde dimethylacetal (16)⁴



Freshly cut sodium (2.3 g, 0.1 mol) was added portion-wise to cold (0 °C) anhydrous ethanol (50 mL) contained within a flame dried 250 mL 3-necked round bottom flask and the resulting mixture was stirred at 0 °C for 15 min. Following complete

cessation of hydrogen gas evolution, thiophenol (*caution* – malodorous!) (10.3 mL, 0.1 mol) in anhydrous ethanol (30 mL) was added to the stirring ethoxide solution over 30 min. Bromoacetaldehyde dimethylacetal (8.5 mL, 43 mmol) in dry ethanol (20 mL) was then added dropwise and the mixture was left to stir for a further 15 min. This mixture was then heated at 50 °C for 16 h. The resultant cloudy solution was cooled to room temperature and was concentrated under reduced pressure. The residual oil was diluted with ethylacetate (75 mL), washed with water (2 × 50 mL), dried and concentrated under reduced pressure to afford a yellow oil. Bulb to bulb distillation yielded the product as a clear oil, b.p. 121 °C at 1 mmHg.

Yield = 5.9 g, 69%.

ν_{max} (NaCl): 2935, 2830, 1583, 1480, 1439, 1119, 1060, 740, 699 cm^{-1} .

δ_{H} (300 MHz): 3.10 (2H, d, $J = 5.5$, SCH₂), 3.35 [6H, s (OCH₃)₂], 4.50 (1H, t, $J = 5.5$, OCHO), 7.17 - 7.20 (1H, m, ArC4-H), 7.24 - 7.29 (2H, m, ArC2-H and ArC6-H of phenyl ring), 7.36 - 7.39 (2H, m, ArC3-H and ArC5-H).

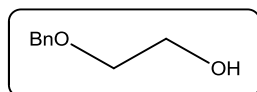
δ_{C} (75 MHz): 36.8 (SCH₂), 53.6 (OCH₃)₂, 103.5 (OCHO), 126.3 (Ar C4), 129.1 (Ar C2 and C6), 130.0 (Ar C3 and ArC5), 137.0 (ArC1).

MS: m/z : 199 (M+H)⁺, 168, 167 (100%), 135, 115, 102.

HRMS calculated for C₁₀H₁₅O₂S [M+H]⁺: 199.0793; found 199.0787.

3.2.2 Preparation of Alcohols

2-Benzyloxyethanol (7)⁵



Method 1. (1:1 Ethylene glycol – Benzyl bromide) A solution of GC grade ethylene glycol (14 mL, 0.25 mol) in anhydrous THF (25 mL) was added *via* dropping funnel to a suspension of “washed” NaH [(10 g, 0.25 mol), 60% dispersion in mineral oil] in 10 : 7, THF : DMF (85 mL) at 0 °C, under a nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature. Neat benzyl bromide (*caution* – lachrymator!) (29.7 mL, 0.25 mol) was added and the reaction mixture was stirred at room temperature for 12 h. Water (125 mL) was added and the layers separated. The aqueous layer was extracted with diethylether (3 × 100 mL). The combined organic extracts were dried and the solvent evaporated *in vacuo* to give a yellow liquid. Flash column chromatography, using the solvent gradient 10% ethyl acetate in hexane to 30% ethyl acetate in hexane as the eluent, yielded the title compound as a clear oil.

Yield = 15.9 g, 42%.

Method 2. (4:1 Ethylene glycol - Benzyl bromide)

Neat benzyl bromide (*caution* – lachrymator!) (41 mL, 0.35 mol) was added dropwise to stirring ethylene glycol (86 mL, 1.4 mol). After 5 min, KOH pellets (40 g, 0.7 mol) were added portion-wise and stirred for a further 5 min at room temperature and then heated to 80 °C for 24 h. After 24 h, the reaction was cooled to room temperature and diluted with ethyl acetate (200 mL). Water (150 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 200 mL) and the organic layers were combined, dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as eluent, yielded the title compound as a clear oil.

Yield = 37.8 g, 72%.

Method 3. (4:1 Ethylene glycol - Benzyl chloride)

Neat benzyl chloride (*caution* – lachrymator!) (92 mL, 0.81 mol) was added dropwise to stirring ethylene glycol (200 mL, 3.23 mol). After 5 min, KOH pellets (90 g, 1.61 mol) were added portion-wise and stirred for a further 5 min at room temperature, and then heated

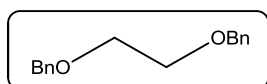
at 80 °C for 24 h. The mixture was then cooled to room temperature and diluted with ethyl acetate (300 mL). Water (225 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 300 mL) and the organic layers were combined, dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent, yielded the title compound as a clear oil.

Yield = 82.5 g, 67%.

ν_{max} (NaCl): 3417, 2926, 2864, 1496, 1454, 1358, 1112, 1067, 738, 698 cm^{-1} .

δ_{H} (400 MHz): 2.97 (1H, bs, OH), 3.53 (2H, t, $J = 4.6$, CH_2OH), 3.69 (2H, t, $J = 4.6$ CH_2OBn), 4.49 (2H, s, CH_2Ph), 7.24 - 7.41 (5H, m, ArH).

1,2-bis(benzyloxy)ethane (9)



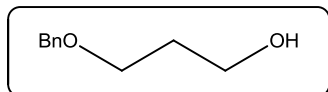
1,2-bis(benzyloxy)ethane was isolated as a side product from the crude reaction mixture from *Method 1*, using flash column chromatography where it was obtained as the first eluting fraction.

Yield = 22.9 g, 37%.

ν_{max} (NaCl): 3030, 2861, 1497, 1453, 1354 cm^{-1} .

δ_{H} (300 MHz): 3.66 (4H, s, $\text{BnOCH}_2 \times 2$), 4.60 (4H, s, $\text{PhCH}_2 \times 2$), 7.25 - 7.35 (10H, m, ArH).

3-Benzyloxypropanol (8)⁶



Method 1. (1:1 Propanediol - Benzyl bromide)

A solution of 1,3-propanediol (33.4 mL, 0.44 mol) in anhydrous THF (70 mL) was added to a suspension of “washed” NaH [(19.34 g, 0.48 mol) 60% dispersion in mineral oil] in 10 : 7, THF : DMF (240 mL) at 0 °C, under a nitrogen atmosphere. Stirring was continued for 3 h at room temperature. Neat benzyl bromide (*caution* – lachrymator!) (48.72 mL, 0.44 mol) was then added and the reaction mixture was stirred at room temperature for 12 h. Water (200 mL) was added and the layers were allowed to separate. The aqueous layer was extracted with diethylether (3 × 200 mL) and the combined organic extracts

were dried and the solvent was evaporated to give a yellow liquid. Flash column chromatography, using 30% ethyl acetate in hexane as eluent, yielded the title compound as a clear oil.

Yield = 26.54 g, 37%.

Method 2. (4:1 Propanediol - Benzyl bromide)

Neat benzyl bromide (*caution* – lachrymator!) (41.27 g, 0.45 mol) was added drop-wise to stirring 1,3-propanediol (107 mL, 1.4 mol). After 5 min, KOH pellets (40 g, 0.7 mol) were added portion-wise and the resulting mixture was stirred for a further 5 min at room temperature. The reaction mixture was then heated to 80 °C for 24 h. After 24 h, the reaction was cooled to room temperature and was diluted with ethyl acetate (150 mL). Water (200 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 300 mL) and the organic layers were combined dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as eluent, yielded the title compound as a clear oil.

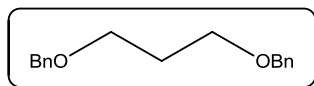
Yield = 39.27 g, 68%.

ν_{\max} (NaCl): 3399, 2944, 2865, 1454, 1365, 1094, 1075, 737, 698 cm^{-1} .

δ_{H} (400 MHz): 1.83 (2H, t, $J = 6.0$, $\text{CH}_2\text{CH}_2\text{OH}$), 2.92 (1H, bs OH), 3.61 (2H, p, $J = 6.0$, CH_2OH), 3.71 (2H, t, $J = 6.0$, CH_2OBn), 4.48 (2H, s, CH_2Ph), 7.22 - 7.39 (5H, m, ArH)

δ_{C} (75 MHz): 32.2 ($\text{CH}_2\text{CH}_2\text{OH}$), 61.6 (CH_2OH), 69.2 (CH_2OBn), 73.8 (CH_2Ph), 127.7, 127.72, 128.5 (All ArC), 138.2 (ArC1).

1,2-bis(benzyloxy)ethane (10)



1,3-bis(benzyloxy)propane was isolated as a side product from the crude reaction mixture from *Method 1*, using flash column chromatography where it was obtained as the first eluting fraction.

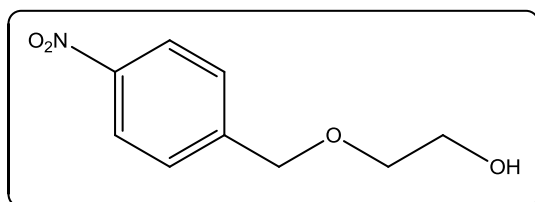
Yield = 87.72 g, 34%.

ν_{\max} (NaCl): 3028, 2859, 1495, 1451, 1355 cm^{-1} .

δ_{H} (300 MHz): 1.91 (2H, t, $J = 6.9$, $\text{BnOCH}_2\text{CH}_2$), 3.56 (2H, t, $J = 6.9$, BnOCH_2), 4.45 (2H, s, PhCH_2), 7.25 - 7.35 (10H, m, ArH).

δ_{C} (75 MHz): 30.2 ($\text{BnOCH}_2\text{CH}_2$), 67.4 (CH_2OBn), 73.9 (CH_2Ph), 127.7, 127.8, 129.1 (all ArC), 134.5 (ArC1).

2-(4-Nitrobenzyloxy)ethanol (11)⁷



Neat *p*-nitrobenzyl bromide (10 g, 46 mmol) was added dropwise to stirring ethylene glycol (100 mL, 1.79 mol). After 5 min, KOH (2.86 g, 51 mmol) was added portion-wise.

The mixture was stirred for a further 5 min at room temperature and then heated at 80 °C for 24 h. After 24 h, the reaction was cooled to room temperature and diluted with ethyl acetate (2 × 80 mL). Water was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 80 mL) and the organic layers were combined, dried and concentrated under reduced pressure. Flash column chromatography, using the solvent gradient 30% ethyl acetate in hexane to 50% ethyl acetate in hexane as the eluent, yielded the title compound as an orange solid.

Yield = 6.5 g, 71%.

mp = 46 - 48 °C (Lit.⁷ m.p. 46.5-47 °C).

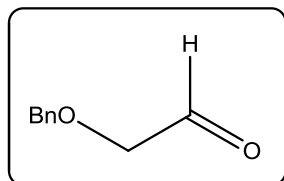
ν_{max} (KBr): 3398, 2870, 1604, 1520, 1459, 1346, 1109, 1069, 736, 697 cm⁻¹.

δ_{H} (300 MHz): 2.24 (1H, bs, OH), 3.66 (2H, t, J = 4.2, CH₂OH), 3.82 (2H, t, J = 4.2, CH₂OCH₂Ar), 4.68 (2H, s, CH₂Ar), 7.52 (2H, d, J = 8.8, Ar C3-H and C5-H), 8.20 (2H, d, J = 8.8, ArC2-H and ArC6-H)

δ_{C} (75 MHz): 61.9 (CH₂OH), 72.0 (CH₂OCH₂Ar), 72.1 (CH₂Ar), 123.7 (ArC3 and ArC5), 127.7 (ArC2 and ArC6), 145.7 (ArC1), 147.5 (ArC4).

3.2.3 Preparation of Aldehydes

2-Benzyloxyacetaldehyde (12)⁸



Method 1.

A flame dried, 3-necked round bottomed flask was charged with a solution of oxalyl chloride (3.3 mL, 36 mmol) in anhydrous DCM (175 mL). This solution was cooled to -78 °C after which freshly distilled DMSO (5.3 mL, 72 mmol) was added. This mixture was then stirred for 10 min, after which time a solution of 2-benzyloxyethanol (5 g, 33 mmol) in doubly distilled DCM (50 mL) was added. The resulting reaction mixture was stirred at -78 °C for 30 min. Triethylamine (23.5 mL, 164 mmol) was added. The resulting solution was stirred for a further 20 min at -78 °C, after which time the solution was allowed to warm to room temperature. Water (200 mL) was added and the resulting layers were separated. The aqueous layer was then extracted with DCM (2 × 80 mL) and the combined organic extracts were washed with 10% w/v HCl (2 × 80 mL), water (2 × 80 mL) and brine (2 × 80 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 10% ethyl acetate in hexane as eluent, yielded the title compound as a clear oil.

Yield = 4.59 g, 89%.

Method 2.

To a solution of 2-benzyloxyethanol (3.0 g, 20.0 mmol) and TEMPO[®] (0.171 g, 1 mmol) in DCM (40 mL), potassium bromide (0.265 g, 2.21 mmol) in saturated aqueous sodium hydrogen carbonate solution (10 mL) was added. The mixture was cooled to -10 °C using salt/ice/acetone bath. Sodium hypochlorite solution (7%) (pH adjusted to 9.5 by addition of 20% sulphuric acid) (27 mL, 26 mmol) was added to the biphasic reaction mixture which was stirred vigorously. After 3 min, the phases were separated, and the organic phase was washed with saturated aqueous sodium thiosulfate solution (2 × 20 mL) and water (2 × 20 mL). The organic layer was dried and concentrated. Flash column chromatography using 10% ethyl acetate in hexane as eluent, yielded the title compound as a clear oil.

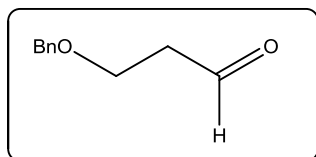
Yield = 1.21 g, 40%.

ν_{\max} (NaCl): 2863, 1737, 1496, 1454, 1123, 1109, 740, 698 cm^{-1} .

δ_{H} (300 MHz): 4.09 (2H, s, CH_2OBn), 4.63 (2H, s, OCH_2Ph), 7.24 - 7.42 (5H, m, ArH) 9.72 (1H, s, CHO).

δ_{C} (75 MHz): 72.6 (CH_2CHO or CH_2Ph), 74.3 (CH_2CHO or CH_2Ph), 127.0, 127.2, 127.6 (all ArC), 135.8 (ArC1), 199.4 (CHO).

3-Benzyloxypropanal(13)⁹



Freshly distilled DMSO (0.87 mL, 13.3 mmol) was charged to a stirring solution of oxalyl chloride (0.58 mL, 6.67 mmol) in doubly distilled DCM (15 mL) at -78°C . This mixture was stirred for 10 min. A solution of 3-benzyloxypropanol (1 g, 6.06 mmol) in doubly distilled DCM (50 mL) was then added. The resulting solution was stirred at -78°C for 30 min. Triethylamine (4.21 mL, 30 mmol) was added neat and this solution was stirred for a further 20 min at -78°C , after which time it was allowed to warm to room temperature. Water (30 mL) was added and the resulting layers were separated. The aqueous layer was extracted with DCM (2×80 mL). The combined organic extracts were washed with 10% w/v HCl (2×40 mL), water (2×40 mL) and brine (2×40 mL), dried and concentrated. Flash column chromatography, using 10% ethyl acetate in hexane as eluent, yielded the title compound as a clear oil.

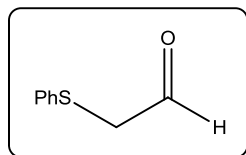
Yield = 0.76 g, 77%.

ν_{\max} (NaCl): 3031, 2864, 1736, 1496, 1454, 1109, 739, 699 cm^{-1} .

δ_{H} (300 MHz): 2.62 (2H, td, $J = 6.3$ and 2.2 , CH_2CHO), 3.76 (2H, t, $J = 6.3$, BnOCH_2) 4.49 (2H, s, OCH_2Ph), 7.22 - 7.37 (5H, m, ArH) 9.75 (1H, t, $J = 2.2$, CHO).

δ_{C} (75 MHz): 43.9 (CH_2CHO), 63.9 (CH_2OBn), 73.2 (CH_2Ph), 127.6, 127.7, 128.8 (All ArC), 137.6 (ArC1), 200.6 (CHO).

Benzenesulphenylacetaldehyde (17)¹⁰



To a stirring solution of benzenesulphenylacetaldehyde dimethylacetal (1 g, 5.05 mmol) in 1,4-dioxane (10 mL), was added 10% aqueous HCl (15 mL). The resulting solution was refluxed for 16 h. The solution was cooled to room temperature and diluted with

diethylether (50 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with diethylether (3 × 50 mL). The organic layers were combined, dried and concentrated under reduced pressure to afford a yellow oil. Bulb to bulb distillation afforded the product as a pale yellow oil, b.p. 65 °C at 0.5 mmHg (Lit¹⁰: b.p. 105 at 7 mmHg).

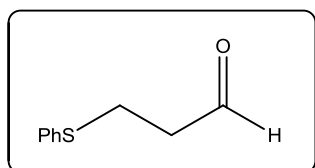
Yield = 0.41 g, 54%.

ν_{max} (NaCl): 3059, 2822, 1721, 1480, 1439, 1024 cm^{-1} .

δ_{H} (300 MHz): 3.59 (2H, d, $J = 3.2$, SCH_2), 7.21-7.36 (5H, m, ArH), 9.54 (1H, t, $J = 3.2$, CHO).

δ_{C} (75 MHz): 67.1 (SCH_2CHO), 127.3, 129.3, 130.0 (All ArC), 135.2 (ArC1) 195.0 (CHO).

3-Benzenesulfonylpropanal (19)¹¹



To a flame dried, 250 mL round bottom flask, thiophenol (*caution* – malodorous!) (15 mL, 14 mmol) in anhydrous chloroform (120 mL) at 0 °C under a nitrogen atmosphere was added anhydrous triethylamine (1 mL, 7.2 mmol) over 10 min.

Acrolein (10 mL, 15 mmol) in anhydrous chloroform (7 mL) was then added dropwise over 15 min at such a rate that the reaction temperature did not exceed 5 °C. The resulting solution was stirred for 1 h at 0 °C and then allowed to warm temperature over 30 min. The solution was diluted with diethylether (200 mL) and washed successively with 2 M aqueous sodium hydroxide (2 × 100 mL), water (100 mL) and brine (100 mL), dried and concentrated under reduced pressure to yield a yellow oil. Bulb-to-bulb distillation afforded the product as a clear yellow oil, (b.p. 135 °C at 1 mmHg).

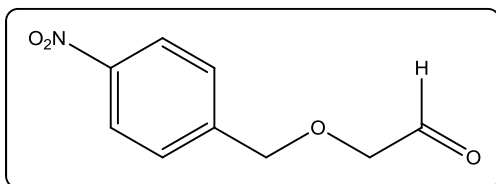
Yield = 15.62 g, 65%.

ν_{max} (NaCl): 3057, 2929, 2829, 1722, 1583, 1480, 1438, 1025, 740, 691 cm^{-1} .

δ_{H} (300 MHz): 2.74 (2H, td, $J = 7.2$ and 1.1, SCH_2CH_2), 3.16 (2H, d, $J = 7.2$, SCH_2CH_2), 7.18 - 7.36 (5H, m, ArH) 9.72 (1H, t, $J = 1.1$, CHO).

δ_{C} (75 MHz): 26.3 (SCH_2CH_2), 43.4 (SCH_2CH_2), 126.6 (ArC4), 129.1 (ArC2 and ArC6), 129.9 (ArC3 and ArC5), 135.1 (ArC1), 200.3 (CHO).

2-(4-Nitrobenzyloxyacetaldehyde) (14)



Freshly distilled DMSO (2.18 mL, 28.06 mmol) was charged to a stirring solution of oxalyl chloride (1.23 mL, 14.03 mmol) in doubly distilled DCM (30 mL) at -78 °C. This mixture was then stirred for 10 min. A solution of 2-(4-nitrobenzyloxy)ethanol (2.5 g, 12.75 mmol) in doubly distilled DCM (50 mL) was added. The resulting solution was stirred at -78 °C for 30 min. Triethylamine (8.81 mL, 63.5 mmol) was added neat and this reaction solution was stirred for a further 20 min at -78 °C after which time it was allowed to warm to room temperature. Water (200 mL) was added. The aqueous layer was washed with DCM (2 x 80 mL). The combined organic extracts were washed with 10% w/v HCl (2 x 80 mL), water (2 x 80 mL) and brine (2 x 80 mL), dried and concentrated under reduced pressure. The title compound was isolated as a pale yellow liquid and used without further purification.

Yield = 3.57 g, 72%.

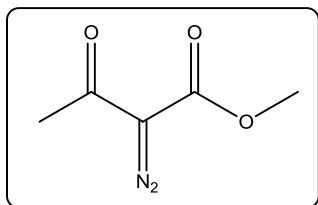
ν_{max} (NaCl): 3080, 2927, 2864, 1728, 1439, 1107, 739, 700 cm^{-1} .

δ_{H} (400 MHz): 4.24 (2H, s, $\text{CH}_2\text{OCH}_2\text{Ar}$), 4.75 (2H, s, OCH_2Ar), 7.88 (2H, d, $J = 8.7$ ArC3-H and ArC5-H), 8.27 (2H, d, $J = 8.7$, C2-H and C6-H), 9.76 (1H, s, CHO).

δ_{C} (125 MHz): 72.2 ($\text{CH}_2\text{OCH}_2\text{Ar}$), 75.9 (CH_2Ar), 123.6 (ArC3 and ArC5), 127.9 (ArC2 and ArC6), 144.7 (ArC1), 147.5 (ArC4), 199.4 (CHO).

3.2.4 Preparation of α -Diazo β -Keto Esters

2-Diazo-3-oxobutyric acid methyl ester (21)¹²



Solid anhydrous K_2CO_3 (11.90 g, 86 mmol) was added to a stirring solution of methylacetoacetate (5 g, 43 mmol) in acetonitrile (50 mL). A solution of *p*-toluenesulfonyl azide (8.57 g, 43 mmol) in acetonitrile (50 mL) was added dropwise *via* dropping funnel to the stirring solution. The resulting solution was stirred for a further 2 h at room temperature. Diethylether (100 mL) was added to precipitate the salts and the resultant mixture was filtered through Celite[®] and the filtrate was concentrated *in vacuo*. 2 : 1 Hexane : ether (150 mL) was added to the residue and the solution was filtered through Celite[®], dried and concentrated under reduced pressure. Flash column chromatography, using 5% ethyl acetate in hexane as the eluent, yielded the title compound as a bright yellow oil.

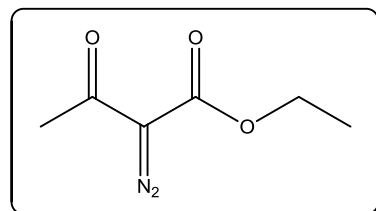
Yield = 3.80 g, 62%.

ν_{\max} (NaCl): 2958, 2142, 1723, 1659, 1366, 1316, 1080 cm^{-1}

δ_H (300 MHz): 2.46 (3H, s, CH_3), 3.85 (3H, s, OCH_3).

δ_C (75 MHz): 28.5 (**C**-4), 52.5 (OCH_3), 162.1 (**C**1), 190.3 (**C**3), no signal observed for **C**= N_2 .

2-Diazo-3-oxobutyric acid ethyl ester (22)¹³



Solid anhydrous K_2CO_3 (10.61 g, 79 mmol) was added to a stirring solution of ethyl acetoacetate (5 g, 38 mmol) in acetonitrile (50 mL). A solution of *p*-toluenesulfonyl azide (7.65 g, 12 mmol) in acetonitrile (50 mL) was added dropwise *via* dropping funnel to the stirring solution. The

resulting solution was stirred for a further 2 h at room temperature. Diethylether (100 mL) was added to precipitate the inorganic salts. The resulting mixture was filtered through Celite[®] and the filtrate was concentrated under reduced pressure. 2 : 1 Hexane : ether (150 mL) was added to the residue and the solution was filtered through Celite[®], dried and concentrated under reduced pressure. Flash column chromatography, using 5% ethyl acetate in hexane as the eluent, yielded the title compound as a bright yellow oil.

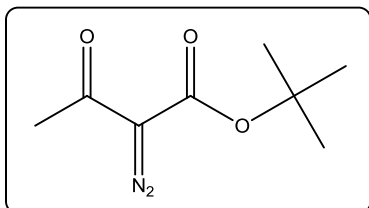
Yield = 4.31 g, 75%.

ν_{\max} (NaCl): 2986, 2140, 1719, 1660, 1372, 1317, 1074 cm^{-1} .

δ_{H} (300 MHz): 1.31 (3H, t, $J = 7.2$, OCH_2CH_3), 2.48 (3H, s, CH_3), 4.32 (2H, q, $J = 7.2$, OCH_2CH_3).

δ_{C} (75 MHz): 14.4 (OCH_2CH_3), 28.5 (**C4**), 61.7 (OCH_2CH_3), 161.7 (**C1**), 190.5 (**C3**), no signal observed for $\text{C}=\text{N}_2$.

2-Diazo-3-oxobutyric Acid *tert*-Butyl Ester (**20**)¹⁴



Solid anhydrous K_2CO_3 (3.49 g, 12 mmol) was added to a stirring solution of *t*-butyl acetoacetate (2 g, 12 mmol) in acetonitrile (20 mL). A solution of *p*-toluenesulfonyl azide (2.49 g, 12 mmol) in acetonitrile (20 mL) was added dropwise *via* dropping funnel to the stirring solution. The

solution was stirred for a further 2 h at room temperature. Diethylether (100 mL) was added to precipitate the salts. The mixture was then filtered through Celite® and the filtrate was concentrated under reduced pressure. 2 : 1 Hexane : ether (150 mL) was added to the residue which was filtered through Celite®, dried and concentrated under reduced pressure. Flash column chromatography, using 5% ethyl acetate in hexane as the eluent, yielded the title compound as a bright yellow oil.

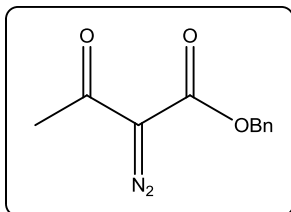
Yield = 1.75 g, 75%.

ν_{max} (NaCl): 2980, 2133, 1712, 1659, 1369, 1320, 1069 cm^{-1} .

δ_{H} (300 MHz): 1.53 [9H, s, $\text{C}(\text{CH}_3)_3$], 2.46 (3H, s, CH_3).

δ_{C} (75 MHz): 28.4 [$\text{C}(\text{CH}_3)_3$], 28.5 (**C4**), 83.6 [$\text{C}(\text{CH}_3)_3$], 161.0 (**C1**), 190.7 (**C3**), no signal observed for $\text{C}=\text{N}_2$.

2-Diazo-3-oxobutyric Acid Benzyl Ester (**23**)¹⁵



Solid anhydrous K_2CO_3 (7.29 g, 52 mmol) was added to a stirring solution of benzyl acetoacetate (5 g, 26 mmol) in acetonitrile (50 mL). A solution of *p*-toluenesulfonyl azide (5.13 g, 26 mmol) in acetonitrile (50 mL) was added dropwise *via* dropping funnel to the stirring solution. The solution was stirred

for 2 h at room temperature. Diethylether (200 mL) was added to precipitate the salts. The mixture was filtered through Celite® and the filtrate concentrated. 2 : 1 Hexane : ether (300 mL) was added to the residue which was filtered through Celite®, dried,

concentrated. Flash column chromatography, using 5% ethyl acetate in hexane as the eluent, yielded the title compound as a bright yellow oil which later formed a low melting solid.

Yield = 4.49 g, 79%.

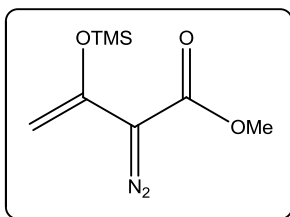
ν_{max} (KBr): 2986, 2141, 1721, 1661, 1372, 1318, 1075, 745, 701 cm^{-1} .

δ_{H} (300 MHz): 2.48 (3H, s, CH_3), 5.27 (2H, s, OCH_2Ph), 7.35 - 7.38 (5H, m, ArH).

δ_{C} (75 MHz): 28.3 (**C4**), 67.0 (OCH_2Ph), 128.4, 128.7, 128.8 (All Ar**C**), 135.2 (Ar**C1**), 161.7 (**C1**), 190.0 (**C3**), no signal observed for **C=N**₂.

3.2.4 Preparation of silyl enol ethers

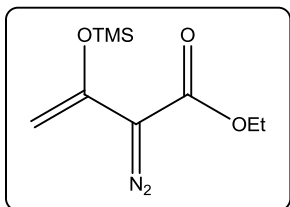
Methyl 3-trimethylsilyloxy-2-diazobut-3-enoate (26)¹⁶



2-Diazo-3-oxobutyric acid methyl ester (2 g, 14 mmol) was dissolved in MeCN (10 mL). Et₃N (2.4 mL, 17 mmol) was added followed by neat TMSCl (1.83 g, 17 mmol) and the resulting solution was stirred at room temperature. Anhydrous NaI (2.52 g, 17 mmol) was then added portion-wise over 5 min. Upon complete addition, the mixture was stirred at room temperature for 2 h before hexane (20 mL) was added. The resultant mixture was stirred vigorously for a further 5 min and then left to stand for 5 min. The upper layer was transferred into a round bottom flask using a pasteur pipette fitted with a plug of cotton wool to filter any precipitate. The filtrate was then concentrated under reduced pressure to a volume of approximately 5 mL and used without further purification. This solution was used in subsequent reactions immediately.

ν_{max} (NaCl): 2931, 2859, 2102, 1711, 1373, 1343, 1085 cm⁻¹.

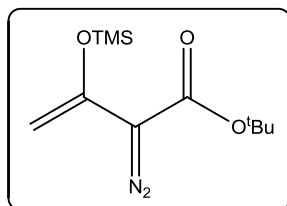
Ethyl 3-trimethylsilyloxy-2-diazobut-3-enoate (28)



2-Diazo-3-oxobutyric acid ethyl ester (2 g, 13 mmol) was dissolved in MeCN (10 mL). Et₃N (2.14 mL, 15 mmol) was added followed by neat TMSCl (1.68 g, 15 mmol) and the resulting solution was stirred at room temperature. Anhydrous NaI (2.29 g, 15 mmol) was then added portion-wise over 5 min. Upon complete addition, the mixture was stirred at room temperature for 2 h before hexane (20 mL) was added. The resultant mixture was stirred vigorously for a further 5 min and then left to stand for 5 min. The upper layer was transferred into a round bottom flask using a pasteur pipette fitted with a plug of cotton wool to filter any precipitate. The filtrate was then concentrated under reduced pressure to a volume of approximately 5 mL and used without further purification. This solution was used in subsequent reactions immediately.

ν_{max} (NaCl): 2956, 2879, 2102, 1715, 1373, 1343, 1085 cm⁻¹.

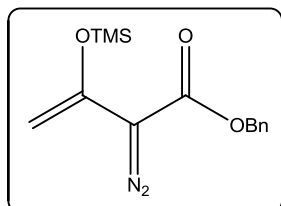
***tert*-Butyl 3-Trimethylsilyloxy-2-diazobut-3-enoate (31)**



2-Diazo-3-oxobutyric acid *t*-butyl ester (2 g, 11 mmol) was dissolved in MeCN (10 mL). Et₃N (1.8 mL, 13 mmol) was added followed by neat TMSCl (1.4 g, 13 mmol) and the resulting solution was stirred at room temperature. Anhydrous NaI (1.93 g, 13 mmol) was added portion-wise over 5 min. Upon complete addition, the mixture was stirred at room temperature for 2 h before hexane (20 mL) was added. The resultant mixture was stirred vigorously for a further 5 min and then left to stand for 5 min. The upper layer was transferred into a round bottom flask using a pasteur pipette fitted with a plug of cotton wool to filter any precipitate. The filtrate was then concentrated under reduced pressure to a volume of approximately 5 mL and used without further purification. This solution was used in subsequent reactions immediately.

ν_{max} (NaCl): 2937, 2761, 2102, 1714, 1372, 1342, 1082.

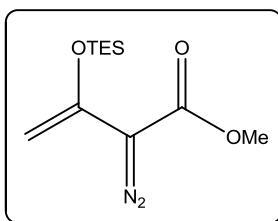
Benzyl 3-Trimethylsilyloxy-2-diazobut-3-enoate (34)



2-Diazo-3-oxobutyric acid benzyl ester (2 g, 9 mmol) was dissolved in MeCN (10 mL). Et₃N (1.5 mL, 11 mmol) was added followed by neat TMSCl (1.2 g, 11 mmol) and the resulting solution was stirred at room temperature. Anhydrous NaI (1.64 g, 11 mmol) was added portion-wise. Upon complete addition, the mixture was stirred at room temperature for 2 h before hexane (20 mL) was added. The resultant mixture was stirred vigorously for a further 5 min and then left to stand for 5 min. The upper layer was transferred into a round bottom flask using a pasteur pipette fitted with a plug of cotton wool to filter any precipitate. The filtrate was then concentrated under reduced pressure to a volume of approximately 5 mL and used without further purification. This solution was used in subsequent reactions immediately.

ν_{max} (NaCl): 2992, 2860, 2100, 1709, 1369, 1348, 1083, 748, 692 cm⁻¹.

Methyl 3-Triethylsilyloxy-2-diazobut-3-enoate (27)



2-Diazo-3-oxobutyric acid methyl ester (1.5 g, 10 mmol) was dissolved in MeCN (10 mL). Et₃N (1.6 mL, 11 mmol) was added followed neat TESCO (1.95 mL, 11 mmol) and the resulting solution was stirred at room temperature. Anhydrous NaI (1.73 g, 11 mmol) was added portion-wise over 5 min. Upon complete addition, the mixture was stirred at room temperature for 2 h before hexane (40 mL) was added. The layers were separated. The hexane was washed with saturated aqueous NaHCO₃ (2 × 50 mL). The combined aqueous layers were extracted with hexane (2 × 70 mL). The organic layers were combined, dried and concentrated under reduced pressure to yield an orange oil which was used without further purification. This oil was used in subsequent reactions immediately.

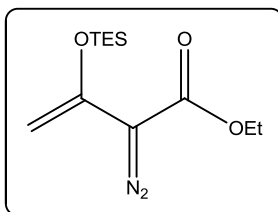
Yield = 2.05 g, 78%.

ν_{max} (NaCl): 2957, 2105, 1718, 1353 1092 cm⁻¹.

δ_{H} (300 MHz): 0.52 (6H, q, $J = 7.6$, SiCH₂CH₃), 0.95 (9H, t, $J = 7.6$, SiCH₂CH₃), 3.79 (3H, s, OCH₃), 4.26 (1H, d, $J = 2.1$, H of vinyl group *cis* to diazo), 4.99 (1H, d, $J = 2.1$, H of vinyl group *trans* to diazo).

Due to lack of stability, ¹³C analysis was not possible.

Ethyl 3-Triethylsilyloxy-2-diazobut-3-enoate (29)



2-Diazo-3-oxobutyric acid ethyl ester (0.3 g, 2 mmol) was dissolved in MeCN (2 mL). Et₃N (0.32 mL, 3 mmol) was added followed by the addition of neat TESCO (0.5 mL, 3 mmol) and the resulting solution was stirred at room temperature. Anhydrous NaI (0.5 g, 3 mmol) was added portion-wise over 5 min. Upon complete addition, the mixture was stirred at room temperature for 2 h before hexane (10 mL) was added. The layers were separated. The hexane was washed with saturated aqueous NaHCO₃ (2 × 10 mL). The combined aqueous layers were extracted with hexane (2 × 10 mL). The organic layers were combined, dried and concentrated under reduced pressure to yield an orange oil which was used without further purification. This oil was used in subsequent reactions immediately.

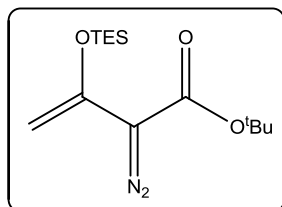
Yield = 0.39 g, 74%.

ν_{max} (NaCl): 2956, 2104, 1716, 1346 1073 cm⁻¹.

δ_{H} (300 MHz): 0.52 (6H, q, $J = 7.6$, SiCH_2CH_3), 0.91 (9H, m, SiCH_2CH_3), 1.30 (3H, t, $J = 7.1$, OCH_2CH_3), 4.25 (1H, d, $J = 2.0$, H of vinyl group *cis* to diazo), 4.26 (2H, q, $J = 7.1$, OCH_2CH_3), 4.99 (1H, d, $J = 2.0$, H of vinyl group *trans* to diazo).

Due to lack of stability, ^{13}C analysis was not possible.

***tert*-Butyl 3-Triethylsilyloxy-2-diazobut-3-enoate (32)**



2-Diazo-3-oxobutyric acid *t*-butyl ester (0.4 g, 2 mmol) was dissolved in MeCN (3 mL) Et_3N (0.4 mL, 3 mmol) was added followed by neat TESCO (0.47 mL, 3 mmol) and the resulting solution was stirred at room temperature. Anhydrous NaI (0.42 g, 3 mmol) was added portion-wise over 5 min. Upon complete addition, the mixture was stirred at room temperature for 2 h before hexane (15 mL) was added. The layers were separated. The hexane was washed with saturated aqueous NaHCO_3 (2 \times 10 mL). The combined aqueous layers were extracted with hexane (2 \times 15 mL). The organic layers were combined, dried and concentrated under reduced pressure to yield an orange oil which was used without further purification. This oil was used in subsequent reactions immediately.

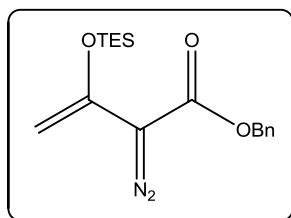
Yield = 0.55 g, 85%.

ν_{max} (NaCl): 2958, 2878, 2099, 1709, 1349 1083 cm^{-1} .

δ_{H} (300 MHz): 0.51 (6H, q, $J = 7.5$, SiCH_2CH_3), 0.96 (9H, t, $J = 7.5$, SiCH_2CH_3), 1.48 (9H, s, $\text{OC}(\text{CH}_3)_3$), 4.26 (1H, d, $J = 2.0$, H of vinyl group *cis* to diazo), 4.99 (1H, d, $J = 2.0$, H of vinyl group *trans* to diazo).

Due to lack of stability, ^{13}C analysis was not possible.

Benzyl 3-Triethylsilyloxy-2-diazobut-3-enoate (35)



2-Diazo-3-oxobutyric acid benzyl ester (0.5 g, 2 mmol) was dissolved in MeCN (3 mL). Et_3N (0.4 mL, 3 mmol) was added followed by neat TESCO (0.47 mL, 3 mmol) and the resulting solution was stirred at room temperature. Anhydrous NaI (0.44 g, 3 mmol) was added portion-wise over 5 min. Upon complete addition, the mixture was stirred at room temperature for 2 h before hexane (10 mL) was added. The layers were separated. The hexane was washed with saturated aqueous

NaHCO₃ (2 × 10 mL). The combined aqueous layers were extracted with hexane (2 × 10 mL). The organic layers were combined, dried and concentrated under reduced pressure to yield an orange oil which was used without further purification. This oil was used in subsequent reactions immediately.

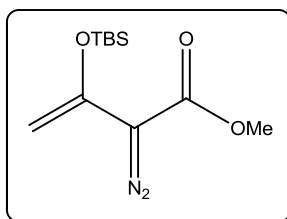
Yield = 0.60 g, 79%.

ν_{max} (NaCl): 2958, 2878, 2103, 1711, 1346, 1073, 742, 697 cm⁻¹.

δ_{H} (300 MHz): 0.52 (6H, q, $J = 7.8$, SiCH₂CH₃), 0.94 (9H, t, $J = 7.8$, SiCH₂CH₃), 4.26 (1H, d, $J = 2.1$, H of vinyl group *cis* to diazo), 4.99 (1H, d, $J = 2.1$, H of vinyl group *trans* to diazo), 5.24 (2H, s, OCH₂Ph), 7.31 - 7.40 (5H, ArH).

Due to lack of stability, ¹³C analysis was not possible.

Methyl 3-*tert*-Butyldimethylsilyloxy-2-diazobut-3-enoate (25)¹⁷



Triethylamine (0.65 mL, 5 mmol) was added to a stirring solution of 2-diazo-3-oxobutyric acid methyl ester (0.5 g, 3.5 mmol) in DCM (7 mL) at 0 °C under a nitrogen atmosphere. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.88 mL, 4 mmol) was added neat over 5 min and the mixture was further stirred

for 30 min at 0 °C. The reaction mixture was then diluted with hexane (30 mL) and saturated aqueous NaHCO₃ solution (40 mL) was added. The layers were separated and the organic phase was washed with saturated aqueous NaHCO₃ solution (30 mL) and brine (30 mL). The organic layer was dried and concentrated under reduced pressure to yield an orange oil which was used without further purification. This oil was used in subsequent reactions immediately.

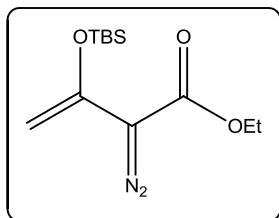
Yield = 0.82 g, 92%.

ν_{max} (NaCl): 2957, 2859, 2103, 1711, 1345, 1074 cm⁻¹.

δ_{H} (300 MHz): 0.23 [6H, s, Si(CH₃)₂], 0.92 [9H, s, C(CH₃)₃], 3.80 (3H, s, OCH₃), 4.25 (1H, d, $J = 2.1$, H of vinyl group *cis* to diazo), 5.00 (1H, d, $J = 2.1$, H of vinyl group *trans* to diazo).

Due to lack of stability, ¹³C analysis was not possible.

Ethyl 3-*tert*-Butyldimethylsilyloxy-2-diazobut-3-enoate (30)



Triethylamine (1.3 mL, 9 mmol) was added to a stirring solution of 2-diazo-3-oxobutyric acid ethyl ester (1 g, 6 mmol) in DCM (10 mL) at 0 °C under a nitrogen atmosphere. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (1.8 mL, 7.7 mmol) was added neat over 5 min and the mixture was stirred for 30 min at 0 °C. The reaction mixture was diluted with hexane (40 mL) and saturated aqueous NaHCO₃ solution (40 mL) was added. The layers were separated and the organic phase was washed with saturated aqueous NaHCO₃ solution (2 × 50 mL) and brine (50 mL). The organic layer was dried and concentrated under reduced pressure to yield an orange oil which was used without further purification. This oil was used in subsequent reactions immediately.

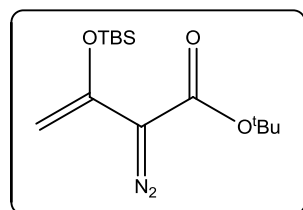
Yield = 1.54 g, 89%.

ν_{max} (NaCl): 2958, 2860, 2102, 1712, 1347, 1086 cm⁻¹.

δ_{H} (300 MHz): 0.24 [6H, s, Si(CH₃)₂], 0.94 [9H, s, C(CH₃)₃], 1.31 (3H, t, *J* = 7.1, OCH₂CH₃), 4.24 - 4.31 (3H, m, OCH₂CH₃ and H of vinyl group *cis* to diazo), 5.02 (1H, d, *J* = 2.1, H of vinyl group *trans* to diazo).

Due to lack of stability, ¹³C analysis was not possible.

tert-Butyl 3-*tert*-Butyldimethylsilyloxy-2-diazobut-3-enoate (33)



Triethylamine (0.56 mL, 4 mmol) was added to a stirring solution of 2-diazo-3-oxobutyric acid *t*-butyl ester (0.5 g, 3 mmol) in DCM (7 mL) at 0 °C under a nitrogen atmosphere. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.75 mL, 3.3 mmol) was added neat over 5 min and the mixture was further stirred for 30 min at 0 °C. The reaction mixture was then diluted with hexane (30 mL) and saturated aqueous NaHCO₃ (30 mL) solution was added. The layers were separated and the organic phase was washed with saturated aqueous NaHCO₃ solution (40 mL) and brine (40 mL). The organic layer was dried and concentrated under reduced pressure to yield an orange oil which was used without further purification. This oil was used in subsequent reactions immediately.

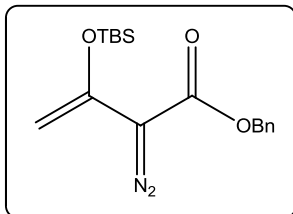
Yield = 0.75 g, 92%.

ν_{max} (NaCl): 2957, 2877, 2104, 1709, 1346, 1074 cm⁻¹.

δ_{H} (300 MHz): 0.22 [6H, s, Si(CH₃)₂], 0.91 [9H, s, SiC(CH₃)₃], 1.52 [9H, s, OC(CH₃)₃], 4.21 (1H, d, J = 2.0, H of vinyl group *cis* to diazo), 4.96 (1H, d, J = 2.0, H of vinyl group *trans* to diazo).

Due to lack of stability, ¹³C analysis was not possible.

Benzyl 3-*tert*-Butyldimethylsilyloxy-2-diazobut-3-enoate (36)



Triethylamine (0.42 mL, 1.4 mmol) was added to a stirring solution of 2-diazo-3-oxobutyric acid benzyl ester (0.2 g, 0.9 mmol) in DCM (3 mL) at 0 °C under a nitrogen atmosphere. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.25 mL, 1 mmol) was added neat over 5 min and the mixture was stirred for 30 min at 0 °C. The reaction mixture was diluted with hexane (10 mL) and saturated aqueous NaHCO₃ solution (10 mL) was added. The layers were separated and the organic phase was washed with saturated aqueous NaHCO₃ solution (10 mL) and brine (10 mL). The organic layer was dried and concentrated under reduced pressure to yield an orange oil which was used without further purification. This oil was used in subsequent reactions immediately.

Yield = 0.27 g, 87%.

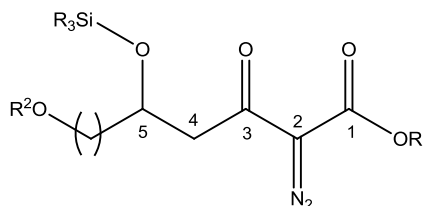
ν_{max} (NaCl): 2957, 2860, 2103, 1712, 1345, 1074, 744, 696 cm⁻¹.

δ_{H} (300 MHz): 0.22 [6H, s, Si(CH₃)₂], 0.91 [9H, s, C(CH₃)₃], 4.23 (1H, d, J = 2.1, H of vinyl group *cis* to diazo), 5.01 (1H, d, J = 2.1, H of vinyl group *trans* to diazo), 5.24 (2H, s, OCH₂Ph), 7.28 – 7.37 (5H, m, ArH).

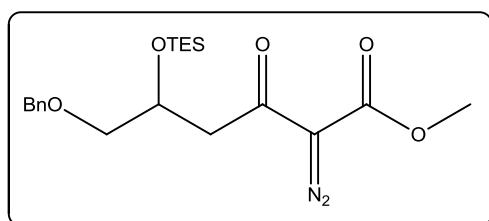
Due to lack of stability, ¹³C analysis was not possible.

3.2.5 Preparation of Mukaiyama Addition Products

Numbering system of Mukaiyama addition products.



Methyl 6-(Benzyloxy)-5-triethylsilyloxy-2-diazo-3-oxohexanoate (40)



Method 1. [Sc(OTf)₃]

To a flame dried, 100 mL 3-neck round-bottom flask containing anhydrous scandium (III) triflate (105 mg, 0.21 mmol) and a stirring bar, and fitted with two 100 mL addition funnels, anhydrous THF (5 mL) was added. To the resulting suspension, simultaneously both methyl 3-triethylsilyloxy-2-diazobut-3-enoate (1.81 g, 7.04 mmol) in anhydrous THF (20 mL) and 2-benzyloxyacetaldehyde (0.79 g, 5.28 mmol) in anhydrous THF (20 mL) were added dropwise *via* separate addition funnels. The reaction mixture was stirred at room temperature overnight. During this time, colour change from orange to pale yellow was observed and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2134 cm⁻¹ was observed). The solution was filtered through Celite® and concentrated under reduced pressure. Flash column chromatography, utilising 5% ethyl acetate in hexane as the eluent, yielded the product as a yellow oil. Yield = 1.46 g, 68%.

Method 2. [Zn(OTf)₂]

To a flame dried round-bottom flask, anhydrous zinc(II) triflate (115 mg, 0.32 mmol) and anhydrous DCM (30 mL) were added. The suspension was cooled to 0 °C. 2-Benzyloxyacetaldehyde (1.23 g, 8.2 mmol) was added, and the suspension was stirred,

before methyl 3-triethylsilyloxy-2-diazobut-3-enoate (2.72 g, 10.6 mmol) was added dropwise *via* dropping funnel to the stirring solution. This solution was stirred at 0 °C for 1 h before being allowed to warm to room temperature and stirred overnight. During this time, colour change from orange to pale yellow was observed and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2134 cm⁻¹ was observed). Upon completion of the reaction, the solution was filtered through Celite® and concentrated under reduced pressure. Flash column chromatography, utilising 5% ethyl acetate in hexane as the eluent, yielded the product as a yellow oil.

Yield = 2.03 g, 60%.

ν_{max} (NaCl): 2955, 2876, 2137, 1719, 1655, 1353 1092, 748, 699 cm⁻¹.

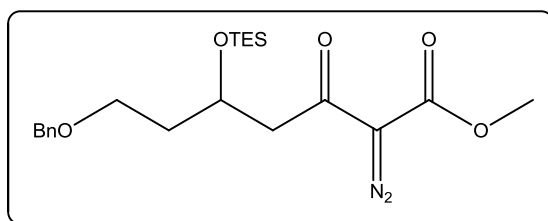
δ_{H} (300 MHz): 0.59 (6H, q, $J = 7.8$, SiCH₂CH₃), 0.94 (9H, t, SiCH₂CH₃), 3.11 (2H, d, $J = 6.2$, 2 x C4-H), 3.38 (1H, dd, H_A of ABX, $J = 15.5$ and 5.9, CH₂OBn), 3.50 (1H, dd, H_B of ABX, $J = 15.5$ and 9.6, CH₂OBn), 3.81 (3H, s, OCH₃), 4.44 (1H, m, H_X of ABX, C5-HOH), 4.52 (2H, s, CH₂Ph), 7.27 – 7.33 (5H, m, ArH).

δ_{C} (75 MHz): 4.8 [Si(CH₂CH₃)₃], 6.8 [Si(CH₂CH₃)₃], 45.2 (C4), 52.3 (OCH₃), 68.0 (C5), 73.3 (C6 or CH₂Ph), 73.4 (C-6 or CH₂Ph), 127.5, 127.6, 128.3 (All ArC), 138.3 (ArC1), 169.9 (C1), 190.5 (C3), no signal observed for C=N₂.

M.S: m/z : 407 (M+H⁺, 100%), 293, 265, 215, 175, 156, 132.

HRMS calculated for C₂₀H₃₁N₂O₅Si [M+H]⁺: 407.2002; found 407.2009.

Methyl 7-(Benzyloxy)-5-triethylsilyloxy-2-diazo-3-oxoheptanoate (41)



Method 1. [Sc(OTf)₃]

To a flame dried, 100 mL 3-neck round-bottom flask containing anhydrous scandium(III) triflate (105 mg, 0.21 mmol) and a stirring bar, fitted with two 100 mL addition funnels, anhydrous THF (5 mL) was added. To this suspension, both methyl 3-triethylsilyloxy-2-diazobut-3-enoate (1.8 g, 7 mmol) in anhydrous THF (20 mL) and 3-benzyloxypropanaldehyde (0.8 g, 5 mmol) in anhydrous THF (20 mL) were added

dropwise simultaneously *via* the separate addition funnels. The reaction mixture was stirred at room temperature overnight. During this time, colour change from orange to pale yellow was observed, and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2133 cm^{-1}). After the reaction was complete, the solution was filtered through Celite[®], the Celite[®] bed was then washed with diethylether (50 mL) and concentrated under reduced pressure. Flash column chromatography, utilising 5% ethyl acetate in hexane as the eluent, yielded the product as a yellow oil. Yield = 1.21 g, 58%.

Method 2. [Zn(OTf)₂]

To a flame dried round-bottom flask, anhydrous zinc(II) triflate (62 mg, 0.17 mmol) and DCM (25 mL) were added. The suspension was cooled to 0 °C. 3-Benzyloxypropanal (0.68 g, 4.22 mmol) was then added and stirred, followed by methyl 3-triethylsilyloxy-2-diazobut-3-enoate (1.45 g, 5.63 mmol). The resulting solution was stirred at 0 °C for 1 h before being allowed to warm to room temperature and stirred overnight. During this time, colour change from orange to pale yellow was observed and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2133 cm^{-1} was observed). After the reaction was complete, the solution was filtered through Celite[®] and concentrated under reduced pressure. Flash column chromatography, utilising 5% ethyl acetate in hexane as the eluent, yielded the product as a yellow oil.

Yield = 1.29 g, 73%.

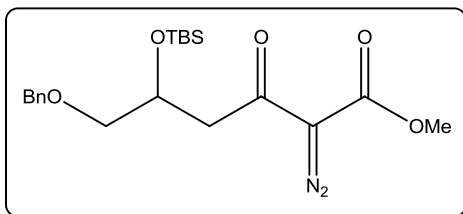
ν_{max} (NaCl): 3030, 2955, 2876, 2137, 1719, 1654, 1315 1080, 743, 699 cm^{-1} .

δ_{H} (300 MHz): 0.52 (6H, q, $J = 7.5$, SiCH_2CH_3), 0.93 (9H, t, $J = 7.5$, SiCH_2CH_3), 1.83 - 1.87 (2H, m, 2 x C6-H), 2.97 (1H, dd, $J = 13.4$ and 7.5 , C4-H), 3.12 (1H, dd, $J = 13.4$ and 7.8 , C4-H), 3.55 (2H, t, $J = 7.9$, CH_2OBn), 3.82 (3H, s, OCH_3), 4.44 (1H, m, H_X of ABX, C5-HOH), 4.52 (2H, s, CH_2Ph), 7.27 – 7.33 (5H, m, ArH).

δ_{C} (75 MHz): 4.8 [$\text{Si}(\text{CH}_2\text{CH}_3)_3$], 6.8 [$\text{Si}(\text{CH}_2\text{CH}_3)_3$], 37.7 (C-6), 47.6 (C-4), 52.1 (OCH_3), 66.5 (C-5), 66.7 (C-7), 72.4 (OCH_2Ph), 127.5, 127.6, 128.3, (All ArC), 138.6 (ArC-1), 169.9 (C-1), 190.5 (C-3), no signal observed for C=N₂.

M.S: m/z : 421 (M+H)⁺, 407, 367, 313, 307 (100 %), [M+2H-TES]⁺, 277, 199.

HRMS calculated for $\text{C}_{21}\text{H}_{33}\text{N}_2\text{O}_5\text{Si}$ [M+H]⁺: 421.2159; found 421.2163.

Methyl 6-(Benzyloxy)-5-*tert*-butyldimethylsilyloxy-2-diazo-3-oxohexanoate (37)¹⁸

To a flame dried, 100 mL 3-neck round-bottom flask containing a stirring bar and fitted with two 100 mL addition funnels, anhydrous scandium(III) triflate (42 mg, 0.18 mmol) and anhydrous THF (5 mL) were added. To the resulting suspension, both methyl 3-*tert*-butyldimethyl-silanyloxy-2-diazobut-3-enoate (1.6 g, 6.25 mmol) in anhydrous THF (30 mL) and 2-benzyloxyacetaldehyde (0.70 g, 4.68 mmol) in anhydrous THF (30 mL) were added dropwise simultaneously *via* separate addition funnels. The reaction mixture was stirred at room temperature overnight. During this time, colour change from orange to pale yellow was observed and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2133 cm⁻¹). Upon completion of the reaction, the solution was filtered through Celite®, the Celite® pad was washed with diethylether (60 mL) and concentrated under reduced pressure. Flash column chromatography, utilising 5% ethyl acetate in hexane as the eluent, yielded the product as a yellow oil.

Yield = 1.59 g, 69%.

ν_{max} (NaCl): 2962, 2881, 2142, 1717, 1657, 1364 1067, 742, 698 cm⁻¹.

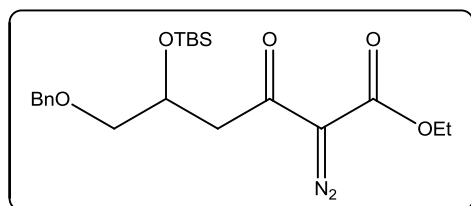
δ_{H} (300 MHz): 0.22 [3H, s, Si(CH₃)₂], 0.52 [3H, s, Si(CH₃)₂], 0.84 [9H, s, SiC(CH₃)₃], 3.02 (1H, dd, H_A of ABX, J = 15.5 and 7.1, C4-H), 3.10 (1H, dd, H_B of ABX, J = 15.5 and 7.1, C4-H), 3.36 (1H, dd, H_A of ABX, J = 9.6 and 5.8, H of CH₂OBn), 3.41 (1H, dd, H_B of ABX, J = 9.6 and 5.4, H of CH₂OBn), 3.75 (3H, s, OCH₃), 4.37 (1H, m, H_X of ABX, C5-H), 4.47 (2H, s, CH₂Ph), 7.27-7.36 (5H, m, ArH).

δ_{C} (75 MHz): -5.0 [Si(CH₃)₂], -4.6 [SiC(CH₃)₃], 18.0 [SiC(CH₃)₃], 25.8 (SiC(CH₃)₃), 45.0 (C4), 52.2 (OCH₃), 68.3 (C5), 73.3 (C6), 74.4 (OCH₂Ph), 127.5, 127.7, 128.3, (All ArC), 138.3 (ArC1), 161.7 (C1), 190.6 (C3), no signal observed for C=N₂.

M.S: m/z : 407 (M+H⁺, 100%), 385, 299, 143, 132, 105.

HRMS calculated for C₂₀H₃₁N₂O₅Si [M+H]⁺: 407.2002; found 407.1990.

Ethyl 6-(Benzyloxy)-5-*tert*-butyldimethylsilyloxy-2-diazo-3-oxohexanoate (42)



To a flame dried, 3-necked 100 mL round-bottom flask containing anhydrous scandium(III) triflate (33 mg, 0.067 mmol) and a stirring bar, fitted with two 100 mL addition funnels, anhydrous THF (5 mL) was added. To the resulting suspension, both

ethyl 3-*tert*-butyldimethylsilyloxy-2-diazobut-3-enoate (0.6 g, 2.2 mmol) in anhydrous THF (20 mL) and 2-benzyloxyacetaldehyde (0.25 g, 1.7 mmol) in anhydrous THF (20 mL) were added dropwise simultaneously *via* separate addition funnels. The reaction mixture was stirred at room temperature overnight. During this time, colour change from orange to pale yellow was observed and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2134 cm^{-1} was observed). Upon completion of the reaction, the solution was filtered through Celite®, the Celite® pad was washed with diethylether (50 mL) and concentrated under reduced pressure. Flash column chromatography of the residue, utilising 5% ethyl acetate in hexane as the eluent, yielded the product as a yellow oil.

Yield = 0.46 g, 65%.

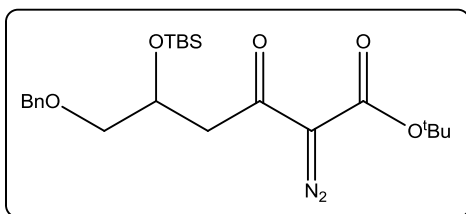
ν_{max} (NaCl): 2959, 2878, 2134, 1715, 1653, 1351, 1087 cm^{-1} .

δ_{H} (300 MHz): 0.22 [3H, s, Si(CH₃)₂], 0.48 [3H, s, Si(CH₃)₂], 0.81 [9H, s, SiC(CH₃)₃], 1.28 (3H, m, J = 7.1, OCH₂CH₃), 3.03 (1H, dd, H_A of ABX, J = 15.5 and 7.2, C4-H), 3.12 (1H, dd, H_B of ABX, J = 15.5 and 7.2, C4-H), 3.38 (1H, dd, H_A of ABX, J = 9.6 and 5.82, H of CH₂OBn), 3.46 (1H, dd, H_B of ABX, J = 9.6 and 5.4, H of CH₂OBn), 4.24 (2H, q, J = 7.12, OCH₂CH₃), 4.39 (1H, m, H_X of ABX, C5-H), 4.49 (2H, s, PhCH₂), 7.25-7.35 (5H, m, ArH).
 δ_{C} (75 MHz): -5.0 [Si(CH₃)₂], -4.6 [Si(CH₃)₂], 14.4 (OCH₂CH₃), 18.0 [SiC(CH₃)₃], 25.7 [SiC(CH₃)₃], 45.0 (C4), 61.4 (OCH₂CH₃), 68.4 (C5), 73.3 (C6), 74.5 (CH₂Ph), 127.5, 127.6, 128.3 (All ArC), 138.3 (ArC1), 161.3 (C1), 190.8 (C3), no signal observed for C=N₂.

M.S: m/z 421 (M+H)⁺ (100 %), 407, 353, 336, 289, 254, 222, 102.

HRMS calculated for C₂₁H₃₃N₂O₅Si [M+H]⁺: 421.2159; found 421.2151.

***tert*-Butyl 6-(Benzyloxy)-5-*tert*-butyldimethylsilyloxy-2-diazo-3-oxohexanoate (43)**



To a flame dried 100 mL 3-neck round-bottom flask containing anhydrous scandium(III) triflate (41 mg, 0.081 mmol) and a stirring bar, fitted with two 100 mL addition funnels, anhydrous THF (2 mL) was added. To this suspension, both *tert*-butyl 3-*tert*-butyldimethyl-silyloxy-2-diazobut-3-enoate (0.81 g, 2.7 mmol) in anhydrous THF (5 mL) and 2-benzyloxyacetaldehyde (0.41 g, 2.7 mmol) in anhydrous THF (5 mL) were added dropwise simultaneously *via* separate addition funnel. The reaction mixture was stirred at room temperature overnight. During this time, colour change from orange to pale yellow was observed and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2134 cm^{-1} was observed). After completion of the reaction, the solution was filtered through Celite®, the Celite® pad was washed with diethylether (20 mL) and concentrated under reduced pressure. Flash column chromatography, utilising 5% ethyl acetate in hexane as the eluent, yielded the product as a yellow oil.

Yield = 0.73 g, 60%.

ν_{max} (NaCl): 2953, 2856, 2134, 1724, 1656, 1312 1096 cm^{-1} .

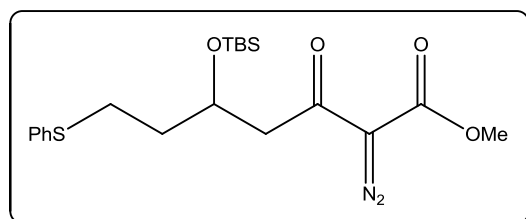
δ_{H} (300 MHz): 0.23 [3H, s, Si(CH₃)₂], 0.48 [3H, s, Si(CH₃)₂], 0.85 [9H, s, SiC(CH₃)₃], 1.53 [9H, s, C(CH₃)₃], 3.03 (1H, dd, H_A of ABX, J = 15.5 and 5.2, C4-H), 3.15 (1H, dd, H_B of ABX, J = 15.5 and 7.4, C4-H), 3.42 (1H, dd, H_A of ABX, J = 9.6 and 5.7, H of BnOCH₂), 3.50 (1H, dd, H_B of ABX, J = 9.4 and 5.5, H of BnOCH₂), 4.44 (1H, m, H_X of ABX, C5-H), 4.53 (2H, s, CH₂Ph), 7.29-7.36 (5H, m, ArH).

δ_{C} (75 MHz): -5.0 [Si(CH₃)₂], -4.5 [Si(CH₃)₂], 18.0 [SiC(CH₃)₃], 25.7 [SiC(CH₃)₃], 28.3 (C(CH₃)₃), 44.7 (C4), 68.4 (C-5), 73.2 (C6), 74.5 (CH₂Ph), 83.1 (C(CH₃)₃), 127.5, 127.9, 128.3 (All ArC), 138.3 (ArC1), 160.4 (C1), 191.2 (C3), no signal observed for C=N₂.

M.S: m/z : 449 (M+H)⁺ (100%), 414, 389, 366, 316, 375, 247, 143, 102.

HRMS calculated for C₂₃H₃₇N₂O₅Si [M+H]⁺: 449.2472; found 449.2455.

Methyl 7-(benzenesulphenyl)-5-tert-butyldimethylsilyloxy-2-diazo-3-oxohexanoate (44)



To a flame dried 25 mL round-bottom flask, anhydrous zinc(II) triflate (21 mg, 0.042 mmol) and DCM (10 mL) were added and the resulting suspension was cooled to 0 °C. 2-Benzenesulphenylpropanal (0.173 g, 1.06 mmol)

was added and the mixture was stirred for 5 min. Methyl 3-*tert*-butyldimethylsilyloxy-2-diazobut-3-enoate (0.36 g, 1.41 mmol) was added dropwise *via* addition funnel and stirred for 1 h at 0 °C before the mixture was allowed to stir at room temperature overnight. During this time, colour change from orange to pale yellow was observed and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2133 cm⁻¹ was observed). After completion of the reaction, the solution was filtered through Celite® and concentrated under reduced pressure. Flash column chromatography, utilising 5% ethyl acetate in hexane as the eluent, yielded the product as a yellow oil.

Yield = 0.191 g, 43%.

ν_{max} (NaCl): 2955, 2857, 2136, 1724, 1654, 1472, 1090, 837, 778, 738, 691 cm⁻¹.

δ_{H} (300 MHz): 0.07 [6H, s, Si(CH₃)₂], 0.83 [9H, s, SiC(CH₃)₃], 1.81-1.89 (2H, m, C6-H), 2.94 (1H, dd, H_A of ABX, *J* = 15.5 and 5.9, C4-H), 3.20 (1H, dd, H_B of ABX, *J* = 15.5 and 6.8, C4-H), 2.95 - 3.09 (2H, m, PhSCH₂), 3.84 (3H, s, OCH₃), 4.35 - 4.43 (1H, m, H_X of ABX, C5-H), 7.18 - 7.35 (5H, m, ArH).

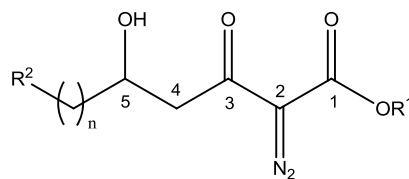
δ_{C} (75 MHz): -4.8 [Si(CH₃)₂], -2.9 [Si(CH₃)₂], 18.0 [SiC(CH₃)₃], 25.7 [SiC(CH₃)₃], 28.3 (C-6), 36.9 (C4), 47.0 (PhSCH₂), 52.3 (OCH₃), 67.9 (C5), 125.8, 128.8, 129.0, (All ArC), 136.4 (ArC1), 161.5 (C1), 190.4 (C3), no signal observed for C=N₂.

M.S: *m/z*: 423 (M+H⁺, 100%), 395, 339, 309, 291, 156.

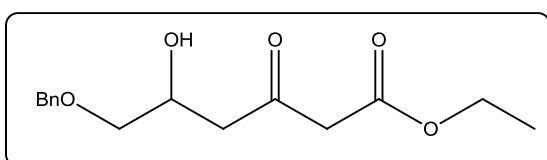
HRMS calculated for C₂₀H₃₁N₂O₄Si [M+H]⁺: 423.1774; found 423.1764.

3.2.6 Preparation of Aldol Addition Product

Numbering system of aldol addition products.



Ethyl 6-Benzyloxy-5-hydroxy-3-oxohexanoate (57)¹⁹



Ethyl acetoacetate (6.0 g, 46 mmol) in anhydrous THF (50 mL) was added dropwise to a stirred solution of LDA [generated by reacting diisopropylamine

(9.2 g, 92 mmol) with *n*-butyllithium (1.6 M in hexanes) (57.5 mL, 92 mmol at -40 °C)] in anhydrous THF (50 mL) at -40 °C under a nitrogen atmosphere. The resulting solution was stirred for 40 min at this temperature to ensure formation of the dianion and then cooled to -78 °C. A solution of 2-benzyloxyacetaldehyde (6.93 g, 46 mmol) in anhydrous THF (70 mL) was added dropwise. Upon complete addition, the mixture was stirred for a further 70 min at -78 °C and then quenched with saturated ammonium chloride solution (100 mL) at this temperature. After warming to room temperature, diethylether was added (100 mL) and the organic layer separated. The aqueous layer was extracted with diethylether (2 × 100 mL) and the combined organic extracts were washed with brine (100 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 5% ethyl acetate in hexane as the eluent, yielded the title compound as a bright yellow oil.

Yield = 2.70 g, 21%.

ν_{max} (NaCl): 3453, 2931, 1740, 1715, 1098, 741, 700 cm^{-1} .

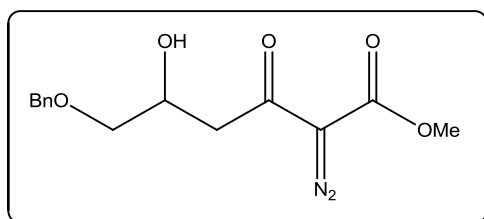
δ_{H} (300 MHz): 1.26 (3H, t, $J = 7.3$, OCH_2CH_3), 2.75 (2H, dd, $J = 7.1$ and 2.6 , C4-H_2), 3.00 (1H, bs, OH), 3.46 (2H, d, $J = 7.6$, BnOCH_2), 3.47 (2H, s, C2-H_2), 4.17 (2H, q, $J = 7.3$, OCH_2CH_3), 4.27 (1H, m, C5-H), 4.53 (2H, s, OCH_2Ph), 7.28-7.36 (5H, m, ArH).

δ_{C} (75 MHz): 14.5 (OCH_2CH_3), 46.7 (C4), 50.3 (C2), 61.9 (OCH_2CH_3), 67.1 (C5), 73.7 (C6), 73.8 (CH_2Ph), 128.2, 128.2, 128.9, (All ArC), 138.9 (ArC1), 167.4 (C1), 202.9 (C-3).

M.S: m/z 281 ($M+H^+$, 100 %), 252, 235, 171, 102.

HRMS calculated for $C_{15}H_{21}O_5$ [$M+H$] $^+$: 281.1380; found 281.1389.

6-Benzyloxy-2-diazo-5-hydroxy-3-oxohexanoic acid methyl ester (38)



Method 1. (Aqueous TFA) (Hydrolysis of methyl 6-(benzyloxy)-5-triethylsilyloxy-2-diazo-3-oxohexanoate)

To a stirred solution of methyl 6-(benzyloxy)-5-triethylsilyloxy-2-diazo-3-oxohexanoate (2 g, 4.91 mmol) in anhydrous THF (20 mL) at 0 °C, was added a solution of trifluoroacetic acid (5 mL) in water (5 mL). The reaction was stirred at 0 °C for 4 h and then neutralised to pH 7 with saturated aqueous Na_2CO_3 solution. Diethylether (30 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with diethylether (3 × 30 mL). The combined organic layers were dried and concentrated under reduced pressure. Flash column chromatography, utilising 30% ethyl acetate in hexane as the eluent, yielded the product as a viscous yellow oil.

Yield = 1.31 g, 91%.

Method 2. (Aqueous TFA) (Hydrolysis of methyl 6-benzyloxy-5-*tert*-butyldimethylsilyloxy-2-diazo-3-oxohexanoate)

To a stirred solution of methyl 6-(benzyloxy)-5-*tert*-butyldimethylsilyloxy-2-diazo-3-oxohexanoate (1.4 g, 3.43 mmol) in anhydrous THF (14 mL) at 0 °C, was added a solution of trifluoroacetic acid (3.5 mL) in water (3.5 mL). The reaction was stirred at 0 °C for 4 h and then neutralised to pH 7 with saturated aqueous Na_2CO_3 solution. Diethylether (25 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with diethylether (3 × 25 mL). The organic layers were combined, dried and concentrated under reduced pressure. Flash column chromatography, utilising 30% ethyl acetate in hexane as the eluent, yielded the product as a viscous yellow oil.

Yield = 0.84 g, 84%.

Method 3. (One-pot Synthesis from Methyl 3-Triethylsilyloxy-2-diazobut-3-enoate)

To a flame dried, 250 mL 3-necked round-bottom flask under a nitrogen atmosphere, containing a stirring bar and fitted with two 100 mL addition funnels, was added anhydrous zinc (II) triflate (800 mg, 1.60 mmol) and 25 mL of anhydrous DCM. To this mixture, both methyl 3-triethylsilyloxy-2-diazobut-3-enoate (9.0 g, 35.15 mmol) in DCM (50 mL) and 3-benzyloxypropanal (3.67 g, 24.40 mmol) in DCM (50 mL) were added dropwise simultaneously *via* separate addition funnels. The reaction mixture was then stirred at room temperature overnight. During this time, the colour change from orange to pale yellow was observed and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2134 cm^{-1} was observed) and ^1H NMR analysis. The DCM was removed under vacuum and the residue was then dissolved in THF (250 mL). The resulting solution was cooled to 0 °C. Trifluoroacetic acid (70 mL) in water (40 mL) was added and the reaction mixture was stirred at 0 °C for 4 h. The reaction pH was then adjusted to 7 with saturated Na_2CO_3 solution. Diethylether (500 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with diethylether (3 × 500 mL). The organic layers were combined, dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent, yielded the product as a viscous yellow oil.

Yield = 4.92 g, 69%.

Method 4. (Utilising PhBCl_2)

2-Diazo-3-oxobutyric acid methyl ester (1.00 g, 7 mmol) was added to doubly distilled DCM (100 mL) at -78 °C. Dichlorophenylborane (1.30 g, 8 mmol) was added neat to this solution under a nitrogen atmosphere. After the resulting solution was stirred for 15 min, triethylamine (1.78 g, 10 mmol) was then added and the resulting mixture was stirred at -78 °C for 3 h. 2-Benzyloxyacetaldehyde (1.54 g, 10 mmol) was added and the solution was stirred at -78 °C for a further 2 h. 1:1 Methanol : pH 7 buffer (0.1 M KH_2PO_4) (25 mL) was added and the solution was left warm to 0 °C. 1 : 1 Methanol : aqueous H_2O_2 (30% v/v) (15 mL) was then added and the mixture was stirred at 0 °C for 30 min before it was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with DCM (2 × 80 mL). The combined organic extracts were washed with saturated NaHCO_3 (2 × 80 mL) and 1M NaOH (2 × 80 mL), dried and concentrated under

reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent, yielded the title compound as a viscous yellow oil
Yield = 0.98 g, 49%.

Method 5. (Utilising MeAlCl₂)

2-Diazo-3-oxobutyric acid methyl ester (1 g, 7 mmol) was added to doubly distilled DCM (60 mL) at -78 °C under a nitrogen atmosphere. Triethylamine (1.06 g, 10.5 mmol) was added and the mixture was stirred. After 10 min, methyl aluminium dichloride (8.45 mL, 8.45 mmol) was added *via* glass syringe at -78 °C and the resulting solution was stirred for 4 h. 2-Benzyloxyacetaldehyde (1.26 g, 8.45 mmol) was added to the reaction mixture, which was neat and stirred at -78 °C for 6 h. 1 : 1 Methanol : pH 7 buffer (0.1 M KH₂PO₄) (15 mL) was added and the solution was left warm to 0 °C. 1 : 1 Methanol : aqueous H₂O₂ (30% v/v) (10 mL) was then added, the mixture was stirred at 0 °C for 30 min and allowed to warm to room temperature before separation of the layers. The aqueous layer was extracted with DCM (2 × 60 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (2 × 60 mL) and 1M NaOH (2 × 60 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent, yielded the title compound as a yellow oil
Yield = 0.42 g, 20%.

ν_{\max} (NaCl): 3482, 2864, 2139, 1721, 1650, 1315, 1116, 743, 700 cm⁻¹

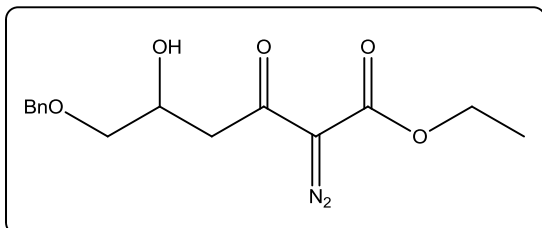
δ_{H} (300 MHz): 3.07 (1H, dd, H_A of ABX, J = 16.9 and 3.93, C-4H), 3.13 (1H, dd, H_B of ABX, J = 16.9 and 8.11, C-4H), 3.49 (1H, dd, H_A of ABX, J = 8.7 and 5.8, CH₂OBn), 3.54 (1H, dd, H_B of ABX, J = 8.7 and 2.9, CH₂OBn), 3.82 (3H, s, OCH₃), 4.29 - 4.36 (1H, m, H_X of ABX, C5-HOH), 4.56 (2H, s, OCH₂Ph), 7.25 - 7.37 (5H, m, ArH).

δ_{C} (75 MHz): 38.4 (C4), 43.9 (OCH₃), 67.7 (C5), 73.7 (BnOCH₂), 74.0 (PhCH₂), 128.0, 128.4, 128.9 (All ArC), 138.3 (ArC1), 162.0 (C1), 192.1 (C3), no signal observed for C=N₂.

M.S: m/z 293 (M+H⁺, 100%), 275, 184, 132.

HRMS calculated for C₁₄H₁₇N₂O₅ [M+H]⁺: 293.1137; found 293.1141.

6-Benzyloxy-2-diazo-5-hydroxy-3-oxohexanoic Acid Ethyl Ester (52)



Method 1. (Aqueous TFA) (Hydrolysis of ethyl 6-benzyloxy-5-*tert*-butyldimethylsilyloxy-2-diazo-3-hexanoate).

To a stirred solution of ethyl 6-benzyloxy-5-*tert*-butyldimethylsilyloxy-2-diazo-3-oxohexanoate (1.9 g, 4.52 mmol) in anhydrous THF (18 mL) at 0 °C, was added a solution of trifluoroacetic acid (4.5 mL) in water (4.5 mL). The reaction mixture was stirred at 0 °C for 4 h and then neutralised to pH 7 with saturated aqueous Na₂CO₃ solution. Diethylether (30 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with diethylether (3 × 30 mL). The organic layers were combined, dried and concentrated under reduced pressure. Flash column chromatography, utilising 30% ethyl acetate in hexane as the eluent, yielded the product as a viscous yellow oil.

Yield = 1.14 g, 83%.

Method 2. (TBAF:BF₃.OEt₂) (Hydrolysis of ethyl 6-benzyloxy-5-*tert*-butyldimethylsilyloxy-2-diazo-3-hexanoate).

TBAF (1M solution on THF, 3.89 mL, 3.89 mmol) was added to boron trifluoride diethyletherate (1.08 g, 7.6 mmol). The resulting solution was added to a stirring solution of ethyl 6-benzyloxy-5-*tert*-butyldimethylsilyloxy-2-diazo-3-hexanoate (0.4 g, 0.95 mmol) in anhydrous THF (8 mL). A separate addition of TBAF (1M solution on THF) (3.89 mL) was added after both 24 h and 48 h and the reaction mixture was stirred at room temperature for 72 h in total before it was diluted with water (20 mL) and diethylether (20 mL). The layers were then separated. The aqueous layer was extracted with diethylether (2 × 10 mL) and the combined organic layers were dried and concentrated under reduced pressure. Flash column chromatography, utilising 30% ethyl acetate in hexane as the eluent, isolated the desired product.

Yield = 0.152 g, 52 %.

Method 3. (Utilising MeAlCl₂)

2-Diazo-3-oxobutyric acid ethyl ester (2.00 g, 12.8 mmol) was added to doubly distilled DCM (200 mL) and the resulting solution was cooled to -78 °C before triethylamine (2.59 g, 25.6 mmol) was added and the mixture was stirred for 15 min. Methyl aluminium dichloride (19 mL, 19 mmol) was then added, and the reaction mixture was stirred for 4 h at -78 °C. 2-Benzyloxyacetaldehyde (2.30 g, 15.4 mmol) was added and the reaction was stirred at -78 °C for 3 h. 1 : 1 Methanol : pH 7 buffer (0.1 M KH₂PO₄) (40 mL) was added and the solution was left to warm to 0 °C. 1 : 1 Methanol : aqueous H₂O₂ (30% v/v) (20 mL) was added and the mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature and the layers were separated. The aqueous layer was extracted with DCM (2 × 80 mL). The combined organic extracts were then washed with saturated NaHCO₃ solution (2 × 80 mL), 1M NaOH (2 × 80 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent, yielded the title compound as a viscous yellow oil.

Yield = 0.824 g, 21%.

Method 4. (Utilising PhBCl₂)

2-Diazo-3-oxobutyric acid ethyl ester (1 g, 6 mmol) was added to doubly distilled DCM (100 mL) and the resulting solution was cooled to -78 °C. Dichlorophenylborane (1.19 g, 7 mmol) was then added neat. After 15 min, triethylamine (1.26 g, 12 mmol) was added and the resulting mixture stirred at -78 °C for 3 h. 2-Benzyloxyacetaldehyde (1.40 g, 9 mmol) was then added and the resulting mixture was stirred at -78 °C for 2 h. 1 : 1 Methanol : pH 7 buffer (0.1 M KH₂PO₄) (30 mL) was added and the mixture was left to warm to 0 °C. 1 : 1 Methanol : aqueous H₂O₂ (30% v/v) (15 mL) was added and left stir at 0 °C for 30 min and then allowed to warm to room temperature. The aqueous layer was extracted with DCM (2 × 80 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (2 × 40 mL), 1M NaOH (2 × 40 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent, yielded the title compound as a yellow oil.

Yield = 0.87 g, 45%.

Method 5. (Diazo transfer to ethyl 6-benzyloxy-5-hydroxy-3-oxohexanoate)

Solid anhydrous K_2CO_3 (0.98 g, 7.14 mmol) was added to a stirring solution of ethyl 6-benzyloxy-5-hydroxy-3-oxohexanoate (1 g, 3.57 mmol) in acetonitrile (10 mL). A solution of *p*-toluenesulphonyl azide (0.70 g, 3.57 mmol) in acetonitrile (10 mL) was added dropwise *via* addition funnel to the stirring solution of ester. The resulting solution was stirred for a further 6 h at room temperature. Diethylether (30 mL) was added to precipitate the inorganic salts, the mixture was then filtered through Celite® and the residue concentrated *in vacuo*. 2 : 1 Hexane-diethylether (50 mL) was added to the filtrate which was filtered through Celite®, dried and concentrated under reduced pressure. Flash column chromatography, using 10% ethyl acetate in hexane as the eluent, yielded the title compound as a yellow oil.

Yield = 0.21 g, 19%.

ν_{\max} (NaCl): 3474, 2866, 2137, 1716, 1651, 1302, 1111 cm^{-1} .

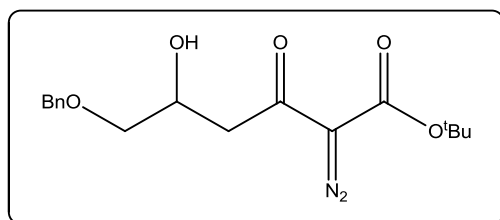
δ_H (300 MHz): 1.32 (3H, t, $J = 7.4$, OCH_2CH_3), 3.01 (1H, dd, H_A of ABX, $J = 16.9$ and 4.1, C-4H), 3.14 (1H, dd, H_B of ABX, $J = 16.9$ and 8.2, C-4H), 3.49 (1H, dd, H_A of ABX, $J = 8.8$ and 4.1, C-6H), 3.54 (1H, dd, H_B of ABX, $J = 8.8$ and 4.5, C-6H), 4.27 (2H, q, $J = 7.4$, OCH_2CH_3), 4.31-4.34 (1H, m, H_X of ABX, C-5HOH), 4.56 (2H, s, OCH_2Ph), 7.25-7.37 (5H, m, ArH).

δ_C (75 MHz): 14.7 (OCH_2CH_3) 44.0 (C4), 62.0 (OCH_2CH_3), 67.7 (C5), 73.7 (C6), 73.8 ($PhCH_2$), 127.9, 128.5, 128.8 (All ArC), 138.3 (ArC1), 161.6 (C1), 192.3 (C3), no signal observed for $C=N_2$.

M.S: m/z : 307 ($M+H^+$, 100%), 293, 279, 132.

HRMS calculated for $C_{15}H_{19}N_2O_5$ [$M+H$] $^+$: 307.1294; found 307.1283.

6-Benzyloxy-2-diazo-5-hydroxy-3-oxohexanoic acid *tert*-butyl ester (48)²⁰



Method 1. (Hydrolysis of *tert*-butyl-6-benzyloxy-5-*tert*-butyldimethylsilyloxy-2-diazo-3-oxohexanoate)

To a stirred solution of *tert*-butyl-6-benzyloxy-5-*tert*-butyldimethylsilyloxy-2-diazo-3-oxohexanoate (2.4 g, 5.35 mmol) in anhydrous THF (24 mL) at 0 °C, was added a solution of trifluoroacetic acid (6 mL) in water (6 mL). The reaction mixture was stirred at 0 °C for 4 h. The reaction was neutralised to pH 7 with saturated aqueous Na₂CO₃ solution. Diethylether (40 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with diethylether (3 x 40 mL). The organic layers were combined, dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent, yielded the product as a viscous yellow oil.

Yield = 1.41 g, 79%.

Method 2. (Utilising PhBCl₂)

2-Diazo-3-oxobutyric acid *tert*-butyl ester (3.52 g, 19 mmol) was added to doubly distilled DCM (280 mL) and the resulting solution was cooled to -78 °C. Dichlorophenylborane (3.62 g, 22 mmol) was then added neat. After 15 min, triethylamine (3.845 g, 38 mmol) was added and the mixture was stirred at -78 °C for 3 h. 2-Benzyloxyacetaldehyde (4.308 g, 28 mmol) was added and the reaction mixture was stirred at -78 °C for 2 h. 1:1 Methanol : pH 7 buffer (0.1 M KH₂PO₄) (100 mL) was added and the mixture was left warm to 0 °C. 1:1 Methanol : aqueous H₂O₂ (30% v/v) (30 mL) was added and the mixture was left stir to 0 °C for 30 min and then allowed to warm to room temperature before the layers were separated. The aqueous layer was extracted with DCM (2 x 80 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution (2 x 80 mL), 1M aqueous NaOH (2 x 80 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 5% ethyl acetate in hexane as the eluent, yielded the title compound as a yellow oil.

Yield = 4.17 g, 65%.

Method 3. (Utilising MeAlCl₂)

2-Diazo-3-oxobutyric acid *tert*-butyl ester (1.00 g, 5.43 mmol) was added to a solution of doubly distilled DCM (100 mL) and the resulting solution was cooled to -78 °C. Triethylamine (1.09 g, 10.5 mmol) was added and the mixture was stirred. After 10 min, methyl aluminium dichloride (6.52 mL, 6.52 mmol) was added *via* a glass syringe and the mixture was stirred for 4 h at -78 °C. 2-Benzyloxyacetaldehyde (1.22 g, 8.15 mmol) was added neat and the reaction mixture was stirred at -78 °C for 3 h. 1 : 1 Methanol : pH 7 buffer (0.1 M KH₂PO₄) (30 mL) was added and the mixture was allowed to warm to 0 °C. 1 : 1 Methanol : aqueous H₂O₂ (30% v/v) (20 mL) was added, the mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. The aqueous layer was extracted with DCM (2 × 40 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (2 × 40 mL), 1M NaOH (2 × 40 mL), dried and concentrated. Flash column chromatography, using 5% ethyl acetate in hexane as the eluent, yielded the title compound as a yellow oil.

Yield = 0.457 g, 23%.

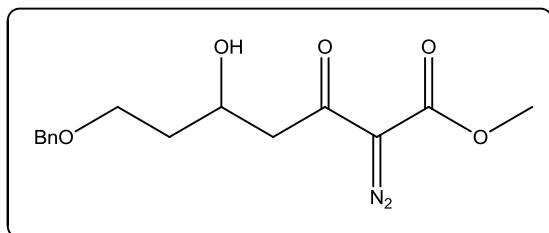
ν_{max} (NaCl): 3471, 2979, 2865, 2133, 171, 1650, 1314, 1136, 745, 668 cm⁻¹.

δ_{H} (300 MHz): 1.52 (9H, s, C(CH₃)₃), 3.04 (1H, dd, H_A of ABX, J = 6.3 and 3.8, C4-H), 3.09 (1H, dd, H_B of ABX, J = 6.6 and 3.8, C4-H), 3.52 (2H, dd H_A and H_B of ABX, J = 4.7 and 1.5, C-6H₂), 4.31 - 4.34 (1H, m, H_X of ABX, C-5HOH), 4.57 (2H, s, OCH₂Ph), 7.25 - 7.37 (5H, m, ArH).

δ_{C} (75 MHz): 28.3 [C(CH₃)₃], 43.5 (C4), 67.3 (C5), 73.4(C6), 73.5 (CH₂Ph), 83.9 [C(CH₃)₃], 127.0, 127.8, 128.4 (All ArC), 138.0 (ArC1), 160.4 (C1), 192.3 (C3), no signal observed for C=N₂.

M.S: m/z : 335 (M+H⁺), 279 [M+2H-[C(CH₃)₃]]⁺, (100%), 261, 132, 98.

7-Benzoyloxy-2-diazo-5-hydroxy-3-oxoheptanoic Acid Methyl Ester (50)



Method 1. (Hydrolysis of Methyl 6-Benzoyloxy-5-triethylsilyloxy-2-diazo-3-oxoheptanoate)

To a stirred solution of methyl 6-benzyloxy-5-triethylsilyloxy-2-diazo-3-oxoheptanoate (10 g, 23.64 mmol) in anhydrous THF (200 mL) at 0 °C, a solution of trifluoroacetic acid (50 mL) in water (50 mL) was added. The reaction mixture was stirred at 0 °C for 4 h. The pH was then adjusted to 7 with saturated Na₂CO₃ solution. Diethylether (300 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with diethylether (3 × 200 mL). The organic layers were combined, dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethylacetate in hexane, yielded the product as a viscous yellow oil.

Yield = 6.25 g, 87%.

Method 2. (One-pot Synthesis from Methyl 3-Triethylsilyloxy-2-diazobut-3-enoate)

To a flame dried, 50 mL 3-necked round-bottom flask under a nitrogen atmosphere, containing a stirring bar and fitted with two 100 mL addition funnels, was added anhydrous zinc (II) triflate (160 mg, 0.32 mmol) and 5 mL of anhydrous DCM. To this mixture, both methyl 3-triethylsilyloxy-2-diazobut-3-enoate (1.8 g, 7.03 mmol) in DCM (10 mL) and 3-benzyloxypropanal (0.8 g, 4.88 mmol) in DCM (10 mL) were added dropwise simultaneously *via* separate addition funnels. The reaction mixture was then stirred at room temperature overnight. During this time, the colour change from orange to pale yellow was observed and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2134 cm⁻¹ was observed) and ¹H NMR analysis. The DCM was removed under vacuum and the residue was then dissolved in THF (52 mL). The resulting solution was cooled to 0 °C. Trifluoroacetic acid (14 mL) in water (14 mL) was added and the reaction mixture was stirred at 0 °C for 4 h. The reaction pH was then adjusted to 7 with saturated Na₂CO₃ solution. Diethylether (150 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with diethylether (3 × 150 mL). The organic layers were combined, dried and concentrated

under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent, yielded the product as a viscous yellow oil.
Yield = 0.865 g, 58%.

Method 3. (Utilising MeAlCl₂)

2-Diazo-3-oxobutyric acid methyl ester (1 g, 7 mmol) was added to doubly distilled DCM (60 mL) and the resulting solution was cooled to -78 °C before triethylamine (1.06 g, 10.5 mmol) was added and the solution was stirred. After 10 min, methyl aluminium dichloride (8.45 mL, 8.45 mmol) was added *via* a glass syringe and stirred for 4 h at -78 °C. 3-Benzyloxypromanal (1.39 g, 8.45 mmol) was added and stirred at -78 °C for 6 h. 1 : 1 Methanol : pH 7 buffer (0.1 M KH₂PO₄) (15 mL) was added and the mixture was left warm to 0 °C. 1 : 1 Methanol : aqueous H₂O₂ (30% v/v) (10 mL) was added, the mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature before the layers were separated. The aqueous layer was washed with DCM (2 × 60 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (2 × 60 mL), 1M NaOH (2 × 60 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent, yielded the title compound as a yellow oil.

Yield = 0.344 g, 16%.

ν_{\max} (NaCl): 3459, 2931, 2872, 2136, 1724, 1653, 1316, 1108, 740, 698 cm⁻¹.

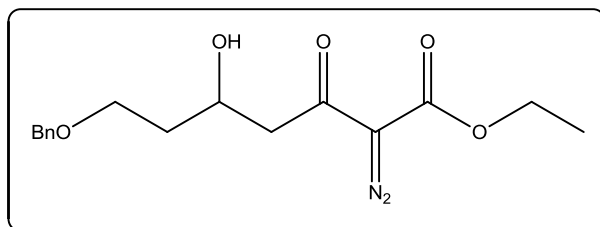
δ_{H} (300 MHz): 1.77 - 1.89 (2H, m, C6-H), 3.11 (2H, d, J = 6.0, C4-H₂), 3.60 - 3.71 (2H, m, BnOCH₂), 3.82 (3H, s, OCH₃), 4.32 (1H, q, J = 6.0, C5-HOH), 4.50 (2H, s, CH₂Ph), 7.23 – 7.37 (5H, m, ArH).

δ_{C} (75 MHz): 32.2 (C-6), 46.9 (C-4), 52.4 (OCH₃), 66.7 (C-5), 66.6 (C-7) 72.2 (CH₂Ph), 127.6, 127.7, 128.6, (All ArC), 138.2 (C-1 of aromatic) 161.6 (C-1), 192.2 (C-3), no signal observed for C=N₂.

M.S: m/z : 307 (M+H⁺, 100%), 279, 263.

HRMS calculated for C₁₅H₁₉N₂O₅ [M+H]⁺: 307.1294; found 307.1301.

7-Benzyloxy-2-diazo-5-hydroxy-3-oxoheptanoic Acid Ethyl Ester (51)



Method 1. (One-pot Synthesis from Ethyl 3-*tert*-Butyldimethylsilyloxy-2-diazobut-3-enoate)

To a flame dried, 50 mL 3-necked round-bottom flask under a nitrogen atmosphere containing a stirring bar and fitted with two 100 mL addition funnels, was added anhydrous zinc(II) triflate (7.7 mg, 0.015 mmol) and 2 mL of anhydrous DCM. To this, both ethyl 3-*tert*-butyldimethyl-silyloxy-2-diazobut-3-enoate (0.25 g, 0.97 mmol) in DCM (6 mL) and 3-benzyloxypropanal (0.12 g, 0.73 mmol) in DCM (6 mL) were added dropwise simultaneously *via* separate addition funnels. The reaction mixture was stirred at room temperature overnight. During this time, colour change from orange to pale yellow was observed and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2133 cm^{-1} was observed). The DCM was removed under vacuum and the residue was then dissolved in THF (12 mL). The solution was cooled to 0 °C and was diluted with THF (6 mL). Trifluoroacetic acid (3 mL) in water (3 mL) was added and the reaction was stirred at 0 °C for 4 h. The reaction pH was then adjusted to 7 with saturated Na_2CO_3 solution. Diethylether (120 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with diethylether (3 \times 20 mL). The organic layers were combined, dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent yielded, the product as a viscous yellow oil.

Yield = 0.142 g, 61%.

Method 2. (Utilising PhBCl_2)

2-Diazo-3-oxobutyric acid ethyl ester (2 g, 12.82 mmol) was added to doubly distilled DCM (120 mL) and the resulting solution was cooled to -78 °C. Dichlorophenylborane (2.44 g, 15.38 mmol) was then added. After 15 min, triethylamine (2.59 g, 25.64 mmol) was added and the solution was stirred at -78 °C for 3 h. 2-(benzyloxy)acetaldehyde (3.15 g, 19.23 mmol) was then added and the reaction mixture stirred at -78 °C for 2 h.

1 : 1 Methanol : pH 7 buffer (0.1 M KH_2PO_4) (30 mL) was added and the solution was allowed to warm to 0 °C. 1 : 1 Methanol : aqueous H_2O_2 (30% v/v) (15 mL) was then added and the mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. The aqueous layer was washed with DCM (2 × 80 mL). The combined organic extracts were washed with saturated NaHCO_3 solution (2 × 100 mL), 1M NaOH (2 × 100 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent yielded, the product as a viscous yellow oil.

Yield = 4.17 g, 65%.

Method 3. (One-pot synthesis from Ethyl 3-Triethylsilyloxy-2-diazobut-3-enoate)

To a flame dried, 50 mL 3-necked round-bottom flask under a nitrogen atmosphere containing a stirring bar and fitted with two 100 mL addition funnels, anhydrous zinc(II) triflate (57 mg, 0.12 mmol) in anhydrous DCM (5 mL) was added. To this mixture, both ethyl 3-triethylsilyloxy-2-diazobut-3-enoate (1.04 g, 3.84 mmol) in DCM (10 mL) and 3-benzyloxypropanal (0.47 g, 2.88 mmol) in DCM (10 mL) were added dropwise, simultaneously *via* separate addition funnels. The reaction mixture was stirred at room temperature overnight. During this time, colour change from orange to pale yellow was observed and reaction completion was confirmed using (a change in the diazo absorbance from 2105 to 2133 cm^{-1} was observed) and ^1H NMR analysis. The DCM was removed under vacuum and the residue was then dissolved in THF (40 mL). This solution was cooled to 0 °C. Trifluoroacetic acid (10 mL) in water (10 mL) was added and the reaction was stirred at 0 °C for 4 h. The reaction pH was adjusted to 7 with saturated Na_2CO_3 solution. Diethylether (120 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with diethylether (3 × 120 mL). The organic layers were combined, dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent yielded, the product as a viscous yellow oil.

Yield = 0.567 g, 53%.

ν_{max} (NaCl): 3449, 2933, 2859, 2139, 1719, 1646, 1322, 1075, 745, 691 cm^{-1} .

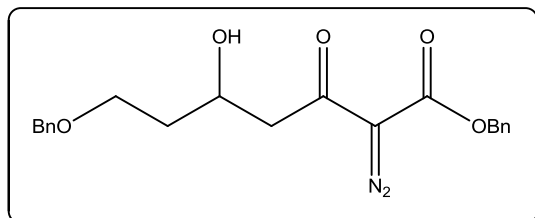
δ_{H} (300 MHz): 1.32 (3H, t, $J = 7.1$, OCH_2CH_3), 1.77 - 1.89 (2H, m, C6-H), 3.04 (2H, d, $J = 6.4$, C-4 H_2), 3.61 - 3.74 (2H, m, CH_2OBn), 4.28 (2H, q, $J = 7.1$, OCH_2CH_3), 4.42 - 4.53 (1H, m, C5-HOH), 4.51 (2H, s, OCH_2Ph), 7.25-7.36 (5H, m, ArH).

δ_C (75 MHz): 29.7 (**C6**), 35.8 (**C7**), 46.7 (**C4**), 52.4 (OCH₃), 66.7 (**C5**), 126.0, 128.5, 129.2 (All Ar**C**), 136.3 (Ar**C1**), 161.6 (**C1**), 192.2, (**C3**). No signal observed for C=N₂.

M.S: m/z 321 (M+H⁺, 100%), 293, 245.

HRMS calculated for C₁₆H₂₁N₂O₅ [M+H]⁺: 321.1450; found 321.1440.

7-Benzoyloxy-2-diazo-5-hydroxy-3-oxoheptanoic Acid Benzyl Ester (54)



2-Diazo-3-oxobutyric acid benzyl ester (1.3 g, 5.96 mmol) was added to doubly distilled DCM (100 mL) and the resulting solution was cooled to -78 °C. Dichlorophenylborane (1.14 g, 7.16 mmol) was added neat *via* a

glass syringe and the resulting reaction mixture was stirred for 15 min at -78 °C. Triethylamine (0.905 g, 8.94 mmol) was then added and the mixture was stirred at -78 °C for 4 h. 3-Benzoyloxypropanal (1.45 g, 8.94 mmol) was added and stirred at -78 °C for 3 h. 1 : 1 Methanol : pH 7 buffer (0.1 M KH₂PO₄) (20 mL) was added and the solution was allowed to warm to 0 °C. 1 : 1 Methanol : aqueous H₂O₂ (30% v/v) (14 mL) was then added and the mixture was stirred at 0 °C for 30 min and allowed to warm to room temperature. The aqueous layer was washed with DCM (2 × 60 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (2 × 60 mL), 1M NaOH (2 × 60 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as the eluent, yielded the title compound as a yellow oil.

Yield = 0.302 g, 11%.

ν_{\max} (NaCl): 3482, 2982, 2865, 2137, 1717, 1649, 1302, 1028, 743, 699 cm⁻¹.

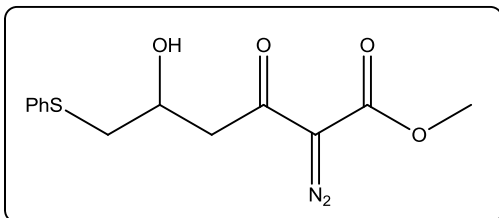
δ_H (300 MHz): 1.78 - 1.86 (2H, m, C6-H), 3.04 (2H, d, J = 6.0, C4-H₂), 3.60-3.71 (2H, m, 2 x CH₂OBn), 4.28 - 4.37 (1H, m, C5-HOH), 4.51 (2H, s, CH₂OCH₂Ph), 5.25 (2H, s, CO₂CH₂Ph), 7.27 - 7.38 (10H, m, ArH).

δ_C (75 MHz): 36.2 (**C6**) 46.9 (**C4**), 66.7 (**C5**), 67.1 (**C7**), 67.8 (CH₂OCH₂Ph), 73.2 (CO₂CH₂Ph), 126.9, 127.7, 128.4, 128.7, 128.8 (all ArCH), 135.0 (Ar**C1** of phenyl ring of benzyl ester), 138.2 (Ar**C1** of phenyl ring of benzyl ether), 161.1 (**C1**), 192.1 (**C3**).

M.S: m/z 383 (M+H⁺, 100%), 355, 258, 132, 97.

HRMS calculated for C₂₁H₂₃N₂O₅ [M+H]⁺: 383.1607; found 383.1592.

6-Benzenesulphenyl-2-diazo-5-hydroxy-3-oxohexanoic acid methyl ester (53)



2-Diazo-3-oxobutyric acid methyl ester (1.20 g, 8.45 mmol) was added to doubly distilled DCM (50 mL) and the resulting solution was cooled to -78 °C. Dichlorophenylborane (2.01 g, 12.68 mmol) was then added neat. After 15 min

triethylamine (1.71 g, 16.90 mmol) was added and the resulting mixture was stirred at -78 °C for 4 h. 2-Benzenesulphenylacetaldehyde (1.93 g, 12.68 mmol) was added and the mixture was stirred at -78 °C for 2 h. 1 : 1 Methanol : pH 7 buffer (0.1 M KH₂PO₄) (40 mL) was added and the mixture was allowed to warm to 0 °C. 1 : 1 Methanol : aqueous H₂O₂ (30% v/v) (20 mL) was then added and the mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and the layers were separated. The aqueous layer was washed with DCM (2 × 40 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (2 × 20 mL), 1M NaOH (2 × 20 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 20% ethyl acetate in hexane as the eluent, yielded the title compound as a yellow oil

Yield = 0.447 g, 18%.

ν_{max} (NaCl): 3482, 2954, 2139, 1719, 1648, 1438, 1312, 742 cm⁻¹.

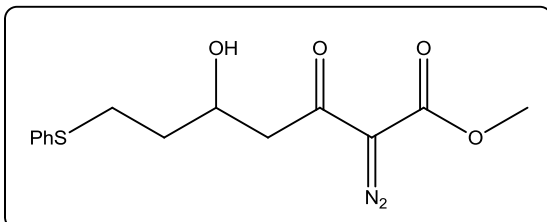
δ_{H} (300 MHz): 3.07 - 3.15 (3H, m, PhSCH₂ and H_A of ABX, C4-H), 3.21 (1H, dd, H_B of ABX, J = 13.5 and 3.8, C4-H), 3.83 (3H, s, OCH₃), 4.19 - 4.27 (1H, m, H_X of ABX, C5-HOH), 7.17 - 7.41 (5H, m, ArH).

δ_{C} (75 MHz): 40.3 (C4), 45.4 (C6) 52.4 (OCH₃), 66.8 (C5), 126.5, 128.9, 129.7, (All ArC), 135.4 (ArC1), 161.5 (C1), 191.7 (C3), no signal observed for C=N₂.

M.S: m/z : 295 (M+H⁺, 100%), 277, 267, 210, 171, 144.

HRMS calculated for C₁₃H₁₅N₂O₄S [M+H-N₂]⁺: 267.0691; found 267.0683.

7-Benzenesulphenyl-2-diazo-5-hydroxy-3-oxoheptanoic Acid Methyl Ester (55)



2-Diazo-3-oxobutyric acid methyl ester (1.50 g, 10.56 mmol) was added to doubly distilled DCM (60 mL) and the resulting solution was cooled to -78 °C. Dichlorophenylborane (2.52 g, 15.84

mmol) was then added. After 15 min, triethylamine (2.14 g, 21.13 mmol) was added and the resulting mixture was stirred at -78 °C for 3 h. 3-Benzenesulphenylpropanal (2.63 g, 15.85 mmol) was added and the mixture was stirred at -78 °C for 2 h. 1 : 1 Methanol : pH 7 buffer (0.1 M KH₂PO₄) (50 mL) was added and the solution was allowed to warm to 0 °C. 1 : 1 Methanol : aqueous H₂O₂ (30% v/v) (25 mL) was then added and the mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature and the layers separated. The aqueous layer was washed with DCM (2 × 50 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (2 × 40 mL), 1M NaOH (2 × 40 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 20% ethyl acetate in hexane as the eluent, yielded the title compound as a yellow oil.

Yield = 1.20 g, 37%.

ν_{max} (NaCl): 3504, 2953, 2138, 1720, 1647, 1437, 1313, 740 cm⁻¹.

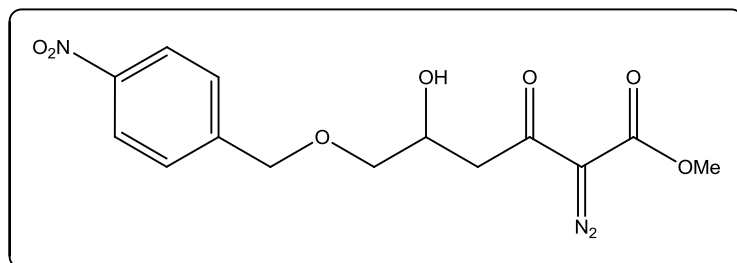
δ_{H} (300 MHz): 1.70 - 1.94 (2H, m, C6-H₂), 2.93 (1H, dd, H_A of ABX, J = 17.5 and 8.9 , C4-H), 3.00 - 3.18 (3H, m, PhSCH₂ and H_B of ABX C4-H), 3.82 (3H, s, OCH₃), 4.22 - 4.31 (1H, m, H_X of ABX, C5-HOH), 7.14 - 7.3 (5H, m, ArH).

δ_{C} (75 MHz): 29.7 (C6) 35.8 (C4), 46.7 (PhSCH₂), 52.4 (OCH₃), 66.7 (C5), 125.9, 128.5, 129.1 (ArCH), 161.6 (C1), 192.2 (C3), no signal observed for C=N₂.

M.S: m/z : 309 (M+H⁺, 100 %), 278, 202.

HRMS calculated for C₁₄H₁₇N₂O₄S [M+H]⁺: 309.0909; found 309.0912.

6-(4-Nitrobenzyloxy)-2-diazo-5-hydroxy-3-oxohexanoic Acid Methyl Ester (39)



To a flame dried, 250 mL 3-necked round-bottom flask containing a stirring bar and fitted with two 100 mL addition funnels, anhydrous scandium(III) triflate (211

mg, 0.42 mmol) and anhydrous THF (20 mL) was added. To this mixture, both methyl 3-*tert*-butyldimethylsilyloxy-2-diazobut-3-enoate (3.4 g, 12.8 mmol) in THF (80 mL) and 2-(4-nitrobenzyloxy)acetaldehyde (2.07 g, 10.56 mmol) in THF (80 mL) were added dropwise and simultaneously *via* separate addition funnels. The reaction mixture was stirred at room temperature overnight. During this time, colour change from orange to

pale yellow was observed and reaction completion was confirmed using IR (a change in the diazo absorbance from 2105 to 2133 cm^{-1} was observed). After the reaction was complete, the solution was filtered through Celite®, which was then washed with diethylether (200 mL) and the combined filtrate was concentrated under reduced pressure. Flash column chromatography of the residue, using 40% ethylacetate in hexane as eluent, isolated the product as a yellow oil.

Yield = 0.333 g, 7%.

ν_{max} (NaCl): 3519, 2907, 2154, 1718, 1641, 1521, 1346 1107, 860, 737 cm^{-1} .

δ_{H} (300 MHz): 3.15 (2H, dd, $J = 4.3$ and 1.5 , C4-**H**₂), 3.59 (2H, dd, $J = 5.1$ and 2.8 , ArCH₂OCH₂), 3.85 (3H, s, OCH₃), 4.33-4.41 (1H, m, C5-HOH), 4.68 (2H, s, ArCH₂), 7.52 (2H, d, $J = 8.7$, ArC2-**H** and ArC6-**H**), 8.21 (2H, d, $J = 8.7$, ArC3-**H** and ArC5-**H**).

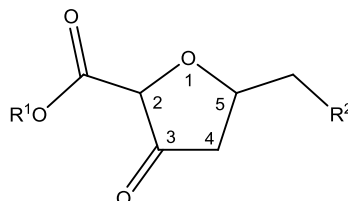
δ_{C} (75 MHz): 43.4 (**C**4), 52.4 (OCH₃), 67.3 (**C**5), 72.1 (OCH₂Ar), 74.0 (**C**6), 123.8 (Ar**C**2 and Ar**C**6), 127.7 (Ar**C**3 and Ar**C**5), 145.7 (Ar**C**CH₂O), 147.4 (Ar**C**4), 161.6 (**C**1), 191.8 (**C**3), no signal observed for **C** = N₂.

M.S: m/z : 338 (M+H⁺, 100%), 317.

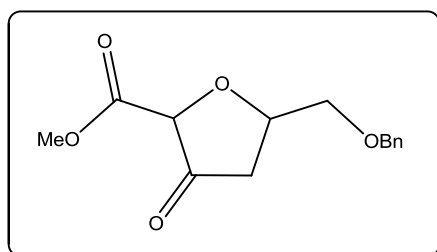
HRMS calculated for C₁₄H₁₅N₃O₇ [M+H]⁺: 338.0988; found 338.0982.

3.2.7 Rh(II) Mediated cyclisations

Numbering system of 3(2*H*)-furanones.



(±)-5-Benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic Acid Methyl Ester (58)



Method 1. (Benzene-DCM)

To a flame dried, 2-necked 100 mL round bottom flask, fitted with a dry condenser and dry dropping funnel, benzene (50 mL) was added and refluxed for 3 h under a nitrogen atmosphere to deoxygenate the system. Rh₂(OAc)₄ (~5 mg) was added and the suspension was refluxed for a further 30 min. A solution of 6-benzyloxy-2-diazo-5-hydroxy-3-oxohexanoic acid methyl ester (0.30 g, 1.03 mmol) in doubly distilled DCM (30 mL) was added dropwise (at a rate of 1 drop per sec) to the suspension. The reaction was monitored by IR (disappearance of 2133 cm⁻¹ peak indicates diazo functionality is no longer present). Upon reaction completion, the solution was allowed to cool to room temperature, filtered through Celite® and concentrated under reduced pressure to yield a yellow oil as a mixture of diastereoisomers (ratio 2:1) which was used without purification.

Yield = 0.24 g, 89%.

Method 2. (1,2-Dichloroethane)

To a flame dried, 250 mL 2-necked round bottom flask, fitted with a dry condenser and dry dropping funnel, 1,2-dichloroethane (30 mL) was added and allowed to reflux for 3 h

under a nitrogen atmosphere, to deoxygenate the system. $\text{Rh}_2(\text{OAc})_4$ (~5 mg) was added and the suspension was refluxed for a further 30 min. A solution of 6-benzyloxy-2-diazo-5-hydroxy-3-oxohexanoic acid methyl ester (1.00 g, 3.42 mmol) in doubly distilled DCM (100 mL) was added (at a rate of 1 drop per sec) to the suspension. The reaction was monitored by IR (disappearance of 2133 cm^{-1} peak indicates diazo functionality is no longer present). Upon reaction completion, the solution was allowed to cool to room temperature, filtered through Celite® and concentrated under reduced pressure to yield a yellow oil as a mixture of diastereoisomers (ratio 1.8:1) which was used without purification.

Yield = 0.78 g, 86%.

ν_{max} (NaCl): 2979, 2867, 1769, 1743, 1454, 1147, 1099 cm^{-1} .

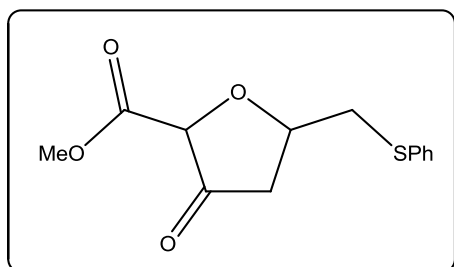
δ_{H} (300 MHz): 2.52 - 2.72 (4H, m, C4-H₂, both diastereoisomers), 3.59 (1H, dd, H_A of ABX, $J = 10.7$ and 3.1 , BnOCH, major diastereoisomer), 3.71 (3H, s, OCH₃, minor diastereoisomer), 3.80 (3H, s, OCH₃, major diastereoisomer), 3.72 - 3.85 (3H, m, BnOCH₂, minor diastereoisomer, and H_B of ABX, BnOCH, major diastereoisomer), 4.50 - 4.64 (4H, m, C2-H, C5-H, OCH₂Ph, both diastereoisomers), 7.25-7.37 (10H, m, ArH, both diastereoisomers).

δ_{C} (75 MHz): 38.4 (C-4, major diastereoisomer), 39.0 (C-4, minor diastereoisomer), 53.2 (OCH₃, minor diastereoisomer), 53.3 (OCH₃, major diastereoisomer), 72.2 (BnOCH₂, major diastereoisomer), 72.3 (BnOCH₂, minor diastereoisomer), 73.8 (CH₂Ph, minor diastereoisomer), 74.0 (CH₂Ph, major diastereoisomer), 76.7 (C5, minor diastereoisomer), 76.8 (C-5, major diastereoisomer), 80.1 (C2, minor diastereoisomer), 80.3 (C2, major diastereoisomer), 127.6, 127.7, 128.9 (All ArC), 138.0 (ArC1), 167.3 (OC=O both diastereoisomers), 207.5 (C3, both diastereoisomers).

m/z 265 ($\text{M}+\text{H}^+$, 100%), 247, 175, 132, 91.

HRMS calculated for $\text{C}_{14}\text{H}_{17}\text{O}_5$ [$\text{M}+\text{H}$]⁺: 265.1076; found 265.1064.

(±)-5-Phenylthiomethyl-3-Oxotetrahydrofuran-2-Carboxylic Acid Methyl Ester (59)



To a flame dried, 2-necked 100 mL round bottomed flask fitted with a dry condenser and dry dropping funnel, 1,2-dichloroethane (10 mL) was added and refluxed for 2 h under a nitrogen atmosphere to deoxygenate the system. $\text{Rh}_2(\text{OAc})_4$ (~5 mg) was added and the suspension was refluxed for a further 30 min. A solution of 6-phenylthio-2-diazo-5-hydroxy-3-oxohexanoic acid methyl ester (0.50 g, 1.7 mmol) in 1,2-dichloroethane (40 mL) was added dropwise to the suspension. The reaction was monitored by I.R (disappearance of 2134 cm^{-1} peak indicates diazo functionality is no longer present). Upon reaction completion, the solution was allowed to cool to room temperature and filtered through Celite® and the filtrate was concentrated under reduced pressure to yield a yellow oil as a mixture of diastereoisomers (ratio 1.3 : 1) which was used without purification.

Yield = 0.33 g, 74%.

ν_{max} (NaCl): 2982, 2883, 1767, 1741, 1451, 1145, 1097 cm^{-1} .

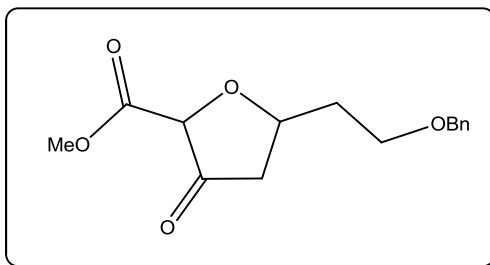
δ_{H} (300 MHz): 2.45-2.52 (2H, m Hz, C4-H, both diastereoisomers), 2.71 (2H, 2 × overlapping dd, H_A of ABX, $J = 12.6$, and 6.7 , C4-H, both diastereoisomers), 3.12 - 3.52 (4H, m, CH_2SPh , both diastereoisomers), 3.78 (3H, s, OCH_3 , minor diastereoisomer), 3.80 (3H, s, OCH_3 , major diastereoisomer), 4.15-4.32 (4H, m, C2-H, C5-H, both diastereoisomers), 7.20-7.43 (10H, m, ArH, both diastereoisomers).

δ_{C} (75 MHz): 38.9 (C-4, minor diastereoisomer), 39.1 (C-4, major diastereoisomer), 40.9 (PhSCH_2 , major diastereoisomer), 41.3 (PhSCH_2 , minor diastereoisomer), 52.9 (OCH_3 , minor diastereoisomer), 53.0 (OCH_3 , major diastereoisomer), 76.2 (C5, minor diastereoisomer), 76.7 (C5, major diastereoisomer), 80.0 (C2, major diastereoisomer), 80.4 (C2, minor diastereoisomer), 127.0 (ArC4), 129.2 (ArC3 and ArC5), 130.2 (ArC2 and ArC6), 134.8 (ArC1, minor diastereoisomer), 135.1 (ArC1, major diastereoisomer), 166.2 (OC=O , minor diastereoisomer), 166.7 (OC=O , major diastereoisomer), 206.2 (C3, minor diastereoisomer), 206.6 (C-3, major diastereoisomer).

M.S: m/z : 267 ($M+1$, 100 %), 171, 137.

HRMS calculated for $\text{C}_{13}\text{H}_{15}\text{O}_4\text{S}$ [$M+H$] $^+$: 267.0696; found 267.0691.

(±)-5-Benzyloxyethyl-3-oxotetrahydrofuran-2-carboxylic Acid Methyl Ester (60)



To a flame dried, 500 mL 2-necked round bottomed flask, fitted with a condenser and dropping funnel, benzene (100 mL) was added and refluxed for 3 h under a nitrogen atmosphere to deoxygenate the system. $\text{Rh}_2(\text{OAc})_4$ (~5 mg) was added and the suspension was refluxed for a further 30 min. A solution of 6-benzyloxy-2-diazo-5-hydroxy-3-oxoheptanoic acid methyl ester (1.6 g, 5.22 mmol) in doubly distilled DCM (200 mL) was added (at a rate of 1 drop per sec) to the suspension. The reaction was monitored by IR (disappearance of 2133 cm^{-1} indicates the diazo functionality was no longer present). Upon reaction completion, the solution was allowed to come to room temperature and filtered through Celite® and the filtrate concentrated under reduced pressure to yield a yellow oil as a mixture of diastereoisomers (ratio 1.22 : 1) which was used without purification.

ν_{max} (NaCl): 2926, 1765, 1740, 1452, 1186, 716 cm^{-1} .

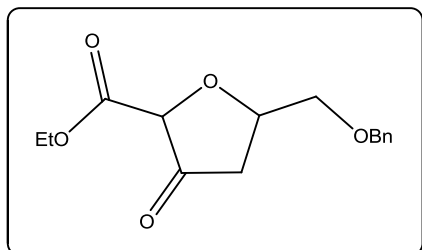
Yield = 1.21 g, 83%.

δ_{H} (300 MHz): 1.92 - 2.26 (4H, m, $\text{CH}_2\text{CH}_2\text{OBn}$, both diastereoisomers), 2.37 (1H, ddd, $J = 18.3, 8.8$ and 1.00 , C4-H, minor diastereoisomer), 2.39 (1H, dd, $J = 18.1$ and 8.7 , C4-H, major diastereoisomer), 2.66 (1H, dd, $J = 18.3$ and 6.4 , C4-H, minor diastereoisomer), 2.67 (1H, dd, $J = 18.1$ and 6.2 , C4-H, major diastereoisomer), 3.63 - 3.72 (2H, m, $\text{CH}_2\text{CH}_2\text{OBn}$, both diastereoisomers), 3.78 (3H, s, OCH_3 , minor diastereoisomer), 3.79 (3H, s, OCH_3 , major diastereoisomer), 4.43 (1H, s, C2-H, minor diastereoisomer), 4.46 - 4.53 (1H, m, C5-H, major diastereoisomer), 4.50 (2H, s, CH_2Ph , major diastereoisomer), 4.51 (2H, s, CH_2Ph , minor diastereoisomer), 4.73 - 4.83 (1H, m, C5-H, minor diastereoisomer), 7.25 - 7.35 (10H, m, ArH)

δ_{C} (75 MHz): 35.7 ($\text{CH}_2\text{CH}_2\text{OBn}$, both diastereoisomers), 42.3 (C4, both diastereoisomers), 52.8 (OCH_3 , both diastereoisomers), 66.29 (CH_2Ph , major diastereoisomer), 73.1 (CH_2Ph , minor diastereoisomer), 74.8 (C5, major diastereoisomer), 76.0 (C5, minor diastereoisomer), 79.7 (C2, minor diastereoisomer), 80.3 (C2, major diastereoisomer), 127.6, 128.3, 128.4 (All ArC, both diastereoisomers), 138.2 (ArC1), 166.3 ($\text{OC}=\text{O}$, major diastereoisomer), 167.0 ($\text{OC}=\text{O}$, minor diastereoisomer), 207.5 (C3, major diastereoisomer), 208.0 (C3, minor diastereoisomer).
M.S: m/z : 279 ($\text{M}+\text{H}^+$, 100%), 225, 189, 132, 91.

HRMS calculated for $C_{15}H_{19}O_5$ $[M+H]^+$: 279.1232; found 279.1233.

(±)-5-Benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic Acid Ethyl Ester (61)



To a flame dried, 250 mL 2-necked round bottom flask fitted with a condenser and dropping funnel, benzene (80 mL) was added and refluxed for 3 h to deoxygenate the system. $Rh_2(OAc)_4$ (~5 mg) was added and the suspension refluxed for a further 30 min. A solution of 6-benzyloxy-2-diazo-5-hydroxy-3-

oxohexanoic acid ethyl ester (0.3 g, 0.966 mmol) in doubly distilled DCM (30 mL) was added dropwise (at a rate of 1 drop per sec) to the suspension. After 20 min, the solution was allowed to come to room temperature and filtered through Celite® and the filtrate was concentrated under reduced pressure to yield a yellow oil consisting of a pair of diastereoisomers whose ratio could not be determined due to extensive overlapping of signals. The product was used without further purification.

Yield = 0.250 g, 92%.

ν_{max} (NaCl): 2924, 2865, 1763, 1744, 1453, 1106, 740, 700 cm^{-1} .

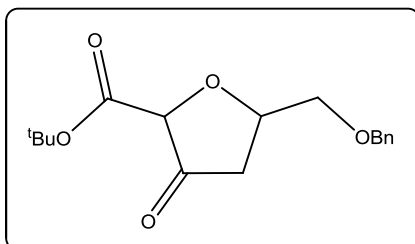
δ_H (300 MHz): 1.24 - 1.36 (6H, m, OCH_2CH_3 both diastereoisomers), 2.60 - 2.65 (4H, m, C4- H_2 both diastereoisomers), 3.46 - 3.52 (4H, m, CH_2OBn , both diastereoisomers), 4.27 (4H, q, J = 7.26, OCH_2CH_3 , both diastereoisomers), 4.52 - 4.63 (8H, m, C2- H , C5- H , OCH_2Ph , both diastereoisomers), 7.25 - 7.37 (10H, m, Ar H , both diastereoisomers)

δ_C (75 MHz): 14.5 (OCH_2CH_3 , minor diastereoisomer), 14.6 (OCH_2CH_3 , major diastereoisomer), 38.4 (C4, major diastereoisomer), 39.2 (C4, minor diastereoisomer), 62.5 (OCH_2CH_3 , minor diastereoisomer), 62.5 (OCH_2CH_3 , major diastereoisomer), 72.2 ($BnOCH_2$, major diastereoisomer), 72.2 ($BnOCH_2$, minor diastereoisomer), 73.87 ($PhCH_2$, minor diastereoisomer), 73.9 ($PhCH_2$, major diastereoisomer), 76.6 (C5, minor diastereoisomer), 76.7 (C5, major diastereoisomer), 80.3 (C2, minor diastereoisomer), 80.4 (C2, major diastereoisomer), 128.0, 128.6, 128.9 (All ArC, both diastereoisomers), 165.7 (OC=O, minor diastereoisomer), 166.5 (OC=O, major diastereoisomer), 206.5 (C3, minor diastereoisomer), 207.2 (C3, major diastereoisomer).

M.S: m/z : 279 ($M+H^+$, 100%), 265, 230, 189, 132, 91.

HRMS calculated for $C_{15}H_{19}O_5$ $[M+H]^+$: 279.1232; found 279.1230.

(±)-5-Benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic Acid *tert*-Butyl Ester (62)²⁰



To a flame dried, 500 mL 2-necked round bottom flask fitted with a condenser and dropping funnel, benzene (70 mL) was added and the suspension was refluxed for 3 h under a nitrogen atmosphere to deoxygenate the system. $\text{Rh}_2(\text{OAc})_4$ (~5 mg) was added and refluxed for a further 30 min. A solution of 6-

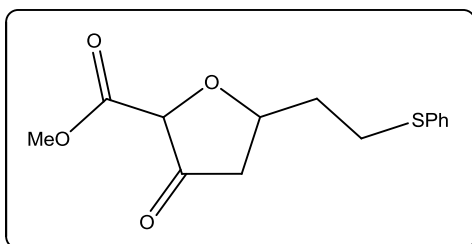
benzyloxy-2-diazo-5-hydroxy-3-oxohexanoic acid *tert*-butyl ester (4.17 g, 12.5 mmol) in doubly distilled DCM (200 mL) was added dropwise (at a rate of 1 drop per sec) to the suspension. After 40 min, the solution was allowed to warm to room temperature and filtered through Celite® and the filtrate concentrated under reduced pressure to yield a yellow oil in a 3 : 2 ratio of diastereoisomers, which was used without purification.

Yield = 3.602 g, 93%.

ν_{max} (NaCl): 2979, 2867, 1769, 1738, 1454, 1141, 1105, 739, 699 cm^{-1} .

δ_{H} (300 MHz): 1.46 [9H, s, $\text{C}(\text{CH}_3)_3$, major diastereoisomer], 1.48 [9H, s, $\text{C}(\text{CH}_3)_3$ minor diastereoisomer], 2.55 - 2.61 (2H, m, C-4H, both diastereoisomers), 3.56 - 3.80 (4H, m, BnOCH_2 , both diastereoisomers), 4.52-4.80 (8H, m, C-2H, C-5H, OCH_2Ph , both diastereoisomers), 7.25 - 7.37 (10H, m, ArH).

(±)-5-Benzenesulfenylethyl-3-oxotetrahydrofuran-2-carboxylic Acid Methyl Ester (63)



To a flame dried, 100 mL 3-necked round bottom flask fitted with a condenser and dropping funnel, benzene (10 mL) was added and refluxed for 3 h under a nitrogen atmosphere to deoxygenate the system. $\text{Rh}_2(\text{OAc})_4$ (catalytic amount) (~5 mg) was added and the resulting suspension was

refluxed for a further 30 min. A solution of 7-benzenesulfenyl-2-diazo-5-hydroxy-3-oxoheptanoic acid methyl ester (0.55 g, 1.76 mmol) in doubly distilled DCM (40 mL) was added to the suspension. The reaction was monitored by IR (disappearance of 2133 cm^{-1} indicates the diazo functionality was no longer present). The reaction was deemed

complete when the diazo peak was no longer evident. Upon reaction completion, the solution was allowed to cool to room temperature, filtered through Celite® and the filtrate concentrated under reduced pressure to yield a yellow oil in a 1.1 : 1 ratio of diastereoisomers which was used without purification.

Yield = 0.415 g, 83%.

ν_{max} (NaCl): 2952, 1770, 1746, 1438, 1147, 741, 692 cm^{-1} .

δ_{H} (300 MHz): 1.93 - 2.34 (5H, m, $\text{CH}_2\text{CH}_2\text{SPh}$, both diastereoisomers and C4-**H**, one diastereoisomer), 2.63 (1H, dd, $J = 18.2$ and 6.1 , C4-**H**, one diastereoisomer), 2.64 (1H, dd, $J = 18.2$ and 6.3 , C4-**H**, one diastereoisomer), 2.98 - 3.22 (4H, m, $\text{CH}_2\text{CH}_2\text{SPh}$, both diastereoisomers), 3.77 (3H, s, OCH_3 , one diastereoisomer), 3.78 (3H, s, OCH_3 , one diastereoisomer), 4.43 (1H, s, C2-**H**, one diastereoisomer), 4.45 - 4.53, (1H, m, C5-**H**, one diastereoisomer), 4.56 (1H, s, C2-**H**, one diastereoisomer), 4.71 - 4.80, (1H, m, C5-**H**, one diastereoisomer), 7.17 - 7.37 (10H, m, Ar**H**, both diastereoisomers).

δ_{C} (75 MHz): 29.4 ($\text{CH}_2\text{CH}_2\text{SPh}$, one diastereoisomer), 29.5 ($\text{CH}_2\text{CH}_2\text{SPh}$, one diastereoisomer), 35.0 ($\text{CH}_2\text{CH}_2\text{SPh}$, one diastereoisomer), 35.2 ($\text{CH}_2\text{CH}_2\text{SPh}$, one diastereoisomer), 41.9 (**C**4, both diastereoisomers), 52.9 (OCH_3), 75.5 (**C**5, one diastereoisomer), 76.7 (**C**5, one diastereoisomer), 79.7 (**C**2, one diastereoisomer), 80.2 (**C**2, one diastereoisomer), 126.3 (**C**4 of phenyl ring, both diastereoisomers), 128.4, 129.5 (All Ar**C**, both diastereoisomers), 135.8 (Ar**C**1, both diastereoisomers), 166.2 ($\text{OC}=\text{O}$, one diastereoisomer), 166.9 ($\text{OC}=\text{O}$, one diastereoisomer), 207.0 (**C**3, one diastereoisomer), 207.4 (**C**3, one diastereoisomer).

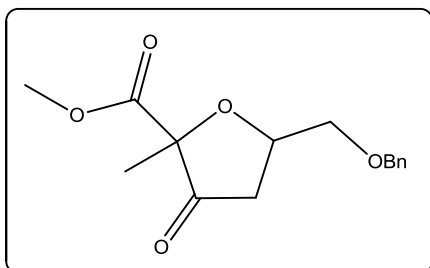
M.S: m/z 281 ($\text{M}+\text{H}^+$), 225, 157, 111, 81, 75.

HRMS calculated for $\text{C}_{14}\text{H}_{17}\text{O}_4\text{S}$ [$\text{M}+\text{H}$] $^+$: 281.0848; found 281.0835.

3.2.8 Methylation Reactions at the 2-Position of 4,5-Dihydro-3(2H)-furanone

(±)-5-Benzyloxymethyl-2-methyl-3-oxotetrahydrofuran-2-carboxylic Acid Methyl Ester (65)

Utilising DBU as a base



DCM (5 mL) in a flame dried 25 mL, round bottom flask was charged with (±)-5 benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid methyl ester (0.2 g, 0.76 mmol) under a nitrogen atmosphere. The solution was cooled to 0 °C. DBU (0.17 g, 1.14 mmol) was added dropwise *via* glass syringe and the mixture was stirred for 5 min, which resulted in a deep red solution. Iodomethane (0.42 g, 3.03 mmol) was then added to the solution and the reaction was sealed with a stopper and stirred overnight. The reaction was then diluted with DCM (20 mL) and washed with 10% w/v HCl (2 × 20 mL), dried and concentrated under reduced pressure. Flash column chromatography of the residue, using 10 - 30% ethyl acetate in hexane as the eluent, separated both diastereoisomers as clear oils.

Yield: (Minor diastereoisomer, less polar fraction, C2-CH₃ is *syn* to C5-H) = 0.029g, 14%.
Yield: (Major diastereoisomer, more polar fraction, C2-CH₃ is *anti* to C5-H) = 0.053g, 25%.

Utilising TMG as a base

A flame dried round bottom flask was charged with DCM (5 mL) and was cooled to 0 °C. (±)-5-Benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid methyl ester (0.2 g, 0.76 mmol) was added to the round bottom flask under a nitrogen atmosphere. TMG (0.13 g, 1.14 mmol) was then added dropwise *via* a glass syringe and the solution was stirred for 10 min. Iodomethane (0.42 g, 3.03 mmol) was added to the red solution and the reaction was sealed with a stopper and allowed to stir overnight. The reaction was then diluted with DCM (20 mL) and washed with 10% w/v HCl (2 × 20 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 10 - 30% ethyl acetate in hexane as the eluent, separated both diastereoisomers as clear oils.

Yield: (Minor diastereoisomer, less polar fraction, C2-CH₃ is *syn* to C5-H) = 0.026g, 12%.
Yield: (Major diastereoisomer, more polar fraction, C2-CH₃ is *anti* to C5-H) = 0.048g, 23%.

Utilising KH as a base

A flame dried round bottom flask containing anhydrous THF (8 mL) was cooled to -20 °C under a nitrogen atmosphere. 18-Crown-6 (0.22 g, 0.83 mmol) was then added. Potassium hydride (0.033 g, 0.833 mmol) was added and the resulting suspension was stirred for 10 min. (±)-5-Benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid methyl ester (0.2 g, 0.76 mmol) was then added to the round bottom flask. Iodomethane (0.14 g, 1.51 mmol) was added to the red solution and the reaction was sealed with a stopper and stirred at -20 °C for 12 h. Water (10 mL), followed by diethylether (10 mL) was added and the layers were separated. The aqueous layer was extracted with diethylether (3 × 10 mL). The organic layers were combined, dried and concentrated under reduced pressure. Flash column chromatography, using 10 - 30% ethyl acetate in hexane as the eluent separated, both diastereoisomers as clear oils.

Yield: (Minor diastereoisomer, less polar fraction, C2-CH₃ is *syn* to C5-H) = 0.020 g, 8%.

Yield: (Major diastereoisomer, more polar fraction, C2-CH₃ is *anti* to C5-H) = 0.034 g, 16%.

ν_{max} NaCl: 2952, 2862, 1769, 1742, 1452, 1269, 1120, 739, 698 cm⁻¹.

Minor Diastereoisomer, δ_{H} (600 MHz): 1.49 (3H, s, C2-CH₃), 2.67 (1H, d, J = 2.3, H_A of ABX, C4-H *syn* to C5-H), 2.68 (1H, d, J = 2.3, H_B of ABX, C4-H *anti* to C5-H), 3.63 (3H, s, OCH₃), 3.69 (1H, dd, J = 10.5 and 4.5, H_A of ABX, BnOCH₂), 3.74 (1H, dd, J = 10.5 and 3.6, H_B of ABX, BnOCH₂), 4.54 - 4.58 (1H, m, H_X of ABX, C5-H), 4.55 (1H, d, J = 12.4, H_A of AB, PhCH₂), 4.60 (1H, d, J = 12.4, H_B of AB, PhCH₂), 7.26 - 7.38 (5H, m, ArH).

δ_{C} (150 MHz): 20.7 (C2-CH₃), 38.1 (C4), 52.8 (OCH₃), 72.1 (BnOCH₂), 73.4 (PhCH₂), 74.2 (C5), 127.5, 127.7, 128.4 (All ArC), 137.7 (ArC1), 169.3 (CO₂CH₃), 209.5 (C3).

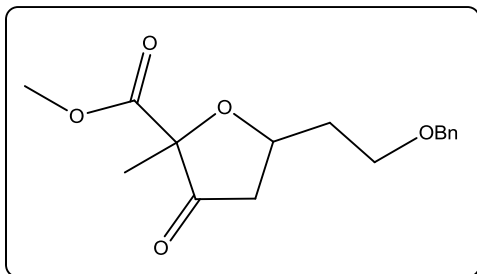
Major Diastereoisomer, δ_{H} (600 MHz): 1.53 (3H, s, C2-CH₃), 2.60 (1H, dd, J = 18.4 and 8.8, H_A of ABX, C4-H *anti* to C5-H), 2.67 (1H, dd, J = 18.4 and 7.0, H_B of ABX, C4-H *syn* to C5-H), 3.65 (1H, dd, J = 10.4 and 4.7, H_A of ABX, BnOCH₂), 3.73 (1H, dd, J = 10.6 and 3.6, H_B of ABX, BnOCH₂), 3.76 (3H, s, OCH₃), 4.59 (1H, d, J = 12.2, H_A of AB, PhCH₂), 4.63 (1H, d, J = 12.2, H_B of AB, PhCH₂), 4.70 - 4.74 (1H, m, H_X of ABX, C5-H), 7.26 - 7.37 (5H, m, ArH).

δ_{C} (150 MHz): 20.5 (C2-CH₃), 37.6 (C4), 52.9 (OCH₃), 72.1 (BnOCH₂), 73.6 (PhCH₂), 74.0 (C5), 127.7, 127.8, 128.5 (All ArCH), 137.8 (ArC1), 169.5 (CO₂CH₃), 210.1 (C3).

M.S: m/z 279 (M+H) (100%), 277, 230, 207, 189, 133, 132.

HRMS calculated for $C_{15}H_{19}O_5$ $[M+H]^+$: 279.1232; found 279.1229.

(±)-5-(2-Benzyloxyethyl)-2-methyl-3-oxotetrahydrofuran-2-carboxylic Acid Methyl Ester (66)



To a flame dried 25 mL, round bottom flask containing DCM (7 mL), (±)-5-benzyloxyethyl-3-oxotetrahydrofuran-2-carboxylic acid methyl ester (0.3 g, 1.09 mmol) was added under a nitrogen atmosphere. The solution was cooled to 0 °C. DBU (0.25 g, 1.63 mmol) was added

dropwise *via* a glass syringe and the mixture was stirred for 5 min, which resulted in a deep red solution. Iodomethane (0.62 g, 4.30 mmol) was added to this solution and the reaction was sealed with a stopper and stirred overnight. The reaction was then diluted with DCM (30 mL), washed with 10% w/v HCl (2 × 30 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 10 - 30% ethyl acetate in hexane as the eluent, yielded both diastereoisomers as an inseparable mixture (d.r. = 5 : 2).

ν_{\max} (NaCl): 2954, 2866, 1770, 1742, 1453, 1271, 1128, 1097, 741, 699 cm^{-1} .

Yield = 0.053 g, 17%.

δ_{H} (300 MHz): 1.45 (3H, s, C2-CH₃, major diastereoisomer), 1.48 (3H, s, C2-CH₃, minor diastereoisomer), 1.93 - 2.05 (2H, m, BnOCH₂CH₂, both diastereoisomers), 2.06 - 2.19 (2H, m, BnOCH₂CH₂, both diastereoisomers), 2.35 (1H, dd, J = 18.5 and 10.0, H_A of ABX, C4-H, minor diastereoisomer), 2.51 (1H, dd, J = 18.0 and 9.3, H_A of ABX, C4-H, major diastereoisomer), 2.62 - 2.73 (1H, m, C4-H, both diastereoisomers), 3.62 - 3.69 (4H, m, BnOCH₂, both diastereoisomers), 3.73 (3H, s, OCH₃, major diastereoisomer), 3.74 (3H, s, OCH₃, minor diastereoisomer), 4.43 - 4.55 (1H, m, C5-H major diastereoisomer), 4.50, (4H, s, PhCH₂, both diastereoisomers) 4.58 - 4.66 (1H, m, C5-H minor diastereoisomer), 7.25 - 7.37 (10H, m, ArH, both diastereoisomers).

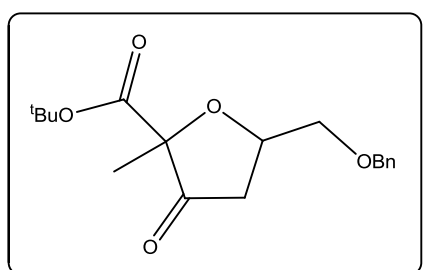
δ_{C} (75 MHz): 19.1 (C2-CH₃, major diastereoisomer), 20.7 (C2-CH₃, minor diastereoisomer), 35.9 (BnOCH₂CH₂, both diastereoisomers), 41.7 (C4, minor diastereoisomer), 41.9 (C4, major diastereoisomer), 52.8 (OCH₃, minor diastereoisomer), 53.0 (OCH₃, major diastereoisomer), 66.4 (BnOCH₂, both diastereoisomers), 72.7 (C5, major diastereoisomer), 73.1(PhCH₂), 73.9 (C5, minor diastereoisomer), 83.6 (C2, major diastereoisomer), 84.1 (C2, minor diastereoisomer),

126.9, 127.7, 128.6 (All ArC, both diastereoisomers), 138.2 (C1 of aromatic, both diastereoisomers), 169.3 (CO₂CH₃, major diastereoisomer), 169.5 (CO₂CH₃, minor diastereoisomer), 210.7 (C3, major diastereoisomer), 210.9 (C3, minor diastereoisomer).

M.S: *m/z* 293 (M+H⁺, 100%), 245, 244, 203, 132.

HRMS calculated for C₁₆H₂₁O₅ [M+H]⁺:293.1389 ; found 293.1388.

(±)-5-Benzyloxymethyl-2-methyl-3-oxotetrahydrofuran-2-carboxylic Acid *tert*-Butyl Ester (64)



To a flame dried 25 mL, round bottom flask containing DCM (5 mL) (±)-5-benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid *tert*-butyl ester (0.4 g, 1.37 mmol) was added under a nitrogen atmosphere. The solution was cooled to 0 °C. DBU (0.31 g, 2.05 mmol) was added dropwise *via* a glass

syringe and the mixture was stirred for 5 min, which resulted in a deep red solution. Iodomethane (0.78 g, 5.48 mmol) was then added to the solution and the reaction was sealed with a stopper and stirred overnight. The mixture was diluted with DCM (30 mL) followed by 10% w/v HCl (30 mL). The layers were separated and the organic layer was washed with 10% w/v HCl (2 × 30 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 10 - 30% ethyl acetate in hexane as the eluent, isolated both diastereoisomers as clear oils.

ν_{\max} NaCl: 2961, 2835, 1769, 1743, 1452, 1129, 1098, 740, 699 cm⁻¹.

Yield: (Major diastereoisomer, more polar fraction, C2-CH₃ is *anti* to C5-H) = 0.158 g, 37%.

Yield: (Minor diastereoisomer, less polar fraction, C2-CH₃ is *syn* to C5-H) = 0.084 g, 20%.

Major Diastereoisomer, δ_{H} (600 MHz, C₆D₆): 1.25 [9H, s, OC(CH₃)₃], 1.59 (3H, s C2-CH₃), 2.31 (2H, d, *J* = 7.6, C4-H), 3.23 (1H, dd, *J* = 10.6 and 4.5, H_A of ABX, BnOCH₂), 3.36 (1H, dd, *J* = 10.6 and 3.7, H_B of ABX, BnOCH₂), 4.25 (1H, d, *J* = 12.2, H_A of AB, CH₂Ph), 4.31 (1H, d, *J* = 12.2, H_B of AB, CH₂Ph), 4.60 - 4.64 (1H, m, H_X of ABX, C5-H), 7.28 - 7.37 (5H, m, ArH).

δ_{C} (150 MHz, C₆D₆): 20.3 (C2-CH₃), 27.7 (OC(CH₃)₃), 37.8 (C4), 71.6 (BnOCH₂), 73.5 (PhCH₂), 75.3 (C5), 82.1 (OC(CH₃)₃), 85.2 (C2), 127.6, 128.1, 128.3 (All ArC), 138.7 (C1 of aromatic), 168.6 (CO₂CH₃), 210.3 (C3).

Minor Diastereoisomer, δ_{H} (600 MHz, C_6D_6): 1.27 [9H, s, $\text{OC}(\text{CH}_3)_3$], 1.44 (3H, s, C2-CH_3), 2.06 (1H, dd, $J = 17.8$ and 7.2 , H_A of ABX, C4-H syn to C5-H), 2.40 (1H, dd, $J = 17.8$ and 8.7 , H_B of ABX, C4-H anti to C5-H), 3.45 (2H, d, $J = 4.52$, BnOCH_2), 4.04-4.08 (1H, m, H_X of ABX, C5-H), 4.36 (1H, d, $J = 12.2$, H_A of AB, PhCH_2), 4.36 (1H, d, $J = 12.2$, H_B of AB, PhCH_2), 7.27 - 7.36 (5H, m, ArH).

δ_{C} (150 MHz, C_6D_6): 19.4 (C2-CH_3), 27.6 ($\text{OC}(\text{CH}_3)_3$), 38.5 (**C4**), 72.0 (BnOCH_2), 73.4 (PhCH_2), 74.4 (**C5**), 81.9 ($\text{OC}(\text{CH}_3)_3$), 84.5 (**C2**), 127.8, 128.0, 128.2 (All ArC), 138.8 (**C1** of aromatic), 168.1 (CO_2CH_3), 210.0 (**C3**).

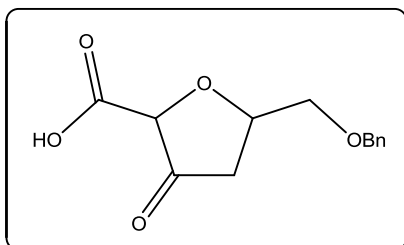
M.S: m/z : 321($\text{M}+\text{H}^+$) (100%), 306, 279, 265, 216, 209, 133, 132, 98, 91, 56.

HRMS calculated for $\text{C}_{18}\text{H}_{24}\text{O}_5$ [$\text{M}+\text{Na}$] $^+$: 343.1521; found 343.1521.

3.2.9 Hydrolysis of Alkyl Ester at the 2-Position of 4,5-Dihydro-3(2*H*)-furanone

(±)-5-Benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic Acid (67)

Calter Method



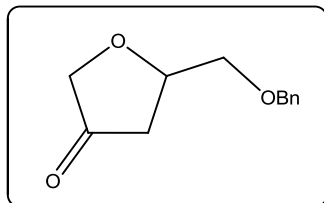
Trifluoroacetic acid (25 mL) was added to a stirring solution of (±)-5-benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid *tert*-butyl ester (1.2 g, 4 mmol) in doubly distilled DCM (50 mL) at 0 °C. After 4 h, the reaction solution was washed with water (2 × 100 mL). The aqueous extracts were

washed with DCM (2 × 100 mL). The combined organic extracts were then dried and concentrated under reduced pressure, to yield a yellow oil which was not further purified. Yield = 0.72 g, 75% (mass balance).

ν_{\max} (NaCl): 3445, 2946, 2873, 1773, 1747, 1454, 1104 cm^{-1} .

δ_{H} (300 MHz): 2.54 - 2.62 (2H, m, C4-H), 3.46 - 3.55 (2H, m, BnOCH_2), 4.26 - 4.55 (4H, m, C2-H, C5-H and CH_2Ph), 7.29 - 7.33 (5H, m, ArH), 8.90 (1H, bs, OH)

(±)-5-Benzyloxymethyl-4,5-dihydro-3(2*H*)-furanone (68)²¹



Method 1.

(±)-5-Benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid (0.69 g, 2 mmol) in acetonitrile (75 mL) was heated at reflux for 16 h and monitored by IR analysis for disappearance of the carboxyl group (absorption at 1750 cm^{-1}). The reaction solution was then cooled and concentrated under reduced pressure. Flash column chromatography of the residue, using 5% ethyl acetate in hexane as eluent, yielded the title compound as a clear oil.

Yield = 78 mg, 11%.

Method 2.

(±)-5-Benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid methyl ester (0.15 g, 0.57 mmol) was dissolved in anhydrous THF (1.5 mL) in a 25 mL round bottom flask with a stirrer bar. To this solution 6M HCl (1.5 mL) was added. This solution was placed in a microwave reactor. The reaction mixture was heated at 150 watts for 6 min and after this time was allowed to cool to room temperature and was diluted with diethylether (15 mL) and neutralised with saturated Na₂CO₃ solution. The layers were separated and the aqueous layer was extracted with diethylether (2 × 15 mL) to ensure all organic material was transferred to organic layer. The combined organic extracts were washed with brine, dried and concentrated under reduced pressure. Flash chromatography, using 5% ethyl acetate in hexane as eluent, yielded the title compound.

Yield = 0.033 g, 29%.

Method 3.

(±)-5-Benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid methyl ester (0.20 g, 0.76 mmol) was dissolved in 1,4-dioxane (2 mL) in a 25 mL round bottom flask with a stirrer bar. To this solution 6M HCl (2 mL) was added. This solution was placed in a microwave reactor. The reaction mixture was heated at 150 watts for 6 min after this time was allowed to cool to room temperature and was diluted with diethylether (15 mL) and neutralised with saturated Na₂CO₃ solution. The layers were separated and the aqueous layer was extracted with diethylether (2 × 15 mL). The organic layers were combined, washed with brine (15 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 5% ethyl acetate in hexane as eluent, yielded the title compound.

Yield = 0.106 g, 68%.

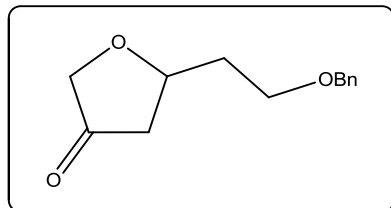
ν_{max} (NaCl): 2864, 1760, 1453, 1063, 738, 698 cm⁻¹.

δ_{H} (400 MHz): 2.43 (1H, dd, H_A of ABX, J = 17.9 and 7.3, C4-H), 2.52 (1H, dd, H_B of ABX, J = 17.9 and 7.3, C4-H), 3.59 (1H, dd, H_A of ABX, J = 10.5 and 4.4, CH₂OBn), 3.72 (1H, dd, H_B of ABX, J = 10.5 and 3.3, CH₂OBn), 3.89 (1H, d, H_A of AB, J = 16.8, C2-H), 4.11 (1H, d, H_B of AB, J = 16.8, C2-H), 4.47 - 4.53 (1H, m, H_X of ABX C5-H), 4.57 (1H, d, H_A of AB J = 12.2 CH₂Ph), 4.60 (1H, d, H_B of AB J = 12.2, CH₂Ph), 7.25 - 7.36 (5H, m, ArH).
 δ_{C} (75 MHz): 38.9 (C4), 71.4 (C2), 72.1 (CH₂OPh), 73.6 (CH₂Ph), 76.73 (C5), 127.5, 127.8, 128.5 (All ArC), 137.8 (ArC1), 214.4 (C3).

M.S: m/z : 207 (M+H⁺), 132 (100%), 115, 91, 74.

HRMS calculated for $C_{12}H_{15}O_3$ $[M+H]^+$: 207.1021 ; found 207.1015.

(±)-5-(2-Benzyloxyethyl)-4,5-dihydro-3(2H)-furanone (69)



Method 1

(±)-5-(2-Benzyloxyethyl)-3-oxotetrahydrofuran-2-carboxylic acid methyl ester (0.17 g, 0.61 mmol) was dissolved in anhydrous THF (1.7 mL) in a 25 mL round bottom flask with a stirrer bar. To this solution 6M HCl (1.7 mL) was added. This solution was placed in a microwave reactor. The reaction mixture was heated at 150 watts for 6 min and after this time was allowed to cool to room temperature and was diluted with diethylether (15 mL) and neutralised with saturated Na_2CO_3 solution. The layers were separated and the aqueous layer was washed with diethylether (2 × 15 mL). The organic layers were combined, washed with brine (15 mL), dried and concentrated under reduced pressure. Flash chromatography, using 5% ethyl acetate in hexane as eluent, yielded the title product as a clear oil.

Yield = 0.041 g, 31%.

Method 2

(±)-5-(2-Benzyloxyethyl)-3-oxotetrahydrofuran-2-carboxylic acid methyl ester (0.40 g, 1.44 mmol) was dissolved in 1,4-dioxane (4 mL) in a 25 mL round bottom flask with a stirrer bar. To this, 6M HCl (4 mL) was added. This solution was placed in a microwave reactor. The reaction mixture was heated at 150 watts for 6 min and afterward was allowed to cool to room temperature and was diluted with diethylether (40 mL) and neutralised with saturated Na_2CO_3 solution. The layers were separated and the aqueous layer was extracted with diethylether (2 × 45 mL). The organic layers were combined, washed with brine (40 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 5% ethyl acetate in hexane as eluent, yielded the title product.

Yield = 0.223 g, 72%.

ν_{max} (NaCl): 2866, 1760, 1454, 1101, 1064, 739, 699 cm^{-1} .

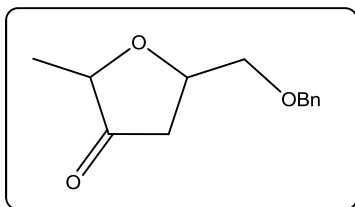
δ_{H} (300 MHz): 1.91 - 2.11 (2H, m, $\text{CH}_2\text{CH}_2\text{OBn}$), 2.23 (1H, H_A of ABX, $J = 17.7$ and 9.4, C4-H), 2.54 (1H, H_B of ABX, $J = 17.7$ and 6.0, C4-H), 3.60 - 3.65 (2H, m, CH_2OBn), 3.81 (1H, H_A of AB, $J = 17.0$, C2-H), 4.02 (1H, H_B of AB, $J = 17.0$, C2-H), 4.36 - 4.45 (1H, m, H_X of ABX C5-H), 4.48 (1H, d, A of AB, $J = 12.1$, H of OCH_2Ph), 4.53 (1H, d, H of AB, $J = 12.1$, H of OCH_2Ph), 7.25 - 7.36 (5H, m, ArH).

δ_{C} (75 MHz): 35.5 ($\text{CH}_2\text{CH}_2\text{OPh}$), 43.1 (C-4), 66.5 (CH_2OBn), 71.2 (C-2), 73.2 (CH_2Ph), 75.9 (C-5), 127.6, 128.4, 128.5 (All ArC), 138.2 (C-1 of aromatic), 215.1 (C-3).

M.S: m/z : 221 ($\text{M}+\text{H}^+$, 100%), 208, 167 115, 91, 74.

HRMS calculated for $\text{C}_{13}\text{H}_{16}\text{O}_3$ $[\text{M}+\text{H}]^+$: 221.1178 ; found 221.1174.

(\pm)-5-Benzyloxymethyl-2-methyl-4,5-dihydro-3(2H)-furanone (70)²²



(\pm)-5-Benzyloxymethyl-3-oxotetrahydrofuran-2-carboxylic acid methyl ester (0.5 g, 1.79 mmol) was dissolved in 1,4-dioxane (5 mL) in a 25 mL round bottom flask with a stirrer bar. To this solution 6M HCl (5 mL) was added and the solution was placed in a microwave reactor. The reaction

mixture was heated at 150 watts for 6 min and was allowed to cool to room temperature before it was diluted with diethylether (30 mL) and neutralised with saturated Na_2CO_3 solution. The layers were separated and the aqueous layer was extracted with diethylether (2 \times 30 mL). The organic layers were combined, washed with brine (30 mL), dried and concentrated. Flash column chromatography, using 5% ethyl acetate in hexane as eluent, yielded both diastereoisomers as an inseparable mixture d.r. = 1.55:1 in favour of the C2-CH₃ *anti* to C5-H.

Yield = 0.227 g, 58%.

ν_{max} (NaCl): 2980, 2866, 1759, 1453, 1107, 739, 699 cm^{-1} .

δ_{H} (300 MHz): 1.26 (3H, d, $J = 6.7$, C2-CH₃, minor diastereoisomer), 1.32 (3H, d, $J = 6.8$, C2-CH₃, major diastereoisomer), 2.34 - 2.62 (4H, m, 2 \times C4-H, both diastereoisomers), 3.53 - 3.75 (2H, m, CH_2OBn , both diastereoisomers), 3.88 (1H, q, $J = 6.8$, C2-H major diastereoisomer), 4.15 (1H, q, $J = 6.7$, C2-H, minor diastereoisomer), 4.32-4.41 (1H, m, C5-H, major diastereoisomer), 4.51-4.58 (1H, m, C5-H, minor diastereoisomer), 4.56 (2H, d, $J = 4.8$, CH_2Ph , minor diastereoisomer), 4.61 (2H, s, CH_2Ph , major diastereoisomer), 7.28 - 7.36 (10H, m, ArH, both diastereoisomers).

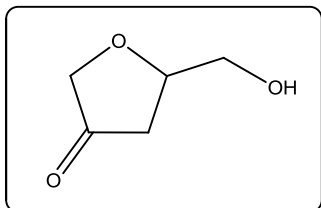
δ_C (75 MHz): 16.1 (**CH**₃, major diastereoisomer), 16.6 (**CH**₃, minor diastereoisomer), 38.1 (**C**-4, major diastereoisomer), 38.9 (**C**-4, minor diastereoisomer), 71.2 (**CH**₂OBn, minor diastereoisomer), 72.7 (**CH**₂OBn, major diastereoisomer), 73.6, (**CH**₂Ph, both diastereoisomer), 73.9 (**C**-5, minor diastereoisomer), 74.8 (**C**-5, major diastereoisomer), 76.0 (**C**-2, minor diastereoisomer), 77.8 (**C**-2, major diastereoisomer), 127.5, 127.8, 128.5 (All Ar**C**, both diastereoisomers), 137.8 (Ar**C**1, both diastereoisomers), 215.4 (**C**3, major diastereoisomer), 216.2 (**C**3, minor diastereoisomer).

M.S: *m/z*: 235 ($M+H^+$, 100%), 225, 186, 132.

HRMS calculated for C₁₃H₁₇O₃ [$M+H$]⁺: 235.1335; found 235.1334.

3.2.10 Derivatisations of Alkyl Chain at the 5-Position of 4,5-Dihydro-3(2H)-furanone

(±)-5-Hydroxymethyl-3(2H)-furanone (71)²⁰



(±)-5-Benzyloxymethyl-4,5-dihydro-3(2H)-furanone (1 g, 4.85 mmol) was added to methanol (25 mL) in a Paar hydrogenation flask. Pd(OH)₂ (10% on carbon) (0.1 g) was then added. The reaction was placed under a hydrogen atmosphere of 35 psi and shaken for 4 h, after which the reaction was sonicated with Celite® (5 g). The reaction was filtered through Celite®, which was then washed with methanol (200 mL) and the combined filtrates were concentrated under reduced pressure to yield the title product as a clear oil.

Yield = 0.40 g, 72%.

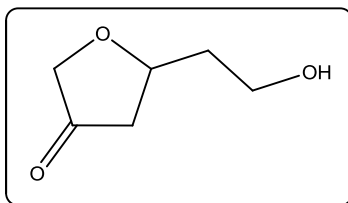
ν_{max} (NaCl): 3423, 2922, 1759, 1180, 1063 cm⁻¹.

δ_{H} (300 MHz): 2.49 (2H, dd, H_A of ABX, J = 7.3 and 2.6, C4-H), 2.51 (2H, dd, H_B of ABX, J = 7.5 and 2.6, C4-H), 2.60 (1H, bs, OH), 3.70 (1H, dd, H_A of ABX, J = 12.1 and 4.5, CH₂OH), 3.92 (1H, dd, J = 12.1 and 4.5, H_B of ABX, CH₂OH), 3.93 (1H, d, H_A of AB, J = 17.0, C2-H), 4.13 (1H, d, H_B of AB, J = 17.0, C2-H), 4.40-4.47 (1H, m, H_X of ABX, C5-H).
 δ_{C} (75 MHz): 38.0 (C-4), 63.8 (CH₂OH), 71.5 (C-2), 78.2 (C-5), 214.4 (C-3).

M.S: m/z : 117 (M+H⁺, 100%), 64.

HRMS calculated for C₁₃H₁₇O₃ [M+H]⁺: 117.0552 ; found 117.0553.

(±)-5-(2-Hydroxyethyl)-3(2H)-furanone (72)



(±)-5-(2-Benzyloxyethyl)-4,5-dihydro-3(2H)-furanone (1 g, 4.38 mmol) was added to methanol (25 mL) in a Paar hydrogenation flask. Pd(OH)₂ (10% on carbon) (0.1 g) was then added. The mixture was placed under a hydrogen atmosphere of 35 psi and shaken for 4 h, after which the reaction was sonicated with Celite® (5 g). The reaction was filtered through Celite®, which was washed with methanol (200 mL) and the combined filtrates were concentrated under reduced pressure to yield the title product as a clear oil.

Yield = 0.367 g, 61%.

ν_{max} (NaCl): 3399, 2946, 2885, 1759, 1177, 1055 cm⁻¹.

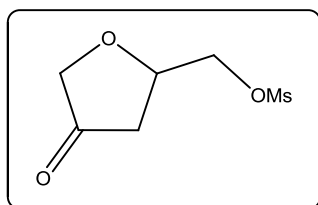
δ_{H} (300 MHz): 1.93 - 2.00 (2H, m, $\text{CH}_2\text{CH}_2\text{OH}$), 2.27 (1H, dd, $J = 17.9$ and 9.5 , H_A of ABX, C4-H), 2.60 (1H, dd, $J = 17.9$ and 6.0 , H_B of ABX, C4-H), 3.68 - 3.88 (3H, m, $\text{CH}_2\text{CH}_2\text{OH}$ and H_A of AB, C2-H), 4.06 (1H, d, H_B of AB, $J = 16.9$, C2-H), 4.41 - 4.51 (1H, m, H_X of ABX, C5-H).

δ_{C} (75 MHz): 37.6 ($\text{CH}_2\text{CH}_2\text{OH}$), 43.0 (C4), 59.4 (CH_2OH), 71.1 (C2), 76.6 (C5), 215.1 (C3).

M.S: m/z 131 (M+1), 118, 115, 105, 89, 77, 74 (100%), 64.

HRMS calculated for $\text{C}_6\text{H}_{11}\text{O}_3$ $[\text{M}+\text{H}]^+$: 131.0708 ; found 131.0713.

(±)-5-methanesulfonyloxymethyl-3(2H)-furanone (73)



(±)-5-Hydroxymethyl-3(2H)-furanone (0.65 g, 5.6 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. Triethylamine (0.85 g, 8.44 mmol) was added and the solution was stirred. Methanesulfonyl chloride (0.96 g, 8.44 mmol) was then added dropwise via a glass syringe. The reaction was stirred at 0 °C

for 2 h, before it was diluted with DCM (20 mL). The mixture was then washed with 10% w/v HCl (20 mL) and brine (2 × 20 mL). The organic layer was dried and concentrated under reduced pressure to yield a light brown oil which was used without further purification.

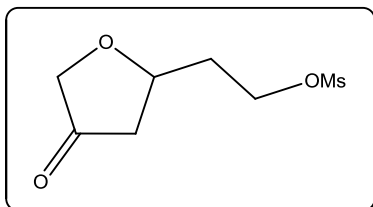
Yield = 0.90 g, 83%.

ν_{max} (NaCl): 3042, 2935, 1760, 1367, 1173, 968, 751 cm^{-1} .

δ_{H} (300 MHz): 2.39 (1H, dd, H_A of ABX, $J = 18.1$ and 7.6 , C4-H), 2.56 (1H, dd, H_B of AB, $J = 18.1$ and 7.1 , C4-H), 3.19 (3H, s, OSO_2CH_3), 3.88 (1H, d, H_A of AB, $J = 16.7$, C2-H), 4.06 (1H, d, H_B of AB, $J = 16.7$, C2-H), 4.30 (1H, dd, H_A of ABX, $J = 11.4$ and 4.9 , H of CH_2OMs), 4.41 (1H, dd, H_B of AB, $J = 11.4$ and 3.0 , H of CH_2OMs), 4.52-4.60 (1H, m, H_X of ABX, C5-H).

δ_{C} (75 MHz): 36.7 (SO_2CH_3), 49.0 (C4), 68.9 ($\text{CH}_2\text{OSO}_2\text{Me}$), 70.3 (C2), 75.2 (C5), 211.3 (C3).

(±)-5-(2-Methanesulfonyloxyethyl)-3(2H)-furanone (74)



(±)-5-(2-Hydroxyethyl)-3(2H)-furanone (0.9 g, 7.03 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. Triethylamine (0.93 g, 9.14 mmol) was added and the solution was stirred. Methanesulfonyl chloride (1.05 g, 9.14 mmol) was then added dropwise *via* a glass syringe.

The reaction mixture was stirred at 0 °C for 2 h before it was diluted with DCM (20 mL). The mixture was then washed with 10% w/v HCl (20 mL) and brine (2 × 20 mL). The organic layer was dried and concentrated under reduced pressure to yield a light brown oil which was used without further purification.

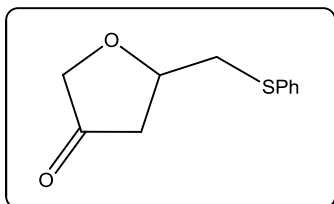
Yield = 1.16 g, 79%.

$\nu_{\text{max}}(\text{NaCl})$: 2939, 1760, 1350, 1172, 1060, 952 cm^{-1} .

δ_{H} (300 MHz): 2.09 - 2.28 (3H, m $\text{CH}_2\text{CH}_2\text{OMs}$ and H_A of ABX of C4-H), 2.64 (1H, dd, H_B of ABX, $J = 17.9$ and 6.1, C4-H), 3.04 (3H, s, OSO_2CH_3), 3.86 (1H, d, H_A of AB, $J = 17.0$, C2-H), 4.06 (1H, d, H_B of AB, $J = 17.0$, C2-H), 4.38-4.49 (3H, m, C5-H and CH_2OMs).

δ_{C} (75 MHz): 34.9 ($\text{CH}_2\text{CH}_2\text{OMs}$) 37.4 ($\text{CH}_2\text{OSO}_2\text{CH}_3$), 42.7 (C4), 68.1 (CH_2OMs), 71.2 (C2), 74.2 (C5), 213.9 (C3).

(±)-5-Benzenesulfonylmethyl-3(2H)-furanone (75)



To sodium hydride (0.54 g, 13.5 mmol, 60% dispersed in mineral oil) washed with hexane (2 × 10 mL) in a flame dried 3-neck round bottom flask, was added anhydrous THF (20 mL) and the suspension was stirred and cooled to 0 °C.

Thiophenol (1.49 mL, 13.5 mmol) was added neat dropwise *via* a syringe and the resulting suspension was stirred for 30 min at 0 °C before being left to warm to room temperature. (±)-5-Methanesulfonylmethyl-3(2H)-furanone (1.74 g, 9 mmol) in anhydrous THF (10 mL) was added dropwise to the suspension and the entire mixture was refluxed overnight. After the reaction was allowed to cool to room temperature, 10% w/v HCl (5 mL) was added. The mixture was diluted with diethylether (50 mL) and washed with water (2 × 30 mL) and brine (30 mL), dried and concentrated under reduced pressure. Flash column chromatography, of the residue using 5% ethyl acetate in hexane as eluent, yielded the title product as a light yellow oil.

Yield = 0.88 g, 49%.

$\nu_{\max}(\text{NaCl})$: 3058, 2926, 1760, 1439, 1169, 1067, 741, 691 cm^{-1} .

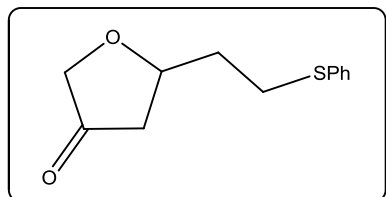
δ_{H} (300 MHz): 2.38 (1H, dd, H_{A} of ABX, $J = 18.1$ and 8.6, C4-H), 2.61 (1H, dd, H_{B} of ABX, $J = 18.1$ and 8.3 C4-H), 3.17 (1H, dd, H_{A} of ABX, $J = 13.7$ and 6.7, H of CH_2SPh), 3.03 (1H, dd, B of ABX, $J = 13.7$ and 5.3, H of CH_2SPh), 3.87 (1H, d, H_{A} of AB, $J = 17.0$, C2-H), 4.08 (1H, d, H_{B} of AB, $J = 17.0$, C2-H), 4.43-4.52 (1H, m, H_{X} of ABX, C5-H), 7.20-7.42 (5H, m, ArH).

δ_{C} (75 MHz): 38.9 (C4), 41.9 (CH_2SPh), 71.5 (C2), 76.6 (C5), 126.8, 129.1, 130.4 (All ArC), 135.3 (ArC1), 213.3 (C3).

m/z : 209 (M+1, 100%), 206, 178, 115, 102.

HRMS calculated for $\text{C}_{11}\text{H}_{13}\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 209.0636; found 209.0641.

(±)-5-(2-Benzenesulfonyl-ethyl)-3(2H)-furanone (76)



To sodium hydride (0.48 g, 12 mmol, 60% dispersed in mineral oil) washed with hexane (2 × 10 mL) in a flame dried 3-neck round bottom flask, was added anhydrous THF (20 mL) and the suspension was stirred and cooled to 0 °C. Thiophenol (1.32 mL, 12 mmol) was then added

dropwise *via* a syringe. The suspension was stirred for 30 min at 0 °C before being left warm to room temperature. (±)-5-(2-Methanesulfonyloxyethyl)-3(2H)-furanone (1.66 g, 8 mmol) in anhydrous THF (10 mL) was then added dropwise to the suspension and this was refluxed overnight. After the reaction was allowed to cool to room temperature, 10% w/v HCl (5 mL) was added to the reaction. The reaction was diluted with diethylether (50 mL) and washed with water (2 × 30 mL) and brine (30 mL), dried and concentrated under reduced pressure. Flash column chromatography, of the residue using 5% ethyl acetate in hexane as eluent, yielded the title product as a light yellow oil.

Yield = 1.21 g, 68%.

$\nu_{\max}(\text{NaCl})$: 2924, 1760, 1480, 1439, 1168, 1068, 740, 690 cm^{-1} .

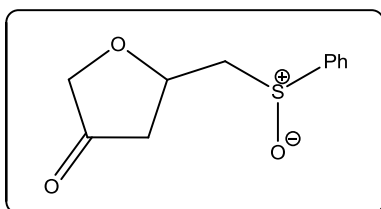
δ_{H} (300 MHz): 1.90 - 2.10 (2H, m, $\text{CH}_2\text{CH}_2\text{SPh}$), 2.16 (1H, dd, H_{A} of ABX, $J = 17.86$ and 9.19, C4-H), 2.55 (1H, dd, H_{B} of ABX, $J = 17.85$ and 6.05, C4-H), 2.98 - 3.17 (2H, m, CH_2SPh), 3.82 (1H, d, H_{A} of AB, $J = 17.01$, C2-H), 4.03 (1H, d, H_{B} of AB, $J = 17.02$, C2-H), 4.34 - 4.44 (1H, H_{X} of ABX, C5-H), 7.16 - 7.37 (5H, m, ArH).

δ_c (75 MHz): 29.6 (**CH₂CH₂SPh**), 34.9 (**CH₂SPh**), 42.7 (**C4**), 71.2 (**C2**), 76.6 (**C5**), 126.2, 129.0, 129.3 (All **ArC**), 135.9 (**ArC1**), 214.5 (**C3**).

m/z : 223 ($M+1$, 100%), 209, 182, 117, 102, 74.

HRMS calculated for $C_{12}H_{15}O_2S$ [$M+H$] $^+$: 223.0793; found 223.0794.

(\pm)-5-(2-benzenesulfinylmethyl)-3(2*H*)-furanone (77)



To a stirring solution of (\pm)-5-benzenesulfinylmethyl-3(2*H*)-furanone (0.04 g, 0.18 mmol) in methanol (3 mL) at 0 °C, was added Oxone[®] (0.065 g, 0.11 mmol) in water (2 mL) dropwise over 5 min. The reaction was allowed to stir at 0 °C for 90 min. The methanol was

evaporated and DCM (5 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (2 \times 5 mL). The organic layers were combined, dried and concentrated Flash column chromatography, using 40% ethyl acetate in hexane as eluent, yielded the title product as a light yellow solid.

Yield = 0.017 g, 39%.

m.p.= 63 - 65°C.

ν_{max} (NaCl): 2966, 2876 1759, 1441, 1171, 1068, 1033, 746, 690 cm^{-1} .

δ_H (600 MHz): 2.26 (1H, dd, H_A of ABX, J = 17.7 and 9.4, **C4-H**, one diastereoisomer), 2.58 - 2.64 (3H, m, **C4-H**, both diastereoisomers), 3.04 - 3.11 (3H, m, **CH₂SOPh**, both diastereoisomers), 3.32 (1H, dd, H_A of ABX, J = 13.4 and 5.9, **CH₂SOPh**, one diastereoisomers) 3.84 (1H, d, H_A of AB, J = 16.7, **C2-H**, one diastereoisomer), 3.94 (1H, d, H_A of AB, J = 16.4, **C2-H**, one diastereoisomer), 4.10 (1H, d, H_B of AB, J = 16.7, **C2-H**, one diastereoisomer), 4.13 (1H, d, H_B of AB, J = 16.6, **C2-H**, one diastereoisomer), 4.46 - 4.52 (1H, H_X of ABX, **C5-H**, one diastereoisomer), 4.46 - 4.52 (1H, H_X of ABX, m, **C5-H**, one diastereoisomer), 4.82 - 4.87 (1H, m, **C5-H**, one diastereoisomer), 7.51 - 7.57 (3H, m, **ArC3-H**, **ArC4-H**, **ArC5-H**, both diastereoisomers), 7.65 - 7.69 (2H, m, **ArC2-H**, **ArC6-H**, both diastereoisomers),

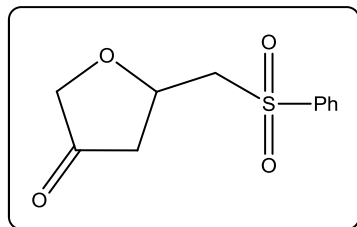
δ_c (125 MHz): 41.0 (**CH₂S(O)Ph**, one diastereoisomer), 41.2 (**CH₂S(O)Ph**, one diastereoisomer), 60.2 (**C4**, one diastereoisomer), 62.3 (**C4**, one diastereoisomer), 70.1 (**C2**, one diastereoisomer), 70.3 (**C2**, one diastereoisomer), 71.1 (**C5**, minor diastereoisomer), 72.0 (**C5**, one diastereoisomer), 122.7 (**ArC4**, one diastereoisomer), 123.1 (**ArC4**, one diastereoisomer), 128.5 (**ArC3** and **ArC5**, one diastereoisomer), 128.6 (**ArC3** and **ArC5**, one diastereoisomer), 130.4 (**ArC2** and **ArC6**, one diastereoisomer), 130.5 (**ArC2**

and ArC6, one diastereoisomer), 143.2 (ArC4, one diastereoisomer), 143.9 (ArC4, one diastereoisomer), 212.6 (C3, one diastereoisomer), 212.7 (C3, one diastereoisomer).

m/z : 225 (M+1, 100%), 125.

HRMS calculated for $C_{11}H_{13}O_3S$ [M+H]⁺: 225.0587 ; found 225.0585.

(±)-5-benzenesulfonylmethyl-3(2H)-furanone (78)



To a stirring solution of (±)-5-benzenesulphenylmethyl-3(2H)-furanone (0.04 g, 0.18 mmol) in methanol (3 mL) at 0 °C, was added Oxone® (0.219 g, 0.36 mmol) in water (3 mL) dropwise over 5 min and was allowed to warm to room temperature and stirred overnight. The methanol was

evaporated and DCM (5 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (2 × 5 mL). The organic layers were combined, dried, and concentrated. . Flash column chromatography, using 40% ethyl acetate in hexane as eluent, yielded the title product as a light yellow solid.

Yield = 0.026 g, 56%.

m.p.= 88 – 90 °C.

ν_{\max} NaCl: 2977, 2949 2831, 1759, 1446, 1306, 1150, 1083, 736, 687 cm^{-1} .

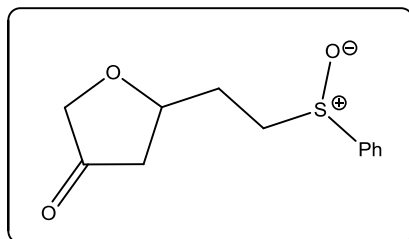
δ_{H} (600 MHz): 2.38 (1H, dd, H_A of ABX, J = 17.7 and 8.5 Hz, C4-H), 2.71 (1H, dd, H_B of ABX, J = 17.7 and 6.1 Hz, C4-H), 3.41 (1H, dd, H_A of ABX, J = 14.3 and 6.7 Hz, CH₂SO₂Ph), 3.62 (1H, dd, H_B of ABX, J = 14.3 and 5.7 Hz, CH₂SO₂Ph), 3.80 (1H, d, H_A of AB, J = 17.1 Hz, C2-H), 3.95 (1H, d, H_B of AB, J = 17.1 Hz, C2-H), 4.69 - 4.73 (1H, m, H_X of ABX, C5-H), 7.56 - 7.61 (2H, m, ArC3-H, ArC5-H), 7.65 - 7.71 (1H, m, ArC4-H), 7.92 - 7.97 (2H, m, ArC2-H, ArC6-H).

δ_{C} (125 MHz): 42.2 (C4), 60.6 (CH₂SO₂Ph), 70.7 (C2), 72.1 (C5), 128.1 (ArC3 and ArC5), 129.3 (ArC4), 134.2 (ArC2 and ArC6), 139.5 (ArC1), 212.6 (C3).

M.S: m/z : 241 (M+1, 100%), 217, 186, 113, 74, 64.

HRMS calculated for $C_{11}H_{13}O_4S$ [M+H]⁺: 241.0535; found 241.0547.

(±)-5-(2-Phenylsulfinylethyl)-3(2H)-furanone (79)



(±)-5-(2-Benzenesulfinylethyl)-3(2H)-furanone (0.40 g, 1.8 mmol) was dissolved in acetic acid (2.4 mL) and cooled to 0 °C. Aq H₂O₂ (30% w/w) (0.432 mL, 2.7 mmol) was added dropwise *via* a glass syringe to the stirring solution. After 90 min saturated aqueous NaHCO₃ solution was added until the pH of the reaction mixture reached was 7. The solution was extracted with DCM (3 × 30 mL). The organic layers were combined and washed with brine (40 mL), dried and concentrated under reduced pressure. Flash column chromatography, using 40% ethyl acetate in hexane as eluent, yielded the title product as a light brown oil as a mixture of diastereoisomers in the ratio of 1 : 1.

Yield = 0.248 g, 58%

ν_{max} (NaCl): 3056, 2918, 1758, 1041, 749, 692 cm⁻¹.

δ_{H} (400 MHz): 1.80 - 1.88 (2H, m, CH₂CH₂SOPh, one diastereoisomer), 2.00 - 2.01 (2H, m, CH₂CH₂SOPh, one diastereoisomer), 2.10 - 2.29 (2H, m, C4-H, both diastereoisomers), 2.56 (1H, dd, H_A of ABX, J = 17.9 and 8.3, C4-H, one diastereoisomer), 2.57 (1H, dd, H_B of ABX, J = 17.9 and 8.3, C4-H, one diastereoisomer), 2.39 [1H, ddd, H_A of ABXX', J = 15.6, 9.4 and 5.5, CH₂CH₂S(O)Ph, one diastereoisomer], 2.53 [1H, ddd, H_A of ABXX', J = 14.4, 9.4, and 5.1, CH₂CH₂S(O)Ph, one diastereoisomer], 3.04 [1H, ddd, H_B of ABXX', J = 15.6, 9.4 and 6.4, CH₂CH₂S(O)Ph, one diastereoisomer], 3.10 [H, ddd, H_B of ABXX', J = 14.4, 9.4 and 5.4, CH₂CH₂S(O)Ph, one diastereoisomer], 3.81 (1H, d, H_A of AB, J = 17.0, C2-H, one diastereoisomer), 3.82 (1H, d, H_A of AB, J = 17.0, C2-H, one diastereoisomer), 3.98 (0.5H, d, H_B of AB, J = 17.0, C2-H, one diastereoisomer), 4.03 (1H, d, H_B of AB, J = 17.0, C2-H, one diastereoisomer), 4.23 - 4.30 (1H, m, C5-H, H_X of ABX, one diastereoisomer), 4.35 - 4.42 (1H, m, C5-H, H_X of ABX, one diastereoisomer), 7.51 - 7.59 (6H, m, ArC3-H, ArC4-H, ArC5-H), 7.51 - 7.59 (4H, m, ArC2-H and ArC6-H).

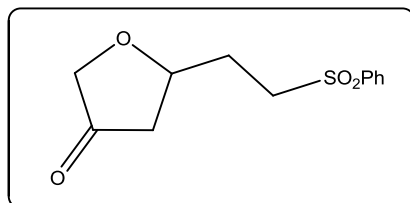
δ_{C} (75 MHz): 27.0 [CH₂CH₂S(O)Ph, one diastereoisomer], 27.7 [CH₂CH₂S(O)Ph, one diastereoisomer], 42.5 (C-4, both diastereoisomers), 52.2 [CH₂S(O)Ph, one diastereoisomer], 52.6 [CH₂S(O)Ph, one diastereoisomer], 71.1 (C2, both diastereoisomers), 76.4 (C5, one diastereoisomer), 76.8 (C5, one diastereoisomer), 123.8 (ArC3 and ArC5, both diastereoisomers), 129.0 (ArC2 and ArC6, both

diastereoisomers), 129.3 (ArC4, both diastereoisomers), 143.1 (ArC1, both diastereoisomers), 214.0 (C3, both diastereoisomers).

M.S: m/z 239 ($M+H^+$, 100%).

HRMS calculated for $C_{12}H_{15}O_3S$ [$M+H$] $^+$: 239.0742 ; found 239.0737.

(±)-5-(2-Phenylsulfonyl-ethyl)-3(2H)-furanone (80)



(±)-5-(2-Benzenesulfonyl-ethyl)-3(2H)-furanone (0.30 g, 1.35 mmol) was dissolved in DCM (5 mL) and cooled to 0 °C. Solid *m*CPBA (70% w/w, 1.54 g, 5.4 mmol) was added portion-wise over 2 min and was stirred at 0 °C for 4 h and then at room temperature

overnight. The reaction was then diluted with DCM (15 mL) and washed successively with 5% aqueous sodium sulphite solution (3 × 20 mL) and 5% aqueous sodium bicarbonate solution (3 × 20 mL). The organic layer was dried and concentrated under reduced pressure. Flash column chromatography, using 40% ethyl acetate in hexane as eluent, yielded the title product as a viscous pale yellow oil.

Yield = 0.175g, 51%.

ν_{\max} (NaCl): 2925, 1760, 1305, 1147, 1086, 746, 688 cm^{-1} .

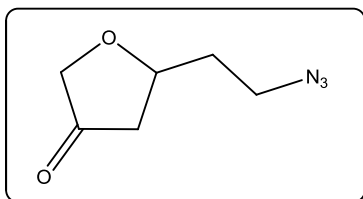
δ_{H} (300 MHz): 1.91 - 2.29 (2H, m, $\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$), 2.19 (1H, dd, H_{A} of ABX, $J = 17.9$ and 8.3, C4-H), 2.61 (1H, dd, H_{B} of ABX, $J = 17.9$ and 6.1, C4-H), 3.26 (1H, ddd, H_{A} of ABXX', $J = 15.8$, 10.3 and 6.1, $\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$), 3.40 (1H, ddd, H_{B} of ABXX', $J = 15.8$, 10.3 and 5.3, $\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$), 3.73 (1H, d, H_{A} of AB, $J = 17.1$, C2-H), 3.91 (1H, d, H_{B} of AB, $J = 17.1$, C2-H), 4.30 - 4.40 (1H, m, H_{X} of ABX, C5-H), 7.85 - 7.86 (2H, m, ArC3-H and ArC5-H), 7.87 - 7.89 (1H, m, ArC4-H), 7.91 - 7.93 (2H, m, ArC2-H and ArC6-H).

δ_{C} (75 MHz): 28.3 ($\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$), 42.5 (C4), 52.5 ($\text{CH}_2\text{SO}_2\text{Ph}$), 71.1 (C2), 75.9 (C5), 128.03 (ArC3 and ArC5), 129.4 (ArC2 and ArC6), 134.0 (ArC4), 137.9 (ArC1 of aromatic), 212.5 (C3).

M.S: m/z 255 ($M+H^+$, 100%), 221, 146, 105, 102, 64.

HRMS calculated for $C_{12}H_{15}O_4S$ [$M+H$] $^+$: 255.0691; found 255.0692.

5-(2-Azidoethyl)-3(2*H*)-furanone (87)



Method 1.

(±)-5-(2-Hydroxyethyl)-3(2*H*)-furanone (0.40 g, 2.94 mmol) was dissolved in acetonitrile (10 mL) and cooled to 0 °C. Imidazole (0.26 g, 3.82 mmol) was added followed by triphenylphosphine (1.00 g, 3.82 mmol). Iodine (0.97 g, 3.82 mmol) was added portion-wise. The reaction was stirred at 0 °C for 2 h and then allowed to warm to room temperature. 15-Crown-5 (0.71 g, 3.23 mmol) and sodium azide (0.21 g, 3.23 mmol) were added and the mixture was heated at 60 °C overnight. The reaction was allowed to cool and diluted with diethylether (30 mL). The reaction was washed with saturated sodium thiosulfate solution (2 × 20 mL) and brine (20 mL). The organic layer was dried and concentrated under reduced pressure. Flash column chromatography, using 10% ethyl acetate in hexane as eluent, yielded the title compound as a clear oil.

Yield = 0.121 g, 26%.

Method 2.

(±)-5-(2-Hydroxyethyl)-3(2*H*)-furanone (0.40 g, 2.94 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. Triethylamine (0.65 g, 6.47 mmol) was added followed by methanesulfonyl chloride (0.37 g, 3.29 mmol), which was added dropwise. The reaction was stirred at 0 °C for 2 h and then allowed to warm to room temperature before 15-crown-5 (0.84 g, 3.82 mmol) and sodium azide (0.24 g, 3.82 mmol) were added and the mixture was refluxed overnight. The reaction was then allowed to cool and diluted with DCM (30 mL). The reaction was washed with 10% w/v HCl (2 × 20 mL), water (2 × 20 mL). The organic layer was dried and concentrated under reduced pressure. Flash column chromatography, using 10% ethyl acetate in hexane as eluent, yielded the title product as a clear oil.

Yield = 0.267 g, 56%.

ν_{max} (NaCl): 2927, 2100, 1761, 1257, 1173, 1062 cm^{-1} .

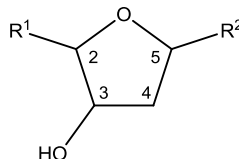
δ_{H} (300 MHz): 1.93 - 2.01 (2H, m, $\text{CH}_2\text{CH}_2\text{N}_3$), 2.22 (1H, dd, H_A of ABX, $J = 17.9$ and 9.4 , C4-H), 2.60 (1H, dd, H_B of ABX, $J = 17.9$ and 6.0 , C4-H), 3.50 (2H, t, $J = 6.7$, $\text{CH}_2\text{CH}_2\text{N}_3$),

3.85 (1H, d, H_A of AB, $J = 17.0$, C2-**H**), 4.06 (1H, d, H_B of AB, $J = 17.0$, C2-**H**), 4.31 - 4.41 (1H, m, H_X of ABX, C5-**H**).

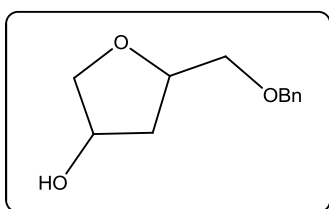
δ_C (75 MHz): 32.9 (**CH**₂CH₂N₃), 42.7 (**C4**), 47.7 (CH₂**CH**₂N₃), 71.2 (**C2**), 75.3 (**C5**), 214.1 (**C3**).

3.2.11 Reduction of 4,5-Dihydro-3(2*H*)-Furanone to 3-Hydroxytetrahydrofuran

Numbering system of 3-Hydroxytetrahydrofuran



(±)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran²⁰



(±)-5-Benzyloxymethyl-3(2*H*)-furanone (0.10 g, 0.49 mmol) was dissolved in methanol (10 mL). Sodium borohydride (20 mg, 0.54 mmol) in water (1 mL) was added to the stirring solution. The reaction was stirred overnight before 10% w/v HCl (10 mL) was added to the reaction. The reaction mixture

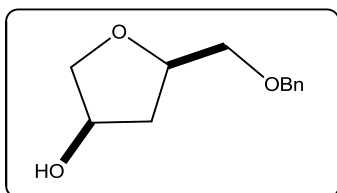
was then extracted with diethylether (2 × 20 mL). The organic layers were combined, washed with brine, dried and concentrated under reduced pressure. Flash column chromatography, using 10 - 30% ethyl acetate in hexane as eluent, yielded two diastereoisomers as clear oils.

Yield: (Major diastereoisomer, less polar fraction) = 0.056 g, 55%.

Yield: (Minor diastereoisomer, more polar fraction) = 0.036 g, 35%.

ν_{max} (NaCl): 3414, 2949, 2866, 1453, 1079, 739, 699 cm⁻¹.

syn-(±)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran (90)

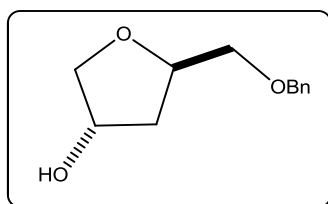


δ_{H} (600 MHz): (Major diastereoisomer, C3-H is *syn* to C5-H) : 1.91 (1H, overlapping ddd appears as dt, J = 14.8 and 2.2, C4-H, *syn* to OH), 2.27 (1H, ddd, J = 14.8, 10.1 and 5.6, C4-H, *anti* to OH), 3.47 (1H, dd, H_A of ABX, J = 10.3 and 2.3, H of BnOCH₂), 3.69 (1H, dd, H_A of ABX, J = 9.5 and 3.2, C2-H, *anti* to OH), 3.73 (1H, dd, H_B of ABX J = 10.3

and 2.2, H of BnOCH₂), 3.94 (1H, dd, H_B of ABX $J = 9.5$ and 1.6 , C2-H, *syn* to OH), 4.03 (1H, broad doublet, $J = 10.7$, C3-OH), 4.22-4.26 (1H, m, C5-H), 4.24 - 4.30 (1H, m, H_X of ABX, C3-H), 4.55 (1H, d, $J = 11.7$, CH₂Ph), 4.70 (1H, d, $J = 11.7$, CH₂Ph), 7.26 - 7.38 (5H, m, ArH).

δ_C (150 MHz): 36.9 (C4), 71.7 (C3), 72.2 (PhCH₂), 73.7 (BnOCH₂), 77.0 (C5), 77.1 (C2), 126.9, 127.1, 128.2 (All ArC), 136.1 (ArC1).

anti-(±)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran (91)



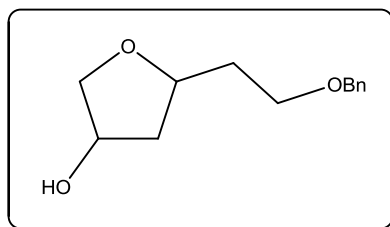
δ_H (600 MHz): (Minor diastereoisomer, C3-H is *anti* to C5-H): 1.90 (1H, overlapping ddd, 7 lines, $J = 13.4$, 9.2 and 5.3 , C4-H, *anti* to OH), 1.97 (1H, dddd appears as overlapping qt, $J = 13.4$ and 6.4 , C4-H, *syn* to OH), 3.50 (1H, dd, H_A of ABX, $J = 10.3$ and 5.6 , H of BnOCH₂), 3.57 (1H, dd, H_B of ABX, $J = 10.3$ and 3.6 , H of BnOCH₂), 3.77 (1H, dt, H_A of ABX, $J = 9.8$ and 1.3 , C2-H), 4.01 (1H, dd, H_B of ABX, $J = 9.8$ and 4.1 , C2-H, *anti* to OH), 4.36 - 4.40 (1H, m, H_X of ABX, C5-H), 4.51 - 4.54 (1H, m, H_X of ABX, C3-H), 4.58 (2H, d, $J = 1.9$, CH₂Ph), 7.26 - 7.34 (5H, m, ArH).

δ_C (150 MHz): 37.9 (C4), 72.2 (BnOCH₂), 72.5 (C3), 73.7 (CH₂Ph), 75.8 (C2), 77.0 (C5), 127.7, 128.5, 129.7 (All ArC), 133.1 (ArC1).

M.S: m/z : 209 (M+1, 100%), 207, 160, 132, 105.

HRMS calculated for C₁₂H₁₇O₃Na [M+Na]⁺: 231.0997; found 231.1001.

(±)-3-Hydroxy-5-(2-benzyloxyethyl)tetrahydrofuran (92)



(±)-5-(2-Benzyloxyethyl)-3(2H)-furanone (0.10 g, 0.49 mmol) was dissolved in methanol (10 mL). Sodium borohydride (22 mg, 0.54 mmol) in water (1 mL) was added to the stirring solution. The reaction was stirred overnight before 10% w/v HCl (10 mL) was added to the

reaction. The reaction was extracted with diethylether (2 × 20 mL). The organic layers were combined, washed with brine, dried and concentrated under reduced pressure. Flash column chromatography, using 10 - 30% ethyl acetate in hexane as eluent, yielded a mixture of diastereoisomers (d.r. = 3:2) as a clear oil.

Yield = 0.063 g, 62%.

ν_{max} (NaCl): 3418, 2921, 2864, 1454, 1086, 739, 699 cm^{-1} .

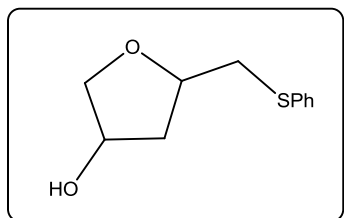
δ_{H} (600 MHz): 1.60 (1H, ddd, $J = 14.0, 6.8$ and 2.6 , C4-**H**, major diastereoisomer), 1.67 (1H, ddd, $J = 15.3, 9.8$ and 5.5 , C4-**H**, minor diastereoisomer), 1.80 - 1.89 (2H, m, $\text{BnOCH}_2\text{CH}_2$, minor diastereoisomer), 1.90 - 2.04 (3H, m, $\text{BnOCH}_2\text{CH}_2$ of major diastereoisomer and C4-**H** of minor diastereoisomer), 2.33 (1H, overlapping ddd, $J = 14.0, 7.8$ and 6.7 , C4-**H**, major diastereoisomer), 3.58 - 3.70 (8H, m, C2-**H**₂ and BnOCH_2 , both diastereoisomers), 3.96 - 4.03 (1H, m, C5-**H**, major diastereoisomer), 4.23 - 4.27 (1H, m, C5-**H**, minor diastereoisomer), 4.40 - 4.43 (1H, m, C3-**H**, major diastereoisomer), 4.45 - 4.48 (1H, m, C3-**H**, minor diastereoisomer), 4.49 - 4.53 (2H, m, CH_2Ph , both diastereoisomers), 7.26 - 7.35 (5H, m, Ar**H**, both diastereoisomers).

δ_{C} (125 MHz): 35.2 ($\text{BnOCH}_2\text{CH}_2$, minor diastereoisomer), 35.8 ($\text{BnOCH}_2\text{CH}_2$, major diastereoisomer), 40.8 (**C**4, major diastereoisomer), 41.9 (**C**4, minor diastereoisomer), 67.4 (**C**2 or BnOCH_2 , major diastereoisomer), 67.6 (**C**2 or BnOCH_2 , minor diastereoisomer), 72.5 (**C**3, major diastereoisomer), 72.6 (**C**3, minor diastereoisomer), 73.1 (CH_2Ph , major diastereoisomer), 75.3 (CH_2Ph , minor diastereoisomer), 75.3 (**C**2 or BnOCH_2 , minor diastereoisomer), 75.4 (**C**5, minor diastereoisomer), 75.5 (**C**2 or BnOCH_2 , major diastereoisomer), 76.2 (**C**3, major diastereoisomer), 127.6, 127.7, 127.8 (All Ar**C**, both diastereoisomers), 128.4 (Ar**C**1, both diastereoisomers).

M.S: m/z : 223 ($\text{M}+\text{H}^+$, 100%), 203, 174, 146, 131, 105.

HRMS calculated for $\text{C}_{13}\text{H}_{18}\text{O}_3\text{Na}$ [$\text{M}+\text{Na}$]⁺: 245.1154; found 245.1156.

(±)-3-Hydroxy-5-(phenylthiomethyl)tetrahydrofuran



(±)-5-Benzenesulphenylmethyl-3(2*H*)-furanone (0.10 g, 0.48 mmol) was dissolved in methanol (5 mL). Sodium borohydride (27 mg, 0.72 mmol) in water (1 mL) was added to the stirring solution and the reaction was stirred overnight. 10% w/v HCl (5 mL) was added to the reaction.

The reaction was extracted with diethylether (2 × 20 mL). The organic layers were

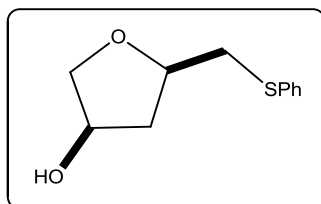
combined, washed with brine, dried and concentrated. Flash column chromatography, using 10 - 30% ethyl acetate in hexane as eluent, yielded two diastereoisomers as clear oils.

Yield: (Major diastereoisomer, less polar fraction) = 0.041g, 42%.

Yield: (Minor diastereoisomer, more polar fraction) = 0.019g, 19%.

ν_{\max} (NaCl): 3367, 2924, 2862, 1332, 1161, 741, 691 cm^{-1} .

***syn*-(±)-3-Hydroxy-5-(phenylthiomethyl)tetrahydrofuran (81)**



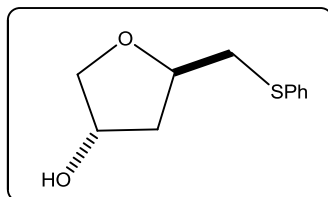
δ_{H} (600 MHz) (Major diastereoisomer, C3-H is *syn* to C5-H): 1.79 (1H, ddd, J = 14.0, 5.3 and 1.8, C4-H, *syn* to OH), 2.34 (1H, overlapping ddd, 7 lines, J = 14.0, 8.4 and 6.3, C4-H, *anti* to OH), 3.23 (2H, d, J = 5.6, PhSCH_2), 3.72 (1H, dd, H_{A} of ABX, J = 9.9 and 4.0, C2-H, *anti* to OH), 3.91 (1H, overlapping dd appears as doublet, J = 9.9, H_{B} of ABX, C2-H, *syn* to OH), 4.14 - 4.19 (1H, m, H_{X} of ABX, C5-H), 4.44 - 4.45 (1H, m, H_{X} of ABX, C3-H), 4.87 (1H, bs, OH), 7.19 (1H, t, J = 7.7, ArC4-H), 7.26 - 7.32 (2H, m, ArC3-H and ArC5-H), 7.40 (2H, m, ArC2-H and ArC6-H).

δ_{C} (150 MHz): 39.4 (PhSCH_2), 39.9 (C4), 72.3 (C3), 76.1 (C2), 77.2 (C5), 127.3 (C4), 129.0 (ArC3 and ArC5), 129.7 (ArC2 and ArC6), 136.0 (ArC1).

M.S: m/z 211 ($\text{M}+\text{H}^+$, 100%), 130.

HRMS calculated for $\text{C}_{13}\text{H}_{18}\text{O}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 233.0790; found 233.0825.

***anti*-(±)-3-Hydroxy-5-(phenylthiomethyl)tetrahydrofuran (82)**



δ_{H} (600 MHz) (Minor diastereoisomer, C3-H is *anti* to C5-H): 1.84 (1H, ddd, J = 14.1, 9.4 and 5.4, C4-H, *anti* to OH), 2.10 (1H, overlapping ddt, J = 14.1, 5.9 and 1.3, C4-H, *syn*

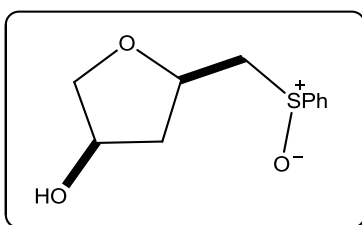
to OH), 3.04 (1H, dd, $J = 13.3$ and 5.6 , H_A of ABX, PhSCH_2), 3.19 (1H, dd, $J = 13.3$ and 5.6 , H_B of ABX, PhSCH_2), 3.76 (1H, overlapping dd appears as doublet, H_A of ABX, $J = 9.8$, C2-**H**, *syn* to OH), 4.04 (1H, dd, H_B of ABX, $J = 9.8$ and 4.2 , C2-**H**, *anti* to OH), 4.35 - 4.39 (1H, m, H_X of ABX, C5-**H**), 4.53 - 4.57 (1H, m, H_X of ABX, C3-**H**), 7.19 (1H, overlapping dd which appears as a t, $J = 7.7$, ArC4-**H**), 7.26 - 7.32 (2H, m, ArC3-**H** and ArC5-**H**), 7.40 (2H, m, ArC2-**H** and ArC6-**H**).

δ_c (150 MHz): 38.8 (PhSCH_2), 31.1 (C4), 72.7 (C3), 75.8 (C2), 76.7 (C5), 126.2 (ArC4), 127.8 (ArC3 and ArC5), 129.5 (ArC2 and ArC6), 135.8 (ArC1).

M.S: m/z : 211 ($M+H^+$, 100%), 132, 130, 116, 102, 89.

HRMS calculated for $\text{C}_{11}\text{H}_{15}\text{O}_2\text{S}$ [$M+H$] $^+$: 233.0848; found 233.0818.

***syn*-(±)-3-Hydroxy-5-(benzenesulfinylmethyl)tetrahydrofuran (83)**



(±)-*syn*-5-Benzenesulphenylmethyl-3-hydroxy-tetrahydrofuran (50 mg, 0.24 mmol) was dissolved in methanol (1 mL). Oxone (25 mg, 0.16 mmol) in water (1 mL) was added to the stirring solution and the reaction was stirred overnight. 10% w/v HCl (2 mL) was added to

the reaction. The reaction was extracted with diethylether (2×10 mL). The organic layers were combined, washed with brine, dried and concentrated. Flash column chromatography, using 40 - 80% ethyl acetate in hexane as eluent, yielded the 2 diastereoisomers as clear oils which could not be separated.

Yield: = 36 mg, 67 %.

(NaCl): 3375, 2917, 2847, 1445, 1215, 1191, 1180, 1140, 1086, 1039, 748, 691 cm^{-1} .

M.S: m/z : 227 ($M+H^+$, 100%).

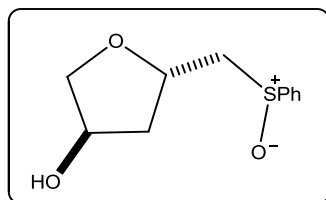
HRMS calculated for $\text{C}_{11}\text{H}_{15}\text{O}_3\text{S}$ [$M+H$] $^+$: 227.0742; found 227.0713.

δ_H (600 MHz): 1.79 (1H, dd, $J = 13.6$ and 5.3 C4-**H**, *syn* to OH, one diastereoisomer), 2.18 (1H, dd, $J = 13.9$ and 5.2 C4-**H**, *syn* to OH, one diastereoisomer), 2.38 - 2.44 (2H, m, C4-**H**, *anti* to OH, both diastereoisomers), 3.01 - 3.12 [3H, m, PhS(O)CH_2 , 2H from one diastereoisomer and 1H from other diastereoisomer], 3.28 [1H, dd, H_B of ABX, $J = 13.6$ and 4.1 , PhS(O)CH_2 , one diastereoisomer], 3.74 (1H, dd, H_A of ABX, $J = 9.8$ and 3.8 , C2-**H**, *anti* to OH, one diastereoisomer), 3.84 (1H, dd, H_A of ABX, $J = 10.0$ and 4.2 , C2-**H**, *anti* to OH, one diastereoisomer), 3.96 (1H, d, $J = 9.8$, H_B of ABX, C2-**H**, *syn* to OH, one diastereoisomer), 4.07 (1H, d, $J = 10.0$, H_B of ABX, C2-**H**, *syn* to OH, one

diastereoisomer), 4.25 - 4.29 (1H, m, H_X of ABX, C5-H, one diastereoisomer), 4.45 - 4.47 (1H, m, H_X of ABX, C5-H, one diastereoisomer), 4.50 - 4.56 (2H, m, H_X of ABX, C3-H, both diastereoisomers), 7.48 - 7.55 (3H, m, ArC3-H, ArC4-H and ArC5-H, both diastereoisomers), 7.65 - 7.69 (2H, t, $J = 7.1$, ArC2-H and ArC6-H).

δ_C (150 MHz): 40.3 (C4, one diastereoisomer), 40.6 (C4, one diastereoisomer), 61.5 (PhS(O)CH₂, one diastereoisomer), 64.4 (PhS(O)CH₂, one diastereoisomer), 72.4 (C3, one diastereoisomer), 72.5 (C3, one diastereoisomer), 72.8 (C2, one diastereoisomer), 73.4 (C2, one diastereoisomer), 76.2 (C5, one diastereoisomer), 77.1 (C5, one diastereoisomer), 123.9 (ArC2 and ArC6, both diastereoisomers), 123.9 (ArC3 and ArC5, both diastereoisomers), 129.4 (ArC4, both diastereoisomers), 131.1 (ArC1, one diastereoisomer), 131.3 (ArC1, one diastereoisomer).

***anti*-(±)-3-Hydroxy-5-(benzenesulfinylmethyl)tetrahydrofuran (84)**



(±)-*anti*-5-Benzenesulphenylmethyl-3-hydroxy-tetrahydrofuran (50 mg, 0.24 mmol) was dissolved in methanol (1 mL). Oxone (25 mg, 0.16 mmol) in water (1 mL) was added to the stirring solution and the reaction was stirred overnight. 10% w/v HCl (2 mL) was added to the reaction.

The reaction was extracted with diethylether (2 × 10 mL). The organic layers were combined, washed with brine, dried and concentrated. Flash column chromatography, using 40 - 80% ethyl acetate in hexane as eluent, yielded the 2 diastereoisomers as clear oils which could not be separated.

Yield: = 39 mg, 72 %.

(NaCl): 3375, 2917, 2847, 1445, 1215, 1191, 1180, 1140, 1086, 1039, 748, 691 cm⁻¹.

M.S: m/z 227 (M+H⁺, 100%).

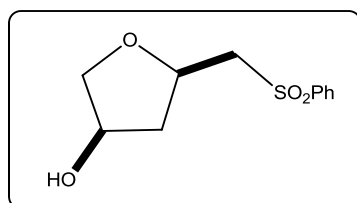
HRMS calculated for C₁₁H₁₅O₃S [M+H]⁺: 227.0742; found 227.0725.

δ_H (600 MHz): 1.75 (1H, overlapping ddd appears as 7 lines, $J = 13.8$, 8.9 and 4.3, C4-H, *anti* to OH, one diastereoisomer), 1.82 (1H, overlapping ddd appears as 7 lines, $J = 14.0$, 9.2 and 5.3, C4-H, *anti* to OH, one diastereoisomer), 2.03 (1H, overlapping ddd appears as 7 lines, $J = 13.8$, 8.9 and 4.8, C4-H, *syn* to OH, one diastereoisomer), 2.11 (1H, overlapping ddd appears as 7 lines, $J = 14.0$, 8.9 and 5.1, C4-H, *syn* to OH, one diastereoisomer), 2.86 (1H, dd, $J = 12.1$ and 9.0, H_A of ABX, PhS(O)CH₂ one diastereoisomer), 2.95 [1H, dd, $J = 14.3$ and 8.4, H_A of ABX, PhS(O)CH₂ one

diastereoisomer], 3.22 [1H, dd, $J = 12.1$ and 6.2 , H_B of ABX, PhS(O)CH_2 , one diastereoisomer], 3.23 [1H, dd, $J = 14.3$ and 6.1 , H_B of ABX, PhS(O)CH_2 , one diastereoisomer], 3.68 (1H, overlapping dd appears as d, H_A of ABX, $J = 10.6$, C2-H, *syn* to OH, one diastereoisomer), 3.75 (1H, overlapping dd appears as d, H_A of ABX, $J = 10.3$, C2-H, *syn* to OH, one diastereoisomer), 3.81 (1H, d, H_B of ABX, $J = 10.6$, C2-H, *anti* to OH, one diastereoisomer), 3.93 (1H, dd, H_B of ABX, $J = 10.1$ and 4.8 , C2-H, *anti* to OH, one diastereoisomer), 4.07 - 4.11 (1H, m, H_X of ABX, C5-H, one diastereoisomer), 4.28 - 4.32 (1H, m, H_X of ABX, C5-H, one diastereoisomer), 4.54 - 4.58 (1H, m, H_X of ABX, C3-H, one diastereoisomer), 4.68 - 4.73 (1H, m, H_X of ABX, C3-H, one diastereoisomer), 7.49 - 7.58 (6H, m, ArC3-H, ArC4-H and ArC5-H, both diastereoisomers), 7.65 - 7.69 (4H, m, ArC2-H and ArC6-H).

δ_c (150 MHz): 41.3 (C4, one diastereoisomer), 41.8 (C4, one diastereoisomer), 60.9 (PhS(O)CH_2 , one diastereoisomer), 62.2 (PhS(O)CH_2 , one diastereoisomer), 71.8 (C3, one diastereoisomer), 72.3 (C3, one diastereoisomer), 72.4 (C5, one diastereoisomer), 73.0 (C5, one diastereoisomer), 74.6 (C2, one diastereoisomer), 77.8 (C2, one diastereoisomer), 123.8 (ArC2 and ArC-6, both diastereoisomers), 123.3 (ArC3 and ArC5, both diastereoisomers), 127.1 (ArC4, both diastereoisomers), 130.2 (ArC1, one diastereoisomer), 130.3 (ArC1, one diastereoisomer).

***syn*-(±)-3-Hydroxy-5-(benzenesulfonylmethyl)tetrahydrofuran (85)**



(±)-*syn*-5-Benzenesulphenylmethyl-3-hydroxy-tetrahydrofuran (50 mg, 0.24 mmol) was dissolved in methanol (1 mL) and Oxone[®] (72 mg, 0.45 mmol) in water (1 mL) was added to the stirring solution. The reaction was stirred overnight. 10% w/v HCl (2 mL) was then

added to the reaction and the mixture was extracted with diethylether (2 × 10 mL). The organic layers were combined, washed with brine, dried and concentrated under reduced pressure. Flash column chromatography, using 40 - 80% ethyl acetate in hexane as eluent, yielded the product as clear oil.

Yield: = 41 mg, 76 %.

δ_H (600 MHz): 1.96 (1H, dd, $J = 13.8$ and 3.2 , C4-H, *syn* to OH), 2.34 (1H, m, C4-H, *anti* to OH), 3.45 (1H, dd, H_A of ABX, $J = 15.0$ and 6.9 , PhSO_2CH_2), 3.62 (1H, dd, H_B of ABX, $J = 15.0$ and 6.9 , PhSO_2CH_2), 3.72 (1H, dd, H_A of ABX, $J = 9.6$ and 4.5 , C2-H, *anti* to

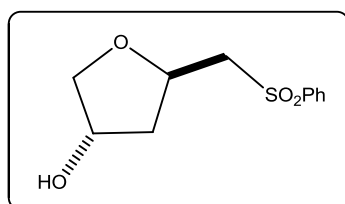
OH), 3.79 (1H, d, $J = 9.6$, H_B of ABX, C2-**H**, *syn* to OH), 4.40 - 4.42 (1H, m, H_X of ABX, C5-**H**), 4.48 - 4.50 (1H, m, H_X of ABX, C3-**H**), 7.57 (2H, t, $J = 7.6$, ArC3-**H** and ArC5-**H**), 7.65 (1H, t, $J = 7.6$, ArC4-**H**), 7.94 (2H, d, $J = 7.3$, ArC2-**H** and ArC6-**H**).

δ_C (150 MHz): 39.5 (**C**-4), 60.2 (PhSO₂CH₂), 71.1 (**C**3), 71.7 (**C**5), 74.9 (**C**2), 127.0 (Ar**C**2 and Ar**C**6), 128.2 (Ar**C**3 and Ar**C**5), 132.7 (Ar**C**4), 139.0 (Ar**C**1).

M.S: m/z : 243 ($M+H^+$, 100%), 225.

HRMS calculated for C₁₁H₁₅O₄ [$M+H$]⁺: 243.0691.1154; found 243.0681.

***anti*-(±)-3-Hydroxy-5-(benzenesulfonylmethyl)tetrahydrofuran (86)**



(±)-*anti*-5-Benzenesulphenylmethyl-3-hydroxy-tetrahydrofuran (50 mg, 0.24 mmol) was dissolved in methanol (1 mL) and Oxone® (72 mg, 0.45 mmol) in water (1 mL) was added to the stirring solution. The reaction was stirred overnight. 10% w/v HCl (2 mL) was then added to

the reaction and the mixture was extracted with diethylether (2 × 10 mL). The organic layers were combined, washed with brine, dried and concentrated under reduced pressure. Flash column chromatography using 40 - 80% ethyl acetate in hexane as eluent, yielded the product as clear oil.

Yield: = 39 mg, 72 %.

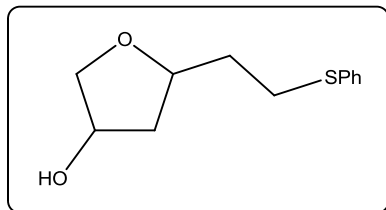
δ_H (600 MHz): 1.82 (1H, overlapping ddd appears as 7 lines, $J = 13.9$, 9.6 and 5.5, C4-**H**, *anti* to OH), 2.20 (1H, overlapping ddd, $J = 13.9$ and 6.1, C4-**H**, *syn* to OH), 3.25 (1H, dd, $J = 14.2$ and 6.1, H_A of ABX, PhSO₂CH₂), 3.48 (1H, dd, $J = 14.2$ and 6.6, H_B of ABX, PhSO₂CH₂), 3.67 (1H, d, H_A of ABX, $J = 10.1$, C2-**H**, *syn* to OH), 4.04 (1H, dd, H_B of ABX, $J = 10.1$ and 4.4, C2-**H**, *anti* to OH), 4.50 - 4.54 (2H, m, H_X of ABX, C3-**H** and C5-**H**), 7.57 (2H, t, $J = 8.1$, ArC3-**H** and ArC5-**H**), 7.66 (1H, t, $J = 7.0$, ArC4-**H**), 7.94 (2H, t, $J = 7.9$, ArC2-**H** and ArC6-**H**).

δ_C (150 MHz): 40.8 (**C**-4), 59.9 (PhSO₂CH₂), 71.0 (**C**-3 and **C**-5), 74.6 (**C**-2), 127.1 (Ar**C**-2 and Ar**C**-6), 128.2 (Ar**C**-3 and Ar**C**-5), 132.8 (Ar**C**-4), 138.7 (Ar**C**-1).

M.S: m/z : 243 ($M+H^+$, 100%), 225.

HRMS calculated for C₁₁H₁₅O₄ [$M+H$]⁺: 243.0691.1154; found 243.0669.

(±)-5-(2-Benzenesulphenylethyl)-3-hydroxy-tetrahydrofuran (93)



(±)-5-(2-Benzenesulphenylethyl)-3(2*H*)-furanone (0.10 g, 0.45 mmol) was dissolved in methanol (5 mL). Sodium borohydride (26 mg, 0.68 mmol) in water (1 mL) was added to the stirring solution. The reaction was stirred overnight before 10% w/v HCl (5 mL) was added

to the reaction. The reaction mixture was extracted with diethylether (2 × 20 mL). The organic layers were combined, washed with brine, dried and concentrated under reduced pressure. Flash column chromatography, using 10 - 30% ethyl acetate in hexane as eluent, yielded a mixture of 2 diastereoisomers as a clear oil (d.r. = 2:1).

Yield = 0.069 g, 70%.

ν_{\max} (NaCl): 3410, 2931, 2583, 1480, 1483, 1089, 739, 691 cm^{-1} .

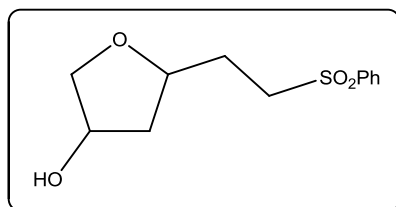
δ_{H} (600 MHz): 1.45 (1H, overlapping ddd appears as qd, $J = 13.8$ and 2.8 , C4-**H**, major diastereoisomer), 1.67 (1H, overlapping ddd 7 lines, $J = 14.6$, 9.6 and 5.5 , C4-**H**, minor diastereoisomer), 1.71 - 1.85 (2H, m, PhSCH₂CH₂, minor diastereoisomer), 1.90 - 1.99 (3H, m, PhSCH₂CH₂ of major diastereoisomer and C4-**H** of minor diastereoisomer), 2.25 (1H, overlapping ddd appears as 5 lines, $J = 13.8$ and 7.4 , C4-**H**, major diastereoisomer), 2.85 - 2.94 (2H, overlapping ddd appears as multiplet, H_A of ABXX', both diastereoisomers, PhSCH₂), 2.98 - 3.03 (2H, m, H_B of ABXX', both diastereoisomers, PhSCH₂), 3.61 (2H, m, H_A of ABX, C2-**H**, both diastereoisomers), 3.75 (2H, m, H_B of ABX, C2-**H**, both diastereoisomers), 3.87 - 3.92 (1H, m, H_X of ABX, C5-**H**, major diastereoisomer), 4.14 - 4.19 (1H, m, H_X of ABX, C5-**H**, minor diastereoisomer), 4.34 - 4.438 (1H, m, H_X of ABX, C3-**H**, major diastereoisomer), 4.38 - 4.41 (1H, m, H_X of ABX, C3-**H**, minor diastereoisomer), 7.16 (1H, t, $J = 7.1$, ArC4-**H**, both diastereoisomers), 7.27 (2H, t, $J = 7.4$, ArC3-**H** and ArC5-**H**, both diastereoisomers), 7.33 (2H, d $J = 7.4$, ArC2-**H** and ArC6-**H**, both diastereoisomers).

δ_{C} (150 MHz): 29.2 (PhSCH₂, both diastereoisomer), 33.9 (PhSCH₂CH₂, minor diastereoisomer), 34.4 (PhSCH₂CH₂, major diastereoisomer), 40.0 (C4, major diastereoisomer), 40.1 (C4, minor diastereoisomer), 71.3 (C3, major diastereoisomer), 71.4 (C3, minor diastereoisomer), 74.2 (C2, minor diastereoisomer), 74.4 (C2, minor diastereoisomer), 75.7 (C5, minor diastereoisomer), 76.5 (C5, major diastereoisomer), 124.9 (ArC4, both diastereoisomers), 127.9 (ArC3 and ArC5, both diastereoisomers), 128.0 (ArC2 and ArC6, both diastereoisomers), 135.47 (ArC1, both diastereoisomers).

M.S: m/z : 225 (M+H⁺, 100%).

HRMS calculated for $C_{12}H_{17}O_2S$ $[M+H]^+$: 225.0947; found 225.0949.

(±)-3-Hydroxy-5-(2-phenylsulfonyl-ethyl)-tetrahydrofuran (94)



(±)-5-(2-Benzenesulfonyl-ethyl)-3(2*H*)-furanone (0.10 g, 0.42 mmol) was dissolved in anhydrous THF (10 mL). Lithium-tri-(*tert*-butoxy)-aluminium hydride (0.20 g, 0.84 mmol) was added to the stirring solution. The reaction was stirred overnight before 10% w/v HCl (10 mL) was

added to the reaction. The mixture was extracted with diethylether (2 × 20 mL). The organic layers were combined, washed with brine, dried and concentrated under reduced pressure. Flash column chromatography, using 10% ethyl acetate in hexane as eluent, yielded a clear gum as a mixture of diastereoisomers (d.r. = 3.2).

Yield = 0.022 g, 23%.

ν_{\max} (NaCl): 3424, 2929, 2853, 1447, 1305, 1143, 1085, 745, 689 cm^{-1} .

δ_{H} (600 MHz): 1.55 (1H, dddd, $J = 13.8, 6.3, 2.5$ and 1.4 , C4-**H**, major diastereoisomer), 1.64 (1H, ddd, $J = 15.0, 9.5$ and 5.5 , C4-**H**, minor diastereoisomer), 1.82 - 1.89 (1H, m, C4-**H**, minor diastereoisomer), 1.98 - 2.11 (2H, m, $\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$, both diastereoisomers), 2.33 (1H, overlapping ddd, $J = 13.8, 7.9$, and 6.7 , C4-**H**, major diastereoisomer), 3.12 - 3.21 (1H, ddd appears as multiplet, $\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$, both diastereoisomers), 3.29 - 3.38 (1H, ddd appears as multiplet, $\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$, both diastereoisomers), 3.66 (2H, dd, H_{A} of ABX, $J = 10.0$ and 4.2 , C2-**H**, both diastereoisomers), 3.78 (2H, overlapping dd appears as d, $J = 10.0$, C2-**H**, both diastereoisomers), 3.89 - 3.94 (1H, m C5-**H**, H_{X} of ABX, major diastereoisomer), 4.11 - 4.16 (1H, m, H_{X} of ABX, C5-**H**, minor diastereoisomer), 4.44 - 4.47 (1H, m C3-**H**, major diastereoisomer), 4.47 - 4.51 (1H, m C3-**H**, minor diastereoisomer), 7.56 - 7.58 (2H, m, ArC3-**H** and ArC5-**H**, both diastereoisomers), 7.64 - 7.68 (1H, m, ArC4-**H**, both diastereoisomers), 7.92 (2H, $J = 7.0$, ArC2-**H** and ArC6-**H**, both diastereoisomer),

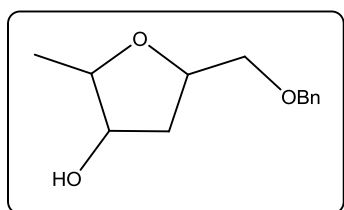
δ_{C} (150 MHz): 28.2 ($\text{PhSO}_2\text{CH}_2\text{CH}_2$, minor diastereoisomer), 28.8 ($\text{PhSO}_2\text{CH}_2\text{CH}_2$, major diastereoisomer), 40.8 (**C4**, major diastereoisomer), 41.4 (**C4**, minor diastereoisomer), 53.3 ($\text{PhSO}_2\text{CH}_2\text{CH}_2$, major diastereoisomer), 53.5 ($\text{PhSO}_2\text{CH}_2\text{CH}_2$, minor diastereoisomer), 72.2 (**C3**, major diastereoisomer), 72.4 (**C3**, minor diastereoisomer), 75.3 (**C2**, minor diastereoisomer) 75.6 (**C2**, major diastereoisomer), 75.9 (**C5**, minor

diastereoisomer), 76.8 (**C5**, major diastereoisomer), 128.0 (Ar**C**-3 and Ar**C5**, both diastereoisomers), 129.4 (Ar**C4**, both diastereoisomers) 133.7 (Ar**C2** and Ar**C6**, both diastereoisomers), 139.1 Ar(**C1**, both diastereoisomers).

M.S: m/z : 257 ($M+H^+$, 100%), 245, 241.

HRMS calculated for $C_{12}H_{17}O_2S$ $[M+H]^+$: 257.0848; found 257.0858.

(±)-5-Benzyloxymethyl-3-hydroxy-2-methyltetrahydrofuran



(±)-5-Benzyloxymethyl-2-methyl-4,5-dihydro-3(2*H*)-furanone (0.15g, 0.68 mmol) was added to anhydrous THF (15 mL) and cooled to -80 °C. L-Selectride® (1M solution in hexane) (4.09 mL, 4.09 mmol) was added *via* glass syringe over 30 min. The reaction was stirred at -80 °C for a further

6 h. The reaction was allowed to come to room temperature overnight before 10% HCl (10 mL) was added to the reaction. The mixture was extracted with diethylether (4 × 20 mL). The organic layers were combined, washed with brine, dried and concentrated under reduced pressure. Flash column chromatography, using 5 - 20% ethyl acetate in hexane as eluent, isolated two diastereoisomers.

Yield: (Major diastereoisomer, less polar fraction) = 0.049 g, 33%.

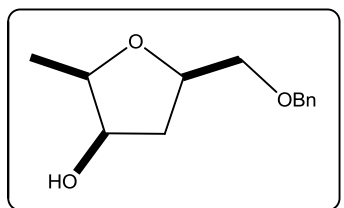
Yield: (Minor diastereoisomer, more polar fraction) = 0.042 g, 28%.

ν_{max} (NaCl): 3434, 2933, 2867, 1454, 1370, 1271, 1091, 740, 699 cm^{-1} .

M.S: m/z : 223 ($M+H^+$, 100%).

HRMS calculated for $C_{13}H_{19}O_3$ $[M+H]^+$: 223.1334 ; found 223.1342.

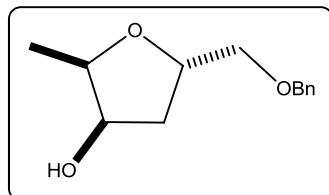
(±)-2*R**,3*R**,5*R**-5-Benzyloxymethyl-3-hydroxy-2-methyltetrahydrofuran (**95**)²³



δ_H (600 MHz) (Major diastereoisomer, C2-H, C3-H and C5-H are all *syn*): 1.28 (3H, d, J = 6.3, C2-CH₃), 1.94 (1H, dd, J = 14.6 and 2.9, C4-H, *syn* to OH), 2.35 (1H, overlapping ddd, J = 14.6, 10.5 and 5.3, C4-H, *anti* to OH), 3.41 (1H, dd, H_A of ABX, J = 10.2 and 2.0, H of CH₂OBn), 3.67 (1H, broad doublet, J = 11.1, OH), 3.70 (1H, dd, H_B of ABX, J = 10.2 and 2.0, H of CH₂OBn), 3.82 (1H, overlapping qd, J = 6.2 and 2.3, C2-H), 3.89 - 3.93 (1H, overlapping ddd, J = 10.2.

5.2 and 2.4, C3-H), 4.20 – 4.22 (1H, m, H_X of ABX, C5-H), 4.54 (1H, d, H_A of AB, *J* = 11.9, CH₂Ph), 4.70 (1H, d, H_B of AB, *J* = 11.9, CH₂Ph), 7.28-7.34 (5H, m, ArH).
 δ_C (150 MHz): 14.2 (C2-CH₃), 37.5 (C4), 71.8 (BnOCH₂), 72.7 (C3), 73.7 (PhCH₂), 76.2 (C5), 80.1 (C2), 127.9, 128.0, 128.6 (All ArC), 137.21 (ArC1).

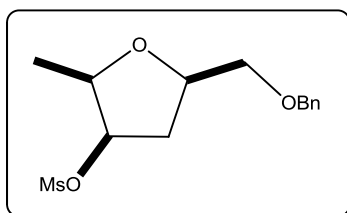
(±)-2*R,3*R**,5*S**-5-Benzyloxymethyl-3-hydroxy-2-methyltetrahydrofuran (96)**



δ_H (600 MHz) (Major diastereoisomer, C2-H, C3-H are *syn* and C5-H is *anti*): 1.26 (3H, d, *J* = 6.4, C2-CH₃), 1.99 (1H, overlapping ddd appears as 7 lines, *J* = 13.2, 8.8 and 4.6, C4-H, *anti* to OH), 2.13 (1H, dd, *J* = 13.2 and 6.7, C4-H, *syn* to OH), 3.48 (1H, dd, H_A of ABX, *J* = 10.2 and 5.5, CH₂OBn), 3.51 (1H, dd, H_B of ABX, *J* = 10.2 and 3.8, CH₂OBn), 4.03 (1H, qd, *J* = 6.4 and 2.9, C2-H), 4.16 - 4.19 (1H, m, C3-H), 4.40 - 4.45 (1H, m, H_X of ABX, C5-H), 4.58 (2H, d, *J* = 1.1, CH₂Ph), 7.26 - 7.34 (5H, m, ArH).
 δ_C (150 MHz): 14.2 (C2-CH₃), 37.9 (C4), 72.7 (BnOCH₂), 73.3 (CH₂Ph), 74.1 (C3), 76.0 (C5), 78.2 (C2), 127.6, 127.7, 128.4 (All ArC), 138.3 (ArC1).
m/z: 223 (M+H⁺, 100%), 221, 132.

3.2.12 Towards a Synthesis of Racemic Muscarine

(±)-5-(Benzyloxymethyl)-3-methanesulfonyloxy-2-methyl-tetrahydrofuran (97)



(±)-2*R**,3*R**,5*R*-5-(2-Benzyloxymethyl)-3-hydroxy-2-methyl-tetrahydrofuran (0.178 g, 0.80 mmol) was added to pyridine (6 mL) and the mixture was cooled to 0 °C. Methanesulfonyl chloride (0.101 g, 0.88 mmol) was added *via* a glass syringe to the reaction. The reaction was stirred for 3 h at 0 °C. Water (6 mL) was then added and the solution was extracted with DCM (3 × 20 mL). The organic layers were combined and washed with 10% HCl (3 × 20 mL) and water (3 × 20 mL). The organic layer was dried and concentrated under reduced pressure to give a clear oil.

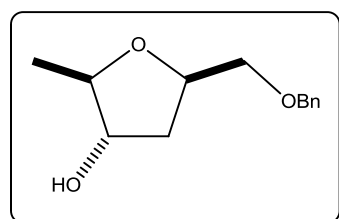
Yield = 198 mg, 82%.

ν_{\max} (NaCl): 2934, 2860, 1354, 1174, 1103, 933, 739, 698 cm⁻¹.

δ_{H} (600 MHz): 1.35 (3H, d, J = 6.3, C2-CH₃), 2.06 (1H, ddd, J = 14.7, 6.3 and 1.4, C4-H, *syn* to OMs), 2.46 (1H, ddd, J = 14.7, 8.3 and 6.4, C4-H, *anti* to OMs), 2.96 (3H, s, SO₃CH₃), 3.53 (1H, dd, H_A of ABX, J = 10.2 and 4.6, H of CH₂OBn), 3.60 (1H, dd, H_B of ABX, J = 10.2 and 6.5, H of CH₂OBn), 3.53 (1H, qd, J = 6.4 and 3.8, C2-H), 4.14-4.16 (1H, m, H_X of ABX, C5-H), 4.56 (1H, d, H_A of AB, J = 12.1, CH₂Ph), 4.62 (1H, d, H_B of AB, J = 12.1, CH₂Ph), 5.06 – 5.09 (1H, m, C3-H) 7.26-7.36 (5H, m, ArH).

δ_{C} (150 MHz): 15.5 (C2-CH₃), 37.7 (C4), 38.5 (SO₃CH₃), 72.7 (BnOCH₂), 74.1 (PhCH₂), 77.3 (C5), 78.6 (C2), 81.8 (C3), 127.7, 127.9, 128.4 (All ArC), 138.0 (ArC1).

(±)-5-Benzyloxymethyl-3-hydroxy-2-methyltetrahydrofuran (98)²⁴



A flame dried 3-necked round bottom flask was charged with a solution of potassium superoxide (233 mg, 3.29 mmol) in anhydrous DMSO (5 mL). 18-Crown-6 (176 mg, 0.66 mmol) was added and the solution was stirred for 5 min. A solution of (±)-2*R**,3*S**,5*R*-5-(benzyloxymethyl)-3-methanesulfonyloxy-2-methyl-tetrahydrofuran (198 mg, 0.66 mmol) in DMSO (4 mL) was subsequently introduced and the reaction mixture was stirred for a further 3 h. Brine (15 mL) was added and the mixture was extracted with diethylether (3 × 30 mL), washed with water (2 × 20 mL), dried and concentrated under reduced pressure. Flash column

chromatography, using 30% ethyl acetate in hexane as eluent, yielded the title compound as a clear oil.

Yield = 85 mg, 56%.

ν_{max} (NaCl): 3422, 2928, 2866, 1454, 1099, 738, 698 cm^{-1} .

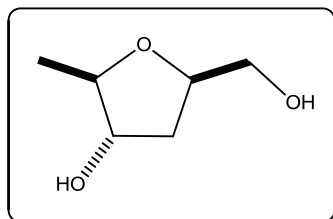
δ_{H} (600 MHz): 1.24 (3H, d, $J = 6.4$, C2-CH₃), 1.87 (1H, ddd, $J = 13.1$, 6.2, and 1.9, C4-H, *anti* to OH), 1.98 (1H, ddd, $J = 13.1$, 9.0 and 6.7, C4-H, *syn* to OH), 3.50 (1H, dd, $J = 10.2$ and 5.9, H_A of ABX, CH₂OBn), 3.54 (1H, dd, $J = 10.2$ and 3.7, H_B of ABX, CH₂OBn), 3.87 (1H, qd, $J = 6.4$ and 2.6, C2-H), 3.98 - 4.00 (1H, m, H_X of ABX, C5-H), 4.30 - 4.34 (1H, m, C3-H), 4.56 (2H, d, $J = 2.3$, CH₂Ph), 7.27 - 7.35 (5H, m, ArH).

δ_{C} (150 MHz): 19.6 (C2-CH₃), 37.2 (C4), 72.7 (BnOCH₂), 73.4 (PhCH₂), 77.0 (C3), 77.4 (C5), 82.7 (C2), 127.6, 127.7, 128.4 (All ArC), 138.3 (ArC1).

M.S: m/z : 223 (M+H⁺), 209, 145, 132, 131 (100%), 105, 91.

HRMS calculated for C₁₃H₁₉O₃ [M+H]⁺: 223.1334 ; found 223.1336.

(±)-5-Hydroxymethyl-3-hydroxy-2-methyl-tetrahydrofuran (99)²⁵



(±)-2*R**,3*S**,5*R*-5-Benzyloxymethyl-3-hydroxy-2-methyltetrahydrofuran (74 mg, 0.56 mmol) was added to methanol (25 mL) in a Paar hydrogenation flask. Pd(OH)₂ (10% on carbon) (11 mg) was then added. The reaction was placed under a hydrogen atmosphere of 35 psi. The reaction

was shaken for 15 h, after which Celite[®] (2 g) was added and the reaction was sonicated for 15 min. The mixture was then filtered through Celite[®], washed with methanol (50 mL) and concentrated under reduced pressure to yield a clear oil.

Yield = 11 mg, 25%.

ν_{max} (NaCl): 3368, 2929, 2875. 1651, 1613, 1454, 1374, 1085, 1039 cm^{-1} .

δ_{H} (600 MHz): 1.23 (3H, d, $J = 6.5$, C5-CH₃), 1.84 (1H, ddd, $J = 14.3$, 6.4 and 3.0, C4-H, *anti* to OH), 2.04 (1H, ddd, $J = 14.3$, 9.1 and 6.4, C4-H, *syn* to OH), 3.51 (1H, dd, H_A of ABX, $J = 13.3$ and 2.9, CH₂OH), 3.77 (1H, dd, H_B of ABX, $J = 13.3$ and 3.0, CH₂OH), 3.91 (1H, qd, $J = 6.5$ and 3.5, C2-H), 3.98-4.01 (1H, m, C3-H), 4.24 - 4.28 (1H, m, H_X of ABX, C5-H).

δ_{C} (150 MHz): 19.6 (C5-CH₃), 35.9 (C4), 64.5 (CH₂OH), 77.5 (C5), 78.4 (C3), 82.6 (C2).

3.2.13 Synthesis of Enantioenriched Desmethylnuscarines and its Analogues

Reduction of (±)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran

Standard Ridley method

Baker's yeast (*Saccharomyces Cerevisiae*, type II) (10 g) and sucrose (10 g) were suspended in tap water (60 mL) in a 250 mL conical flask. Two drops of antifoam 289 were added and the suspension was allowed to incubate at 29 °C for 30 min. A solution of (±)-5-benzyloxymethyl-4,5-dihydro-3(2*H*)-furanone (0.1 g) in DMSO (1 mL) was added over 1 min to the fermenting yeast suspension and the reaction agitated for a further 24 h. The mixture was then filtered through a bed of Celite®. The filter cake was washed with distilled water (50 mL) and ethyl acetate (25 mL). The cake was then removed into a conical flask and sonicated with ethyl acetate (75 mL) for 20 min and filtered from the ethyl acetate solution. The combined organic extracts were washed with brine (3 × 100 mL). The combined aqueous layers were saturated with NaCl and extracted with ethyl acetate (3 × 75 mL). The combined organic layers were dried and concentrated under reduced pressure. Flash column chromatography, using 5 - 40% ethyl acetate in hexane as eluent, yielded two diastereoisomers as clear oils. These were identified as: (-)-(3*S*, 5*S*)-3-hydroxy-5-benzyloxymethyltetrahydrofuran, less polar fraction, Yield: 32 mg, 33% and (+)-(3*S*, 5*R*)-3-hydroxy-5-benzyloxymethyltetrahydrofuran, more polar fraction, Yield: 29 mg, 30%.

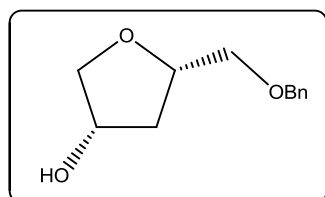
Modified Method.

Baker's yeast (*Saccharomyces Cerevisiae*, type II) (10 g) and sucrose (10 g) were suspended in tap water (60 mL) in a 250 mL conical flask. Two drops of antifoam 289 were added and the suspension was allowed to incubate at 29°C for 30 min. A solution of (±)-5-benzyloxymethyl-4,5-dihydro-3(2*H*)-furanone (0.1 g) in DMSO (1 mL) was added over 1 min to the fermenting yeast suspension and the reaction agitated for a further 24 hr. Celite® (10 g) was then added to the reaction along with THF (60 mL) and the mixture was stirred vigorously for 30 min. The reaction was filtered through a bed of Celite®. The filter cake was washed with water (50 mL) and THF (50 mL). The filter cake was removed and transferred to a conical flask along with THF (100 mL) and sonicated for 30 min and filtered. The filtrates were combined and the THF was removed *in vacuo*, the aqueous

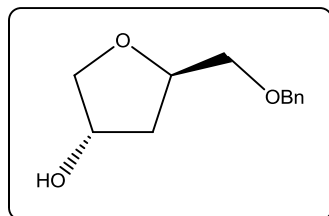
layer was extracted with diethylether (3 × 60 mL). The combined organic extracts were washed with brine (100 mL) and were dried and concentrated under reduced pressure. Flash column chromatography, using 5 - 40% ethyl acetate in hexane as eluent, yielded two diastereoisomers as clear oils which was identified as:

(-)-(3*S*,5*S*)-3-hydroxy-5-benzyloxymethyltetrahydrofuran, less polar fraction, Yield: 44 mg, 45%

(+)-(3*S*,5*R*)-3-hydroxy-5-benzyloxymethyltetrahydrofuran, more polar fraction Yield: 42 mg, 43%.



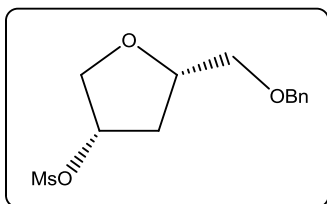
(-)-(3*S*,5*S*)-3-hydroxy-5-benzyloxymethyltetrahydrofuran (100)²⁰, first fraction, less polar.
 $[\alpha]_D^{20} = -19.9^\circ$ ($c=1.0$, CHCl_3), $[\text{lit}^{20}. +119^\circ$ ($c=0.94$, CHCl_3)],
 66% ee.



(+)-(3*S*,5*R*)-3-hydroxy-5-benzyloxymethyltetrahydrofuran (101)²⁰, second fraction, more polar.
 $[\alpha]_D^{20} = +17.7^\circ$ ($c=1.0$, CHCl_3), $[\text{lit}^{20}. +36^\circ$ ($c=0.78$, CHCl_3)],
 94% ee.

The spectroscopic prosperities (¹H and ¹³C NMR spectra) of both compounds, **90** and **91**, corresponded directly with those of the compounds in racemic form.

(+)-(3S,5S)-5-(Benzyloxymethyl)-3-(methanesulfonyl)-tetrahydrofuran (114)²⁰



Method A (MsCl in pyridine)

To (-)-(3S,5S)-3-hydroxy-5-benzyloxymethyltetrahydrofuran (0.40 g, 1.92 mmol) in a round bottom flask, pyridine (20 mL) was added and the solution was cooled to 0 °C. Methanesulfonyl chloride (0.17 mL, 2.12 mmol) was added *via* a glass syringe to the reaction. The reaction was stirred for 3 h at 0 °C. Water (50 mL) was added and the solution was extracted with DCM (3 × 60 mL). The organic layers were combined, washed with 10% w/v HCl (3 × 50 mL) and water (3 × 50 mL). The organic phase was dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as eluent, yielded the title product as a clear oil.

Yield = 0.401 g, 74%.

Method B. (MsCl with triethylamine)

(-)-(3S,5S)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran (0.85 g, 4.09 mmol) was added to DCM (40 mL) and the solution was cooled to 0°C. Triethylamine (0.54 g, 5.32 mmol) was added dropwise to the solution and the mixture was stirred for 15 min at 0°C. Methanesulfonyl chloride (0.44 mL, 5.32 mmol) was then added *via* a glass syringe to the reaction over 15 min. The reaction was stirred for 2 h at 0°C. Water (30 mL) was then added and the layers were separated. The aqueous layer was extracted with DCM (3 × 40 mL). The organic layers were combined, washed with 10% w/v HCl (3 × 30 mL) and water (3 × 30 mL). The organic was dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as eluent, yielded the title product as a clear oil.

Yield = 0.96 g, 83%.

$[\alpha]_D^{20} = +8.15^\circ$ (c=1.0, CHCl₃), [lit²⁰. $+5.3^\circ$ (c=1.0, CHCl₃)],

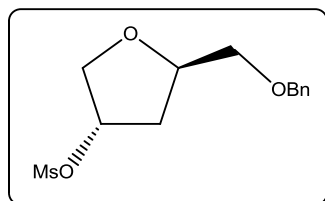
ν_{\max} (NaCl): 2926, 2859, 1356, 1173, 1088, 954, 898, 718, 698 cm⁻¹.

δ_H (600 MHz): 2.06 (1H, overlapping dddd, $J = 14.6, 6.5, 2.40$ and 1.6 , C4-**H** *syn* to SO₂CH₃), 2.41 (1H, overlapping ddd appears as 7 lines, $J = 14.7, 8.0$ and 7.0 , C4-**H** *anti*

to SO₂CH₃), 2.97 (3H, s, CH₃SO₂), 3.56 (1H, dd, *J* = 10.1 and 4.5, H_A of ABX, CH₂OBn), 3.59 (1H, dd, *J* = 10.21 and 6.3, H_B of ABX, CH₂OBn), 3.85 (1H, dd, *J* = 11.2 and 4.4, H_A of ABX, C2-H *anti* to SO₂CH₃), 4.13-4.17 (1H, m, H_X of ABX, C5-H), 4.18 (1H, d, *J* = 11.2, H_B of ABX, C2-H *syn* to SO₂CH₃), 4.57 (1H, d, *J* = 12.0, H_A of AB, H of CH₂Ph), 4.61 (1H, d, *J* = 12.0, H_B of AB, H of CH₂Ph), 5.26-5.29 (1H, m, H_X of ABX, C3-H), 7.26 - 7.36 (5H, m, ArH).

δ_C (150 MHz): 35.3 (C4), 38.6 (SO₂CH₃), 71.8 (CH₂OBn), 73.1 (C2), 73.5 (CH₂Ph), 77.7 (C5), 80.2 (C3), 127.7, 127.8, 128.45 (All ArC), 138.0 (ArC1).

(+)-(3*S*, 5*R*)-5-(Benzyloxymethyl)-3-(methanesulfonyl)-tetrahydrofuran²⁰



Method A. (MsCl in pyridine)

(+)-(3*S*,5*R*)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran (0.20 g, 0.96 mmol) was added to pyridine (8 mL) and the solution was cooled to 0°C. Methanesulfonyl chloride (0.083 mL, 1.06 mmol) was added *via* a glass syringe to the reaction. The reaction was stirred for 3 h at 0°C. Water (6 mL) was added and the solution extracted with DCM (3 × 20 mL). The organic layers were combined, washed with 10% w/v HCl aqueous HCl (3 × 20 mL) and water (3 × 20 mL). The organic phase was dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as eluent, yielded the title product as a clear oil.

Yield = 0.190 g, 69%.

Method B. (MsCl with triethylamine)

(-)-(3*S*,5*S*)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran (1.00 g, 4.80 mmol) was added to DCM (50 mL) and the solution was cooled to 0°C. Triethylamine (0.54 g, 5.28 mmol) was added dropwise and the mixture was stirred for 15 min at 0°C. Methanesulfonyl chloride (0.61 mL, 5.28 mmol) was then added *via* a glass syringe to the reaction over

15 min. The reaction was stirred for 2 h at 0°C. Water (40 mL) was then added and the layers were separated. The aqueous layer was extracted with DCM (3 × 50 mL). The organic layers were combined, washed with 10% w/v HCl (3 × 40 mL) and water (3 × 40 mL). The organic phase was dried and concentrated under reduced pressure. Flash column chromatography, using 30% ethyl acetate in hexane as eluent, yielded the product as a clear oil.

Yield = 1.17 g, 86%.

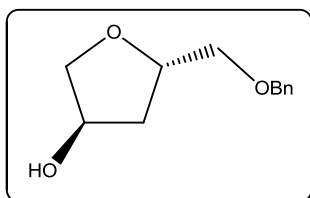
$[\alpha]_D^{20} = -13.75^\circ$ (c=1.0, CHCl₃) [lit.²⁰ -17.1° (c=1.0, CHCl₃)],,

ν_{\max} (NaCl): 2928, 2866, 1454, 1099, 738, 698 cm⁻¹.

δ_H (600 MHz): 2.11 (1H, overlapping dddd appears as 7 lines, $J = 14.3, 8.9$ and 5.9 , C4-**H** *anti* to SO₂CH₃), 2.29 (1H, dd, $J = 14.3$ and 6.6 , C4-**H** *syn* to SO₂CH₃), 3.03 (3H, s, CH₃SO₂), 3.50 (1H, dd, $J = 10.1$ and 4.9 , H_A of ABX, C2-**H**), 3.61 (1H, dd, $J = 10.1$ and 3.6 , H_B of ABX, C2-**H**), 4.02 (1H, d, $J = 10.8$, H_A of ABX, CH₂OBn), 4.14 (1H, dd, $J = 10.8$ and 4.3 , H_B of ABX, CH₂OBn), 4.33-4.36 (1H, m, H_X of ABX, C5-**H**), 4.56 (1H, d, $J = 12.5$, H_A of AB, CH₂Ph), 4.58 (1H, d, $J = 12.5$, H_B of AB, CH₂Ph), 5.31-5.34 (1H, m, H_X of ABX, C3-**H**), 7.26-7.36 (5H, m, ArH).

δ_C (150 MHz): 35.4 (C4), 38.6 (SO₂CH₃), 71.6 (C2), 73.1 (CH₂OBn), 73.5 (CH₂Ph), 77.3 (C5), 80.1 (C3), 127.7, 127.8, 128.4 (All ArC), 138.0 (ArC1).

(-)-(3*R*,5*S*)-3-Hydroxy-hydroxymethyltetrahydrofuran (112)²⁰



A flame dried 3-necked round bottom flask was charged with a solution of potassium superoxide (1.03 g, 14.42 mmol) in dry DMSO (25 mL). 18-Crown-6 (0.63 g, 2.40 mmol) was introduced and the solution was stirred for 5 min. A solution of

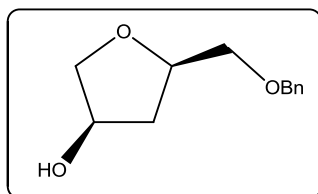
(+)-(3*S*,5*S*)-5-(benzyloxymethyl)-3-methanesulfonyloxytetrahydrofuran (1.30 mg, 4.80 mmol) in DMSO (15 mL) was subsequently introduced and the reaction mixture was stirred overnight. Brine (30 mL) was added and the mixture was extracted with diethylether (3 × 50 mL), washed with water (2 × 20 mL), dried and concentrated under reduced pressure. Flash column chromatography, using a gradient of 10% to 30% ethyl acetate in hexane as eluent, yielded the title product as a clear oil.

Yield = 0.58 g, 58%.

$[\alpha]_D^{20} = -2.75^\circ$ ($c=1.0$, CHCl_3), $[\text{lit.}^{20} = -4.1^\circ$ ($c=1.0$, CHCl_3)], 65% ee (Chiral HPLC analysis).

Spectral characteristics were in agreement with the racemic compound **91**.

(+)-(3*R*, 5*R*)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran (113)²⁰



A flame dried 3-necked round bottom flask was charged with a solution of potassium superoxide (1.03 g, 14.42 mmol) in dry DMSO (25 mL). 18-Crown-6 (0.63 g, 2.40 mmol) was introduced and the solution was stirred for 5 min. A solution of

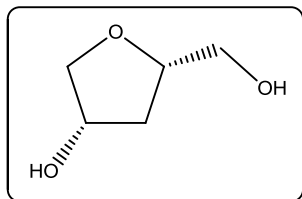
(+)-5-(benzyloxymethyl)-3-methanesulfonyloxymethyltetrahydrofuran (1.30 mg, 4.80 mmol) in DMSO (15 mL) was subsequently introduced and the reaction mixture was stirred overnight. Brine (30 mL) was added and the mixture extracted with diethylether (3 × 50 mL), washed with water (2 × 20 mL), dried and concentrated under reduced pressure. Flash column chromatography using a gradient of 10% to 30% ethyl acetate in hexane as eluent, yielded the title product as a clear oil.

Yield = 0.49 g, 48%.

$[\alpha]_D^{20} = +37.75^\circ$ ($c=1.0$, CHCl_3), $[\text{lit. } [\alpha]_D^{17} = +28.0^\circ$ ($c=1.0$, CHCl_3)], 95% ee (Chiral HPLC analysis).

Spectral characteristics were in agreement with the racemic compound **90**.

(-)-(3*S*, 5*S*)-3-Hydroxy-5-hydroxymethyltetrahydrofuran (115)²⁰



(-)-(3*S*, 5*S*)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran (150 mg, 0.72 mmol) was added to methanol (25 mL) in a Paar hydrogenation flask. $\text{Pd}(\text{OH})_2$ (10% on carbon) (37 mg) was added. The reaction was placed under a hydrogen atmosphere of 35 psi. The reaction was shaken for 15 h after which Celite[®]

(5 g) was added and the reaction was sonicated for 15 min. The mixture was filtered through Celite[®], washed with methanol (50 mL) and concentrated. Flash column chromatography, using 50% acetone in hexane as eluent, yielded the title product as a clear oil.

Yield = 54 mg, 64%.

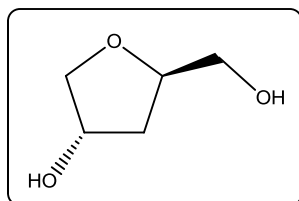
$[\alpha]_D^{20} = -18.20^\circ$ ($c=1.0$, CHCl_3) [lit.²⁰ -20.3° ($c=1.0$, CHCl_3)],

ν_{max} (NaCl): 3380, 2935, 2877, 1059, 1030 cm^{-1} .

δ_{H} (600 MHz): 1.89 (1H, overlapping dddd appears as two sets of 5 line multiplets, $J = 14.9, 3.2$ and 1.4 , C4-**H** *anti* to OH), 2.32 (1H, ddd, $J = 14.9, 9.8$ and 5.8 , C4-**H** *syn* to OH), 3.58 (1H, d, H_{A} of ABX, $J = 10.9$, **CH₂OH**), 3.71 (1H, dd, H_{A} of ABX, $J = 9.9$ and 3.2 , C2-**H**), 3.89 (1H, overlapping dd, H_{B} of ABX, $J = 10.9$ and 2.2 , H of **CH₂OH**), 3.94 (1H, overlapping dd, H_{B} of ABX, $J = 9.9$ and 1.3 , C2-**H**), 4.17 – 4.20 (1H, m, H_{X} of ABX, C5-**H**), 4.36 (1H, bs, H_{X} of ABX, C3-**H**).

δ_{C} (150 MHz): 36.9 (**C4**), 64.4 (**CH₂OH**), 71.7 (**C3**), 76.9 (**C2**), 78.1 (**C5**).

(+)-(3S, 5R)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran(116)²⁰



(+)-(3S,5R)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran (150 mg, 0.72 mmol) was added to methanol (25 mL) in a Paar hydrogenation flask. $\text{Pd}(\text{OH})_2$ (10% on carbon) (37 mg) was added. The reaction was placed under a hydrogen atmosphere of 35 psi. The reaction was shaken for 15 h after which Celite[®]

(5 g) was added and the reaction was sonicated for 15 min. The mixture was then filtered through Celite[®], washed with methanol (50 mL) and concentrated under reduced pressure. Flash column chromatography, using 50% acetone in hexane as eluent, yielded the product as a clear oil.

Yield = 57 mg, 68%.

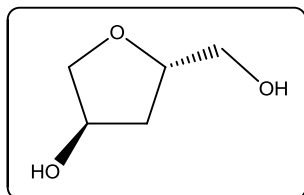
$[\alpha]_D^{20} = +8.30^\circ$ ($c=1.0$, CHCl_3) [lit.²⁰ $+22.4^\circ$ ($c=1.5$, CHCl_3)],

ν_{max} (NaCl): 3382, 2935, 2876, 1061, 975 cm^{-1} .

δ_{H} (600 MHz): 1.87 - 1.95 (1H, m, C4-**H**), 2.17 - 2.19 and 2.23 - 2.26 (1H, two sets of m, C4-**H**), 3.52 (1H, overlapping ddd appears as q, H_{A} of ABX, $J = 11.6$ and 5.8 , **CH₂OH**), 3.74 - 3.78 (1H, overlapping ddd appears as q, H_{B} of ABX, $J = 2.9$ and 5.9 , H of **CH₂OH**), 3.79 (1H, d, $J = 9.7$, H_{A} of ABX, C2-**H**), 3.97 (1H, dd, H_{B} of ABX, $J = 9.7$ and 4.1 , C2-**H**), 4.29 - 4.33 (1H, m, H_{X} of ABX, C5-**H**), 4.51 - 4.54 (1H, m, H_{X} of ABX, C3-**H**).

δ_{C} (150 MHz): 36.8 (**C4**), 64.3 (**CH₂OH**), 72.7 (**C3**), 75.7 (**C2**), 77.4 (**C5**).

(-)-(3*R*,5*S*)-3-Hydroxy-hydroxymethyltetrahydrofuran (118)



(-)-(3*S*,5*S*)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran (335 mg, 1.54 mmol) was added to methanol (25 mL) in a Paar hydrogenation flask. Pd(OH)₂ (10% on carbon) (83 mg) was added. The reaction was placed under a hydrogen atmosphere of 35 psi. The reaction was shaken for 15 h after which Celite[®]

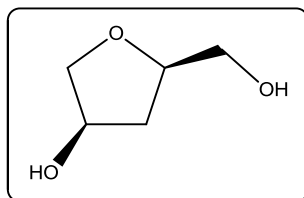
(5 g) was added and the reaction was sonicated for 15 min. The mixture was then filtered through Celite[®] which was then washed with methanol (100 mL) and concentrated under reduced pressure. Flash column chromatography, using 50% acetone in hexane as eluent, yielded the title product as a clear oil.

Yield = 120 mg, 64%.

[α]_D²⁰ = -2.45° (c=1.0, CHCl₃),

Spectral characteristics were in agreement with the opposite enantiomer **116**.

(+)-(3*R*,5*R*)-3-Hydroxy-hydroxymethyltetrahydrofuran (117)



(+)-(3*S*,5*R*)-3-Hydroxy-5-benzyloxymethyltetrahydrofuran (485 mg, 2.22 mmol) was added to methanol (25 mL) in a Paar hydrogenation flask. Pd(OH)₂ (10% on carbon) (121 mg) was added. The reaction was placed under a hydrogen atmosphere of 35 psi. The reaction was shaken for 15 h after

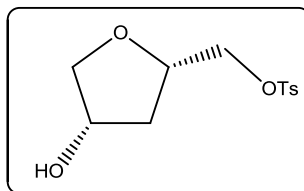
which Celite[®] (5 g) was added and the reaction was sonicated for 15 min. The mixture was filtered through Celite[®], which was then washed with methanol (120 mL) and concentrated under reduced pressure. Flash column chromatography, using 50% acetone in hexane as eluent, yielded the title product as a clear oil.

Yield = 210 mg, 78%.

[α]_D²⁰ = +25.15° (c=1.0, CHCl₃).

Spectral characteristics were in agreement with the opposite enantiomer **115**.

(-)-(3*S*,5*S*)-3-Hydroxy-5-(*p*-toluenesulfonyloxymethyl)-tetrahydrofuran (119)²⁰



(-)-(3*S*,5*S*)-3-Hydroxy-5-hydroxy-methyltetrahydrofuran (20 mg, 0.17 mmol) was dissolved in pre-cooled (-20°C) pyridine (2 mL). Freshly purified tosyl chloride³ (32 mg, 0.17 mmol) was added in one portion. The mixture was stirred at -20°C for 24

h, at 4°C for 24 h and at room temperature for 24 h. 10% w/v HCl (10 mL) was then added and the reaction mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried and concentrated under reduced pressure. Flash column chromatography, using a gradient of 0 - 1% methanol in chloroform as eluent, yielded the title product as a clear oil.

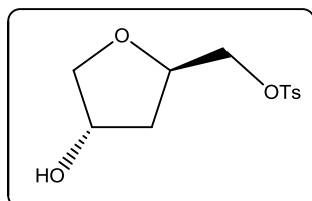
Yield = 13 mg, 34%.

$[\alpha]_D^{20} = -9.30^\circ$ (c=1.0, CHCl₃),

ν_{\max} (NaCl): 3418, 2925, 2868, 1360, 1175, 1097, 967, 814 cm⁻¹.

δ_H (600 MHz): 1.63 (1H, br s, OH), 1.77-1.78 and 1.79-1.80 (1H, 2 x multiplets, C4-H *syn* to OH), 2.27 (1H, ddd appears as 7 lines, $J = 14.0, 8.2$ and 6.1 , C4-H *anti* to OH), 2.45 (3H, s, CH₃), 3.72 (1H, dd, $J = 9.8$ and 3.8 , H_A of ABX, C2-H *anti* to OH), 3.83 (1H, d, $J = 9.8$, H_B of ABX, C2-H *syn* to OH), 4.09-4.12 (1H, m, H_A of ABX, CH₂OTs), 4.16-4.20 (2H, m, H_B of ABX, CH₂OTs and H_X of ABX, C5-H), 4.43 (1H, br s, H_X of ABX, C3-H), 7.35 (2H, d, $J = 8.1$, ArC3-H and ArC5-H), 7.35 (2H, d, $J = 8.1$, ArC2-H and ArC6-H).
 δ_C (150 MHz): 21.7 (CH₃), 37.1 (C4), 71.3 (CH₂OTs), 71.8 (C3), 75.6 (C5), 76.2 (C2), 128.0 (ArC3 and ArC5), 129.9 (ArC2 and ArC6), 132.9 (ArC4), 145.0 (ArC1).

(+)-(3S,5R)-3-Hydroxy-5-(*p*-toluenesulfonyloxymethyl)-tetrahydrofuran (120)²⁰



(+)-(3S,5R)-3-Hydroxy-5-hydroxymethyltetrahydrofuran (11 mg, 0.09 mmol) was dissolved in pre-cooled (-20°C) pyridine (1mL). Freshly purified tosyl chloride³ (18 mg, 0.09 mmol) was added in one portion. The reaction mixture was stirred at -20°C for 24 h, at +4°C for 24 h and at room temperature for

24 h. 10% w/v HCl (5 mL) was added and the reaction mixture was extracted with DCM (3 × 5 mL). The combined organic layers were dried and concentrated under reduced pressure. Flash column chromatography, using a gradient 0 - 1% methanol in chloroform as eluent, yielded the title product as a clear oil.

Yield = 11 mg, 42%.

$[\alpha]_D^{20} = +22.30^\circ$ (c=0.4, CHCl₃), [lit.²⁰ +20.4° (c=1.0, CHCl₃)],

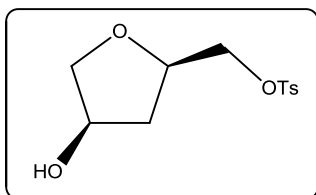
ν_{\max} (NaCl): 3378, 2917, 2845, 1351, 1174, 812 cm⁻¹.

δ_H (600 MHz): 1.23 (1H, br s, OH), 1.90 (1H, overlapping ddd appears as seven lines, $J = 13.8, 9.1$ and 5.3 , C4-H *anti* to OH), 1.99 (1H, dd, $J = 13.8$, and 6.4 , C4-H, *syn* to OH), 2.45 (3H, s, CH₃), 3.72 (1H, d, $J = 9.8$, H_A of ABX, C2-H *anti* to OH), 3.89 (1H, dd, $J =$

9.8 and 4.0, H_B of ABX, C2-**H** *syn* to OH), 4.03 (1H, dd, $J = 10.44$ and 4.80 , H_A of ABX, H of CH₂OTs), 4.11 (1H, dd, $J = 10.44$ and 3.78 , H_B of ABX of H of CH₂OTs), 4.34 - 4.38 (1H, m, H_X of ABX, C5-**H**), 4.52 (1H, br s, H_X of ABX, C3-**H**), 7.35 (2H, d, $J = 8.2$, ArC3-**H** and ArC5-**H**), 7.80 (2H, d, $J = 8.2$, ArC2-**H** and ArC6-**H**).

δ_c (150 MHz): 21.7 (**CH**₃), 37.4 (**C**₄), 71.0 (CH₂OTs), 72.3 (**C**₃), 75.2 (**C**₅), 75.9 (**C**₂), 127.0 (Ar**C**₃ and Ar**C**₅), 129.9 (Ar**C**₂ and Ar**C**₆), 132.9 (Ar**C**₄), 144.9 (Ar**C**₁).

(+)-(3*R*,5*R*)-3-Hydroxy-5-(*p*-toluenesulfonyloxymethyl)-tetrahydrofuran (121)



(+)-(3*R*,5*R*)-3-Hydroxy-5-hydroxymethyltetrahydrofuran (83 mg, 0.72 mmol) was dissolved in pre-cooled (-20°C) pyridine (5mL). Freshly purified tosyl chloride³ (140 mg, 0.72 mmol) was added in one portion. The reaction mixture was stirred at -20°C for 24 h, at 4°C for 24 h and at room temperature for 24

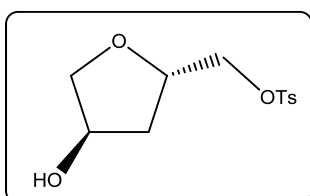
h. 10% w/v HCl (30 mL) was added and the mixture was extracted with DCM (3 × 30 mL). The combined organic layers were dried and concentrated under reduced pressure. Flash column chromatography, using a gradient 0 - 1% methanol in chloroform as eluent, yielded the product as a clear oil.

Yield = 90 mg, 46%.

$[\alpha]_D^{20} = +22.30^\circ$ (c=1.0, CHCl₃).

Spectral characteristics were in agreement with the enantiomer **119**.

(-)-(3*R*,5*S*)-3-Hydroxy-5-(*p*-toluenesulfonyloxymethyl)-tetrahydrofuran (122)



(-)-(3*R*,5*S*)-3-hydroxy-5-hydroxymethyltetrahydrofuran (108 mg, 0.92 mmol) was dissolved in precooled (-20°C) pyridine (5 mL). Freshly purified tosyl chloride (180 mg, 0.92 mmol) was added in one portion. The reaction mixture was stirred at -20°C for 24 h, at 4°C for 24 h and at room temperature for 24

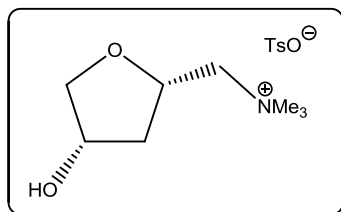
h. 10% w/v HCl (30 mL) was added and the mixture was extracted with DCM (3 × 40 mL). The combined organic layers were dried and concentrated under reduced pressure. Flash column chromatography, using a gradient 0 - 1% methanol in chloroform as eluent, yielded the product as a clear oil.

Yield = 109 mg, 73%.

$[\alpha]_D^{20} = -9.30^\circ$ (c=1.0, CHCl₃).

Spectral characteristics were in agreement with the enantiomer **120**.

(-)-(3S,5S)-Desmethylepipimuscaine (108)



To a microwave tube, (-)-(3S,5S)-3-hydroxy-5-(*p*-toluenesulfonyloxymethyl)tetrahydrofuran (16 mg, 0.06 mmol) dissolved in ethanolic trimethylamine solution (30 – 35 %, NMe₃ in ethanol) (3 mL) was added. The microwave tube was sealed and the reaction was heated to 80°C for 16

h. The microwave tube was then allowed to cool to room temperature and the reaction was concentrated under reduced pressure. The residue was dissolved in water (6 mL) and washed with ethyl acetate (4 mL). The organic layer was washed further with water (3 x 6 mL). The combined aqueous layers were concentrated under reduced pressure, by azeotropic distillation with toluene, to give the crude product as viscous golden oil.

Yield = 12 mg, 60%.

$[\alpha]_D^{20} = -11.25^\circ$ ($c=1.0$, ⁱPrOH).

ν_{\max} NaCl: 3401, 2921, 2884, 1488, 1187, 1121, 1034, 1011, 818 cm⁻¹.

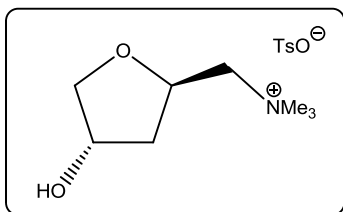
δ_H (600 MHz, D₂O): 1.63 (1H, dd, $J = 14.3$ and 6.0 , C4-**H** *syn* to OH), 2.39 (3H, s, CH₃), 2.53 (1H, overlapping ddd appears as 7 lines, $J = 14.3$, 8.3 and 6.2, C4-**H** *anti* to OH), 3.18 [9H, br s, N(CH₃)₃], 3.51 (1H, overlapping dd, $J = 14.1$ and 1.5 , H_A of ABX, CH₂NMe₃), 3.64 (1H, dd, $J = 14.1$ and 9.8 , H_B of ABX, CH₂NMe₃), 3.83 (1H, dd, $J = 10.2$ and 4.27 , H_A of ABX. C2-**H**), 3.92 (1H, overlapping dt, $J = 10.2$ and 1.5 , H_B of ABX. C2-**H**), 4.50 - 4.54 (2H, m, H_X of ABX, of both C3-**H** and C5-**H**), 7.37 (2H, d, $J = 8.3$, ArC3-**H** and ArC5-**H**), 7.70 (2H, d, $J = 8.3$, ArC2-**H** and ArC6-**H**).

δ_C (150 MHz): 20.5 (CH₃), 38.7 (C4), 53.9, [N(CH₃)₃], 69.6 (t, $J_{C-N} = 2.9$, CH₂NMe₃), 70.2 (C3 or C5), 72.6 (C3 or C5), 75.7 (C2), 125.4 (ArC3 and ArC5), 129.5 (ArC2 and ArC6), 139.5 (ArC4), 142.5 (ArC1).

M.S: m/z : 160 (M+H⁺, 100 %), 117, 76, 74.

HRMS calculated for C₈H₁₈NO₂ [M]⁺: 160.1338; found 160.1343.

(+)-(3*S*,5*R*)-Desmethylepiallomuscarine (109)



To a microwave tube, (-)-(3*S*,5*R*)-3-hydroxy-5-(*p*-toluenesulfonyloxymethyl)-tetrahydrofuran (4 mg, 0.02 mmol) dissolved in ethanolic trimethylamine solution (30 – 35%, NMe₃ in ethanol) (2 mL) was added. The microwave tube was sealed and the reaction was heated to 80°C for

16 h. The microwave tube was then allowed to cool to room temperature and the reaction was concentrated under reduced pressure. The residue was dissolved in water (4 mL) and washed with ethyl acetate (3 mL). The organic layer was washed further with water (3 x 4 mL). The combined aqueous layers were concentrated under reduced pressure, by azeotropic distillation with toluene, to give the crude product as viscous golden oil
Yield = 3 mg, 61%.

$[\alpha]_D^{20} = +7.20^\circ$ ($c=0.75$, $i\text{PrOH}$).

ν_{max} (NaCl): 3391, 2925, 2854, 1488, 1099, 1210, 1188, 1034, 815 cm^{-1} .

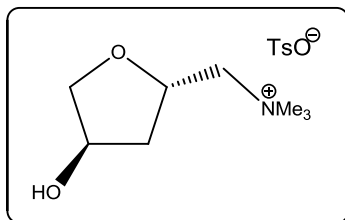
δ_{H} (600 MHz, D₂O): 1.86 (1H, overlapping ddd appears as 7 lines, $J = 13.8, 9.0$ and 4.6 , C4-**H**, *syn* to OH), 2.19 (1H, dd, $J = 13.8$ and 6.2 , C4-**H** *anti* to OH), 2.41 (3H, s, **CH**₃), 3.22 [9H, br s, N(**CH**₃)₃], 3.49 (1H, d, $J = 2.5$, H_A of ABX, **CH**₂NMe₃), 3.50 (1H, d, $J = 2.5$, H_B of ABX, **CH**₂NMe₃), 3.85 (1H, d, $J = 10.0$, H_A of ABX, C2-**H** *anti* to OH), 3.99 (1H, dd, $J = 10.0$ and 3.6 , H_B of ABX, C2-**H**, *syn* to OH), 4.54 (1H, br t, H_X of ABX, C5-**H**), 4.71-4.75 (1H, m, H_X of ABX, C3-**H**), 7.38 (2H, d, $J = 8.2$, ArC3-**H** and ArC5-**H**), 7.70 (2H, d, $J = 8.2$, ArC2-**H** and ArC6-**H**).

δ_{C} (150 MHz): 20.5 (**CH**₃), 38.6 (**C**4), 53.8, 53.9, 53.9 [N(**CH**₃)₃], 69.1 (t, $J_{\text{C-N}} = 2.8$, **CH**₂NMe₃), 70.5 (**C**5), 71.9 (**C**3), 75.7 (**C**2), 125.4 (Ar**C**3 and Ar**C**5), 129.5 (Ar**C**2 and Ar**C**6), 139.5 (Ar**C**4), 142.5 (Ar**C**1).

m/z 160 ($M+1$, 100 %), 146, 76, 74.

HRMS calculated for C₈H₁₈NO₂ [M]⁺: 160.1338; found 160.1342.

(-)-(3*R*,5*S*)-Desmethylnuscarine (110)



To a microwave tube, (-)-(3*R*,5*S*)-3-Hydroxy-5-(*p*-toluenesulfonyloxymethyl)tetrahydrofuran (72 mg, 0.26 mmol) dissolved in ethanolic trimethylamine solution (30 – 35 %, NMe₃ in ethanol) (6 mL) was added. The microwave

tube was sealed and the reaction was heated to 80°C for 16 h. The microwave tube was then allowed to cool to room temperature and the reaction was concentrated under reduced pressure. The residue was dissolved in water (6 mL) and washed with ethyl acetate (4 mL). The organic layer was washed further with water (3 x 6 mL). The combined aqueous layers were concentrated under reduced pressure, by azeotropic distillation with toluene, to give the crude product as viscous golden oil.

Yield = 45 mg, 51%.

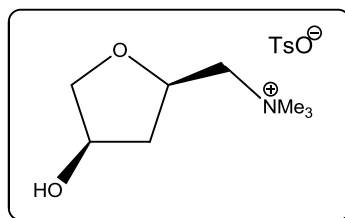
$[\alpha]_D^{20} = -4.70^\circ$ ($c=1.0$, ⁱPrOH).

Spectral characteristics were in agreement with the opposite enantiomer **109**.

m/z : 160 ($M+1$, 100 %), 146, 74, 60.

HRMS calculated for C₈H₁₈NO₂ [M]⁺: 160.1338; found 160.1332.

(+)-(3*R*,5*R*)-Desmethyllomuscarine (111)



To a microwave tube, (+)-(3*R*,5*R*)-3-hydroxy-5-(*p*-toluenesulfonyloxymethyl)tetrahydrofuran (65 mg, 0.24 mmol) dissolved in ethanolic trimethylamine solution (30 – 35 %, NMe₃ in ethanol) (6 mL) was added. The microwave

tube was sealed and the reaction was heated to 80°C for 16 h. The microwave tube was allowed to cool to room temperature and the reaction was concentrated under reduced pressure. The residue was dissolved in water (4 mL) and washed with ethyl acetate (3 mL). The organic layer was washed further with water (3 x 4 mL). The combined aqueous layers were concentrated under reduced pressure, by azeotropic distillation with toluene, to give the crude product as viscous golden oil.

Yield = 38 mg, 48%.

$[\alpha]_D^{20} = +14.25^\circ$ ($c=1.0$, ⁱPrOH).

m/z : 160 ($M+1$, 100 %), 146, 76, 74.

HRMS calculated for C₈H₁₈NO₂ [M]⁺: 160.1338; found 160.1331.

Spectral characteristics were in agreement with the opposite enantiomer **108**.

3.2.14 Synthesis of Enantioenriched Epimuscarine

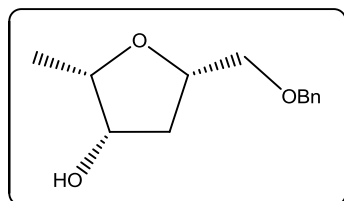
(±)-3-Hydroxy-2-methyl-5-benzyloxymethyltetrahydrofuran (70)

Modified Method.

Baker's yeast (*Saccharomyces Cerivisiae*, type II) (10 g) and sucrose (10 g) were suspended in tap water (60 mL) in a 250 mL conical flask. Two drops of antifoam 289 were added and the suspension was allowed to incubate at 29°C for 30 min. A solution of (±)-5-benzyloxymethyl-2-methyl-4,5-dihydro-3(2*H*)-furanone (0.1 g) in DMSO (1 mL) was added over 1 min to the fermenting yeast suspension and the reaction agitated for a further 24 hr. Celite® (10 g) was added to the reaction along with THF (60 mL) and the resulting mixture was stirred vigorously for 30 min. The reaction was filtered through a bed of Celite®. The filter cake was washed with water (50 mL) and THF (50 mL). The filter cake was removed and transferred to a conical flask along with THF (100 mL) and sonicated for 30 min and filtered under vacuum. The filterates were combined and the THF was removed *in vacuo*, the aqueous layer was extracted with diethylether (3 × 60 mL). The combined organic extracts were washed with brine (100 mL). The organic layers were dried and concentrated. Flash column chromatography using 5 - 40% ethyl acetate in hexane yielded two diastereoisomers as clear oils.

First fraction, least polar fraction: (+)-(2*S*,3*S*,5*S*)-3-hydroxy-2-methyl-5-benzyloxymethyltetrahydrofuran. Yield = 40 mg, 41%.

Second fraction, most polar fraction contained both (+)-(2*R*,3*S*,5*R*)-3-hydroxy-5-benzyloxymethyltetrahydrofuran (13 mg, 14%) and (+)-(2*R*,3*S*,5*S*)-3-hydroxy-5-benzyloxymethyltetrahydrofuran (21 mg, 22%). Combined yield = 34 mg, 35%.



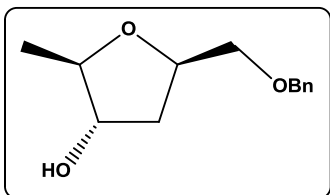
(+)-(2*S*,3*S*,5*S*)-3-hydroxy-2-methyl-5-benzyloxymethyltetrahydrofuran (102)²³,

first fraction, less polar.

$[\alpha]_D^{20} = +22.00^\circ$ ($c=1.0$, CHCl_3) [$\text{lit.}^{23} = +55.6^\circ$ ($c=0.5$,

CHCl_3)], 71% ee.

Spectral characteristics of compound corresponded directly with those of the racemic compound **95**.



(+)-(2*R*,3*S*,5*R*)-3-hydroxy-5-benzyloxymethyltetrahydrofuran (103)

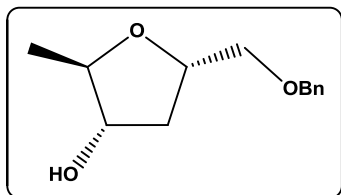
δ_{H} (600 MHz) (C2-H, and C5-H are *syn* and C3-H are *anti*): 1.09 (3H, d, $J = 6.9$, C2-CH₃), 1.84 (1H, dd, $J = 14.3$ and 2.5, C4-H, *syn* to OH), 2.40 (1H, overlapping ddd appears as 7

lines, $J = 14.3$, 10.3 and 6.2, C4-H, *anti* to OH), 3.45 (1H, dd, H_A of ABX, $J = 7.8$ and 2.5, CH₂OBn), 3.68 (1H, d, H_B of ABX, $J = 7.8$, CH₂OBn), 3.82 (1H, overlapping qd, $J = 6.9$ and 2.08, C2-H), 3.90-3.93 (1H, m, C3-H), 4.30-4.34 (1H, m, C5-H), 4.55 (1H, d, H_A of AB, $J = 12.2$, PhCH₂), 4.67 (1H, d, H_B of AB, $J = 12.2$, PhCH₂), 7.27-7.33 (5H, m, ArH).

δ_{C} (150 MHz): 14.1 (C2-CH₃), 35.5 (C4), 72.4 (BnOCH₂), 72.7 (C3), 73.7 (PhCH₂), 76.3 (C5), 83.9 (C2), 127.8, 128.1, 128.7 (All ArC), 137.3 (ArC1).

M.S: m/z : 223(M+H⁺, 100 %), 131, 91.

HRMS calculated for C₁₃H₁₉O₃ [M+H]⁺: 223.1334; found 223.1385.



(+)-(2*R*,3*S*,5*S*)-3-hydroxy-5-benzyloxymethyltetrahydrofuran (104)

δ_{H} (600 MHz) (C3-H, and C5-H are *syn* and C2-H are *anti*): 1.45 (3H, d, $J = 6.9$, C2-CH₃), 1.86 (1H, ddd, $J = 13.2$, 6.0

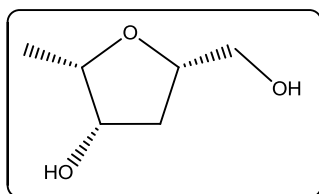
and 2.9, C4-H *syn* to OH), 1.95 (1H, ddd, $J = 13.2$, 9.3 and 6.7, C4-H, *anti* to OH), 3.49 (1H, dd, H_A of ABX, $J = 10.3$ and 5.4, CH₂OBn), 3.53 (1H, dd, H_B of ABX, $J = 10.3$ and 3.2, CH₂OBn), 3.88 (1H, overlapping qd, $J = 6.9$ and 4.2, C2-H), 3.96 (1H, overlapping ddd appears as 5 lines, $J = 4.0$ and 3.1, C3-H), 4.30-4.38 (1H, m, C5-H), 4.56 (1H, d, H_A of AB, $J = 12.2$, PhCH₂), 4.59 (1H, d, H_B of AB, $J = 12.2$, PhCH₂), 7.28-7.34 (5H, m, ArH).

δ_{C} (150 MHz): 18.5 (C2-CH₃), 36.0 (C4), 71.7 (BnOCH₂), 72.3 (PhCH₂), 77.0 (C3), 77.2 (C5), 82.6 (C2), 127.8, 128.1, 128.7 (All ArC), 137.3 (ArC1).

M.S: m/z : 223(M+H⁺, 100 %), 131, 91.

HRMS calculated for C₁₃H₁₉O₃ [M+H]⁺: 223.1334; found 223.1339.

(+)-(2S,3S,5S)-3-Hydroxy-2-methyl-5-hydroxymethyltetrahydrofuran (123)²³



(+)-(2S,3S,5S)-3-Hydroxy-2-methyl-5-benzyloxymethyl-tetrahydrofuran (172 mg, 0.79 mmol) was added to methanol (25 mL) in a Paar hydrogenation flask. Pd(OH)₂ (10 % on carbon) (40 mg) was added. The reaction was placed under a hydrogen atmosphere of 35 psi. The reaction was shaken

for 16 h after which Celite® (5 g) was added and the reaction was sonicated for 15 min. The reaction was filtered through Celite®, which was then washed with methanol (50 mL) and concentrated. Flash column chromatography, using 50% acetone in hexane as eluent, yielded the title product as a clear oil.

Yield = 63 mg, 61 %.

[α]_D²⁰ = +36.60° (c=1.0, CHCl₃), [lit.²⁶ = +51.6° (c=0.5, CHCl₃)].

ν_{max} (NaCl): 3352, 2934, 2875, 1080 cm⁻¹.

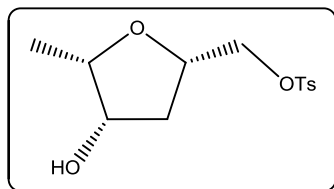
δ_{H} (600 MHz): 1.29 (3H, d, J = 6.20, C2-CH₃), 1.91 (1H, dd, J = 13.91 and 2.92, C4-H *anti* to OH), 2.40 (1H, overlapping ddd appears as 7 lines, J = 14.58, 10.09 and 5.38, C4-H *syn* to OH), 2.51 (1H, br.s, OH), 3.22 (1H, br.s, OH), 3.53 (1H, d, H_A of ABX, J = 11.44, CH₂OH), 3.83-3.88 (2H, m, CH₂OH and C2-H), 3.97-4.00 (1H, m, C5-H), 4.17 (1H, d, C3-H),

δ_{C} (150 MHz): 14.0 (C2-CH₃), 37.6 (C4), 64.3 (CH₂OH), 72.7 (C5), 77.1 (C3), 80.0 (C2).

M.S: m/z : 133 (M+H⁺, 100 %), 115, 91.

HRMS calculated for C₆H₁₃O₃ [M+H]⁺: 133.0865; found 133.0862

(+)-(2S,3S,5S)-3-Hydroxy-2-methyl-5-(*p*-toluenesulfonylmethyl)-tetrahydrofuran (124)²⁶



(+)-(2S,3S,5S)-3-Hydroxy-2-methyl-5-hydroxymethyl-tetrahydrofuran (47 mg, 0.36 mmol) was dissolved in pre-cooled (-20°C) pyridine (4 mL). Freshly purified³ tosyl chloride (71 mg, 0.36 mmol) was added in one portion. The

reaction mixture was stirred at -20°C for 24 h, 4°C for 24 h and stirred at room temperature for 24 h. 10% w/v HCl (10 mL) was added and the reaction mixture extracted with DCM (3 × 10 mL). The combined organic layers were dried and concentrated. Flash column chromatography, using 0 - 1% methanol in chloroform as eluent, yielded the title product as a clear oil.

Yield = 48 mg, 47%.

$[\alpha]_D^{20} = +14.30$ ($c=1.0$, CHCl_3), $[\text{lit.}^{26} = +37.4^\circ$ ($c=0.5$, CHCl_3)].

ν_{max} (NaCl): 3422, 2963, 2875, 1356, 1260, 1175, 1088, 976, 805 cm^{-1} .

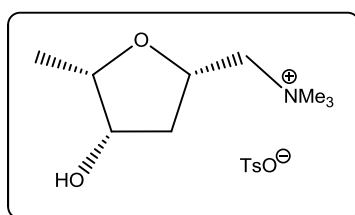
δ_{H} (600 MHz): 1.22 (3H, d, $J = 7.0$, C2- CH_3), 1.81 (1H, dd, $J = 14.4$ and 5.0 , C4- H *syn* to OH), 2.34 (1H, ddd appears as 7 lines, $J = 14.4$, 9.5 and 5.7 , C4- H *anti* to OH), 2.45 (3H, s, CH_3), 3.80 (1H, m, C2- H), 4.05-4.10 (2H, m, C3- H and CH_2OTs), 4.12-4.15 (1H, m, C5- H), 4.18 (1H, dd, $J = 10.3$ and 4.6 , H_B of ABX of CH_2OTs), 7.35 (2H, d, $J = 8.0$, ArC3- H and ArC5- H), 7.81 (2H, d, $J = 8.0$, ArC2- H and ArC6- H).

δ_{C} (150 MHz): 13.8 (C2- CH_3), 20.5 (CH_3), 36.4 (C4), 71.5 (CH_2OTs), 73.0 (C3), 74.6 (C5), 79.6 (C2), 128.1 (ArC3 and ArC5), 129.9 (ArC2 and ArC6), 132.9 (ArC4), 145.0 (ArC1).

M.S: m/z : 287 ($\text{M}+\text{H}^+$, 100 %), 191, 133, 115.

HRMS calculated for $\text{C}_{13}\text{H}_{19}\text{SO}_5$ $[\text{M}+\text{H}]^+$: 287.0953; found 287.0958.

(+)-(2S,3S,5R)-Epimuscarine (125)²⁶



To a microwave tube, (+)-(2S,3S,5R)-3-hydroxy-2-methyl-5-(*p*-toluenesulfonylmethyl)-tetrahydrofuran (27 mg, 0.09 mmol) dissolved in ethanolic trimethylamine solution (30 – 35%) (6 mL). The microwave tube was sealed and the reaction was heated to 80°C. The microwave tube was

then allowed to cool to room temperature and the reaction was concentrated under reduced pressure. The residue was dissolved in water (12 mL) and washed with ethyl acetate (12 mL). The organic layer was washed further with water (3 x 12 mL). The combined aqueous layers were concentrated under reduced pressure, by azeotropic distillation with toluene, recrystallised from acetone to give the product as white powder. M.P. = 153-154 °C (158 °C²⁶).

Yield = 16 mg, 52%. m.p.

$[\alpha]_D^{20} = +18.60^\circ$ ($c=1.0$, $i\text{PrOH}$), $[\text{lit.}^{26} = +36.5^\circ$ ($c=1.0$, EtOH)].

ν_{max} (NaCl): 3433, 2927, 2856, 1484, 1095, 815 cm^{-1} .

δ_{H} (600 MHz): 1.25 (3H, d, $J = 6.3$, C2- CH_3), 1.63 (1H, ddd, $J = 14.6$, 8.0 and 1.8 , C4- H , *syn* to OH), 2.40 (3H, s, CH_3), 2.62 (1H, overlapping ddd appears as 7 lines, $J = 14.6$, 9.2 and 6.5 , C4- H *anti* to OH), 3.20 (9H, s, $\text{N}(\text{CH}_3)_3$), 3.51 (1H, d, $J = 12.1$, H_A of ABX, CH_2NMe_3), 3.57 (1H, dd, $J = 12.1$ and 9.8 , H_B of ABX, CH_2NMe_3), 3.93 (1H, qd, $J = 6.3$ and 2.3 , C2- H), 4.25-4.27 (1H, m, C3- H), 4.44 - 4.45 (1H, m, C5- H), 7.38 (2H, d, $J = 8.2$, ArC3- H and ArC5- H), 7.70 (2H, d, $J = 8.2$, ArC2- H and ArC6- H).

δ_C (150 MHz): 13.3 (C2-**C**H₃), 20.5 (Ar**C**H₃), 39.1 (**C**4), 53.9, 53.9, 54.0 (N(**C**H₃)₃), 70.2 (t, J_{C-N} = 2.92 , **C**H₂NMe₃), 71.2 (**C**3 or **C**5), 71.4 (**C**3 or **C**5), 80.7 (**C**2), 125.4 (Ar**C**3 and Ar**C**5), 129.4 (Ar**C**2 and Ar**C**6), 139.4 (Ar**C**4), 142.5 (Ar**C**1).

M.S: m/z 174 (M^+ , 100 %), 115, 101, 60.1.

HRMS calculated for C₆H₂₀NO₂ [$M+H$]⁺: 174.1494; found 174.1500.

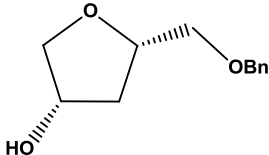
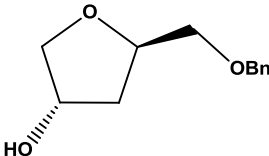
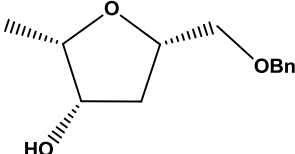
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4 Appendix

Summary of HPLC chromatographic conditions.

Compound	Column	Temp. (°C)	Mobile Phase (Hex:IPA)	Retention Time (Min.)
	AS-H*	25	98 : 2 1 mL min ⁻¹	44.73 (3R,5R), 59.18 (3S, 5S).
	AS-H*	25	98 : 2 1 mL min ⁻¹	13.07 (3S, 5R), 45.88 (3R, 5S).
	AS-H*	25	90:10 1 mL min ⁻¹	14.08 16.68

*Diacel CHIRALPAK AS-H 250mm x 4.6mm x 5µm

