Enantioselective Chemoenzymatic Synthesis of 3-Hydroxytetrahydrofurans

Liam Greaney, B.Sc.

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to

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Analytical and Biological Chemistry Research Facility (ABCRF),
Department of Chemistry,
University College Cork.

Supervisors: Prof. Anita R. Maguire and Dr. Daniel G. McCarthy

Head of Chemistry Department: Prof. Martyn Pemble

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

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Liam Greaney

Table of Contents

Abstract

The research described in this thesis is concerned with the synthesis and stereoselective transformations of 4,5-dihydro-3(2H)-furanones and their 3-hydroxy derivatives. In Chapter 1, a review of synthetic routes to 3-hydroxytetrahydrofurans is presented. This incorporates the wide range of applications for these types of compounds.

Preparative routes to and stereoselective transformations of the furanones investigated in this study are discussed in Chapter 2. The bulk of the work centers on stereoselective carbonyl group reductions to generate the 3-hydroxytetrahydrofuran derivatives in racemic form followed by kinetic resolution *via* lipase mediated esterification, resulting in enantioenriched 3-acetoxy and 3-hydroxytetrahydrofuran derivatives. In many cases, these processes proceed in a highly enantioselective manner. The influence of the lipase species and concentration of enzyme employed on the yield and stereochemical outcome of the reactions is examined in detail. Access to the complementary series of furanone and hydroxytetrahydrofuran derivatives by oxidation or reduction of the enantioenriched compounds was achieved through conventional synthetic methods. Chapter 2 also contains details of a novel synthetic route to a range of 2,3,5-trisubstituted furans from α-hydroxyenones and 4,5-dihydro-3(2H)-furanones. The mechanistic rationale for these transformations and the migratory aptitude of alkyl groups towards the formation of these furans is discussed in detail. Finally, Chapter 2 outlines the synthesis of a series of diarylcyclopentenones that were synthesised as part of our investigations.

Chapter 3 contains a description of the synthetic procedures and biotransformations carried out together with key analytical and spectroscopic properties of the compounds studied and where appropriate, their analysis using chiral HPLC analysis.

Acknowledgments

Firstly, I would like to express my sincere gratitude to Prof. Anita Maguire and Dr. Dan McCarthy for their supervision, and guidance throughout my Ph.D. I have been lucky enough to learn a great deal throughout the course of my studies and without them this would not have been possible. Their advice and suggestions during the preparation of this thesis are also gratefully acknowledged. Thanks to Dr. Simon Lawrence and Dr. Kevin Eccles for the X-ray crystallography work; Dr. Florence McCarthy and Mick O'Shea for Mass Spectrometry work; Dr. Nuala Maguire for all HPLC related matters; Debbie for the organisation of meetings and last, but by no means least, Dr. Lorraine Bateman for her help with all things NMR. Many an hour was spent figuring out one of the many 'interesting products' during the course of my Ph.D. (as well as Munster rugby and GAA related matters) that needed extensive NMR work and without her support would probably still be trying to figure out the structures!!! ALMAC Sciences for the use of their biocatalysts. This thesis was made possible by financial support from Cork County Council and UCC, through undergraduate demonstrating.

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Christmas Dinners will live long in the memory!! The ARM's of Alan, Francis, Dave, Nico, Seb, Andy, Angela, Orla Mc, Marie, Orlagh O', Sinead, Chris, Sarah, Paul, Rebecca, Naomi, Carla, Graham, Leslie-Ann, Aoife and Catherine. I was lucky enough to share a lab with a good portion of this group and without their good company would have made the days even longer. To those that shared the 'Industry Suite' which also served as the nerve centre for Synthos FC's assault on the Cork Nite Leagues. It was a glorious season full of laughs, tears (mainly of laughter) and drama that was ultimately derailed half-way through with the Christmas party…….memories that we will have forever!

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As most from my time in UCC will know, I had many sporting endeavours that may have impacted laboratory time. Cobh GAA, a club that I hold very dear to my heart; the struggle for success and silverware goes on…….hopefully it's not too far away. Cobh Pirates RFC, I was a bit of a late starter but from the very start was made welcome and got huge encouragement and support. Cobh Camogie Club, the phrase 'from little acorns mighty oaks trees grow' is particularly apt. It was a pleasure to share the journey that we had together.

Finally, and most importantly to my family. I have many aunts, uncles and cousins that supported and encouraged me throughout my studies. To Kieran, I'm so proud to have taken the Ph.D. journey with you. You are a constant source of inspiration and your resilience in matters is truly astounding. Last, and certainly by no means least, thanks to Mam and Dad, Eileen and Liam (Snr.). The sacrifices that you have made for both of us will never be repaid and without your support (financial included!!) this body of work would not have been possible. I don't say it enough but I love you both very much.

Abbreviations

Ac	Acetyl
AcOH	Acetic Acid
Ac_2O	Acetic Anhydride
aq.	Aqueous
Ar	Aryl
AZT	Azidothymidine
9-BBN	9-Borobicyclo[3.3.1]nonane
Bn	Benzyl
b.p.	Boiling Point
Boc	t-butoxycarbonyl
bs	Broad Singlet
Bz	Benzoyl
CAL	*Candida antarctica* Lipase
CbzCl	Benzylchloroformate
CCL	*Candida cylindracea* Lipase
COSY	Correlation Spectroscopy
CSA	10-Camphorsulfonic acid
CSO	Camphorsulfonyloxaziridine
d	Doublet
DBMP	2,6-Di-t-butyl-4-methylpyridine
DBU	Diazabicyclo[5.4.0]undec-7-ene
1,2-DCB	1,2-Dichlorobenzene
DCBBr	Dichlorobenzyl bromide
1,2-DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of Doublets
ddd	Doublet of Doublets of Doublets
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless Enhancement by Polarisation Transfer
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride

Abbreviations

DIPE	Diisopropylether
DMAP	*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethylsulphoxide
d.r.	Diastereomeric ratio
e.e.	Enantiomeric excess
EDG	Electron-donating group
equiv. or eq.	Equivalents
ESI	Electrospray ionization
Et	Ethyl
Et_2O or Ether	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron-withdrawing group
g	Gram
GOESY	Gradient Enhanced Nuclear Overhauser Effect Spectroscopy
h	Hour
HETCOR	Heteronuclear Chemical Shift Correlation
HMBC	Heteronuclear Multiple Bond Coherence
HMPT	Hexamethylphosphoramide
HMQC	Heteronuclear Multiple-Quantum Correlation
HPLC	High Performance Liquid Chromatography
HSQC	Heteronuclear single quantum coherence
HRMS	High Resolution Mass Spectroscopy
Hz	Hertz
Im	Imidazole
i-Pr	Isopropyl
IR	Infrared
L-Selectride®	Lithium tri-*sec*-butylborohydride
LDA	Lithium diisopropylamine
Lit.	Literature
m	Multiplet

m-CPBA	3-Chloroperoxybenzoic acid
MDA	Methyl diazoacetate
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligram
MHz	Megahertz
mL	Millilitre
mmol	Millimole
mol	Mole
m.p.	Melting point
MOM	Methoxymethyl
MS	Mass spectroscopy
MSA	Methanesulfonic Acid
Ms	Mesyl (Methanesulfonyl)
NBS	*N*-Bromosuccinimide
NMO	4-Methylmorpholine-N-oxide
NMR	Nuclear magnetic resonance
NMP	*N*-Methylpyrrolidin-2-one
MW	Microwave
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
n-Bu	*n*-Butyl
OAc	Acetate
o/n	Overnight
PCC	Pyridinium chlorochromate
PFA	Paraformaldehyde
Ph	Phenyl
PLE	Pig Liver Esterase
PMB	4-Methoxybenzyl
PMP	4-Methoxyphenyl
ppm	Parts per Million
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine

Abbreviations

q	Quartet
r.t.	Room temperature
s	Singlet
t	Triplet
sat.	Saturated
SIBX	Stabilised 2-iodoxybenzoic acid
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS or TBS	*t*-Butyldimethylsilyl
TBDPS	*t*-Butyldiphenylsilyl
t-Bu	*t*-Butyl
TES	Triethylsilyl
Tf	Triflate (trifluoromethylsulfonyl)
TFA	Trifluoroacetic acid
tfa	Trifluoroacetate
Tf_2O	Trifluoromethanesulfonic Anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Tetramethylsilane or Trimethylsilyl
TOCSY	Total Correlation Spectroscopy
TPAP	Tetrapropylammonium Perrutheate
Ts	Tosyl (4-toluenesulfonyl)
UV	Ultraviolet

"It is not the critic who counts; not the man who points out how the strong man stumbles, or where the doer of deeds could have done them better. The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strives valiantly; who errs, who comes short again and again, because there is no effort without error and shortcoming; but who does actually strive to do the deeds; who knows great enthusiasms, the great devotions; who spends himself in a worthy cause; who at the best knows in the end the triumph of high achievement, and who at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those cold and timid souls who neither know victory nor defeat."

- Theodore Roosevelt

Introduction

1.0 Introduction

1.1 Introduction to 3-Hydroxytetrahydrofurans

3-Hydroxytetrahydrofurans (Figure 1.1.1) are a class of compounds that have garnered attention due to their prevalence in the area of natural product synthesis where they occur as the main structural motif of the compound, as an intermediate in total syntheses or as subunits of larger compounds. Many of these compounds exhibit biological activity and have been utilised as anti-cancer, anti-viral and anti-inflammatory agents. 2-and 4-Hydroxytetrahydrofurans are isomeric with the 3-hydroxy structures, although the former systems are more correctly classed as hemiacetals. There are many instances of interesting and important 3-hydroxy systems reported, many of which will be discussed within this review; compounds such as the Muscarines (Section 1.2), Pachastrassamine (Section 1.4) and Longianone (Section 1.7).

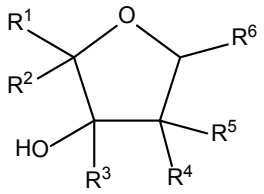
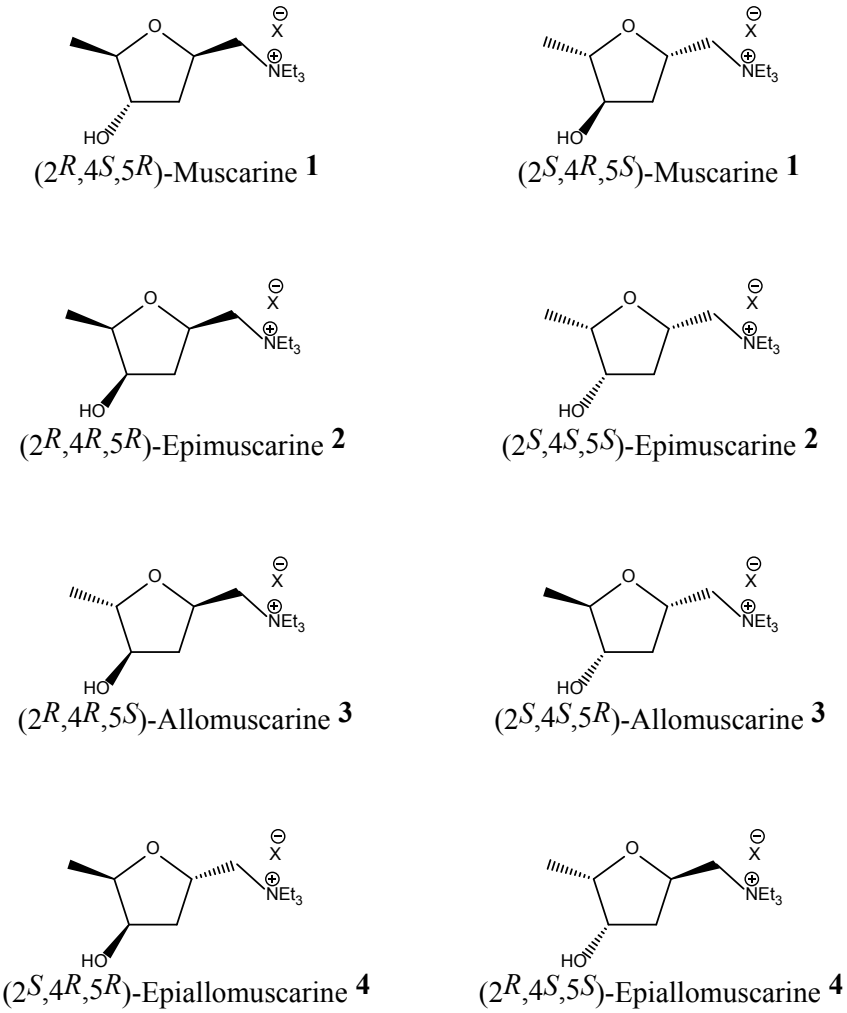


Figure 1.1.1 General Structure of a 3-Hydroxytetrahydrofuran

1.2 Muscarine Alkaloids



($2R$,$4S$,$5R$)-Muscarine **1** ($2S$,$4R$,$5S$)-Muscarine **1**

($2R$,$4R$,$5R$)-Epimuscarine **2** ($2S$,$4S$,$5S$)-Epimuscarine **2**

($2R$,$4R$,$5S$)-Allomuscarine **3** ($2S$,$4S$,$5R$)-Allomuscarine **3**

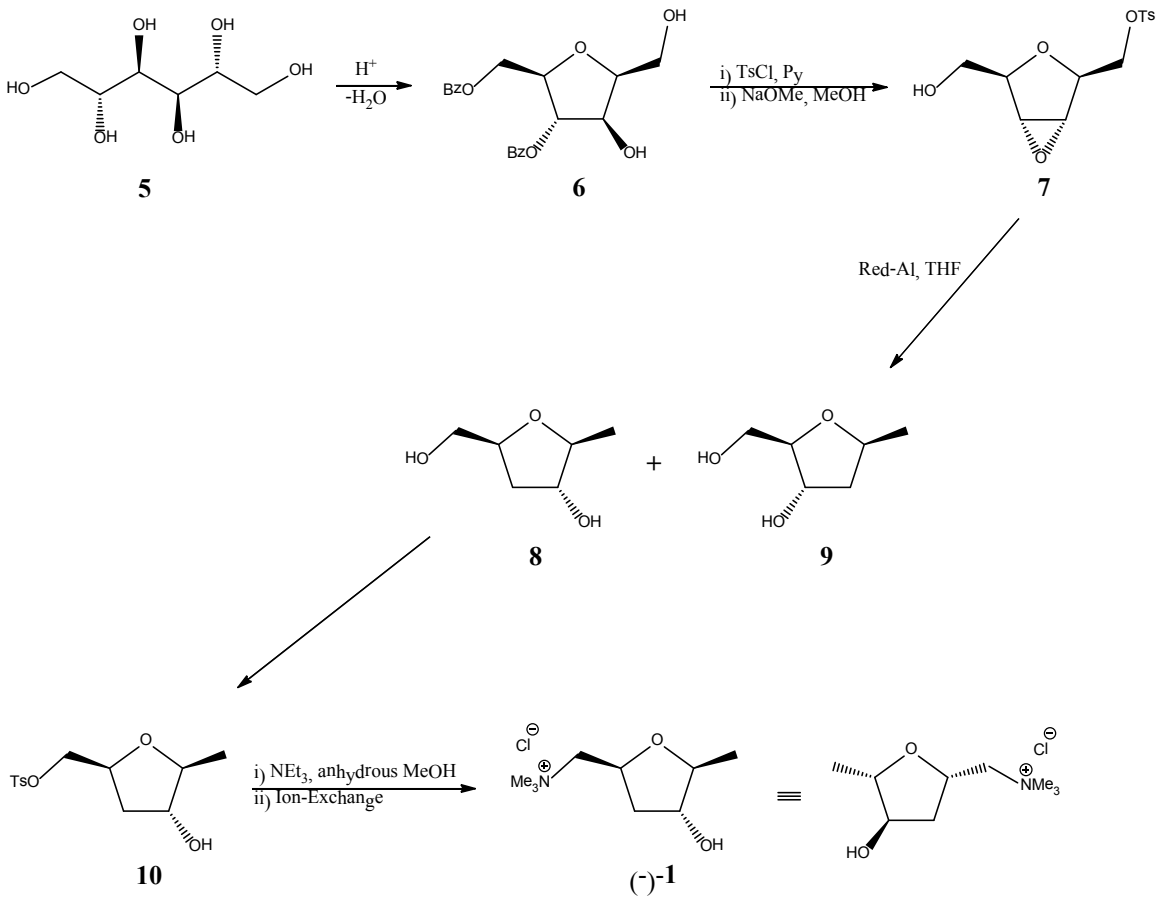
($2S$,$4R$,$5R$)-Epiallomuscarine **4** ($2R$,$4S$,$5S$)-Epiallomuscarine **4**

Figure 1.2.1 Eight Stereoisomers of Muscarine

The term 'Muscarine', through popular usage, refers to the naturally occurring cationic constituent of the salt rather than to any specific compound. Each stereoisomer exists as a quaternary ammonium salt with a counter ion, with halides and tosyl anions the most prevalent in the literature. There are eight possible stereoisomers of muscarine; muscarine as shown in Figure 1.2.1.

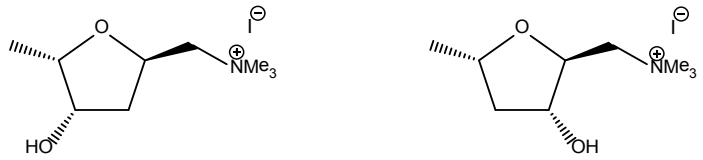
1.2.1 'Muscarines' From Carbohydrates

Mubarak and Brown[1] developed a synthetic route to (-)-muscarine, (-)-**1**, in 1980, starting from readily available D-mannitol (Scheme 1.2.1.1). In the synthesis, an acid-catalysed dehydration of D-mannitol **5** produced **6** *via* 2,5-anhydro-D-glucitol. Reaction of this with excess tosyl chloride in pyridine afforded a ditosylate, where subsequent reaction with sodium methoxide in methanol yielded epoxide **7**. Reduction of **7** using Red-Al (sodium bis-(2-methoxyethoxy)-aluminium hydride) in THF gave a highly regioselective 12:1 mixture of diols **8** and **9** respectively. This diol mixture was monotosylated and chromatographic separation yielded the desired tosylate **10**, which was subsequently treated with triethylamine in anhydrous methanol followed by ion exchange furnishing the desired muscarinic product **1**.



Scheme 1.2.1.1

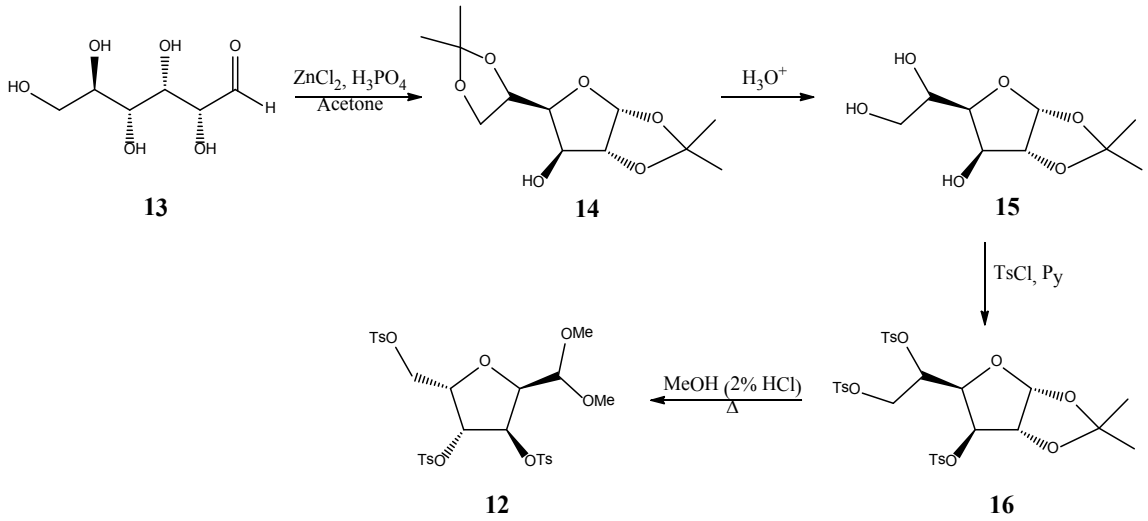
Wang and Joullie[2] devised syntheses of (2*R*,4*S*,5*S*)-epiallomuscarine **4** and (2*S*,3*R*,5*S*)-isoepiallomuscarine **11** (Figure 1.2.1.1) from α-D-glucose.



4 **11**

Figure 1.2.1.1 Structures of **4** and **11**

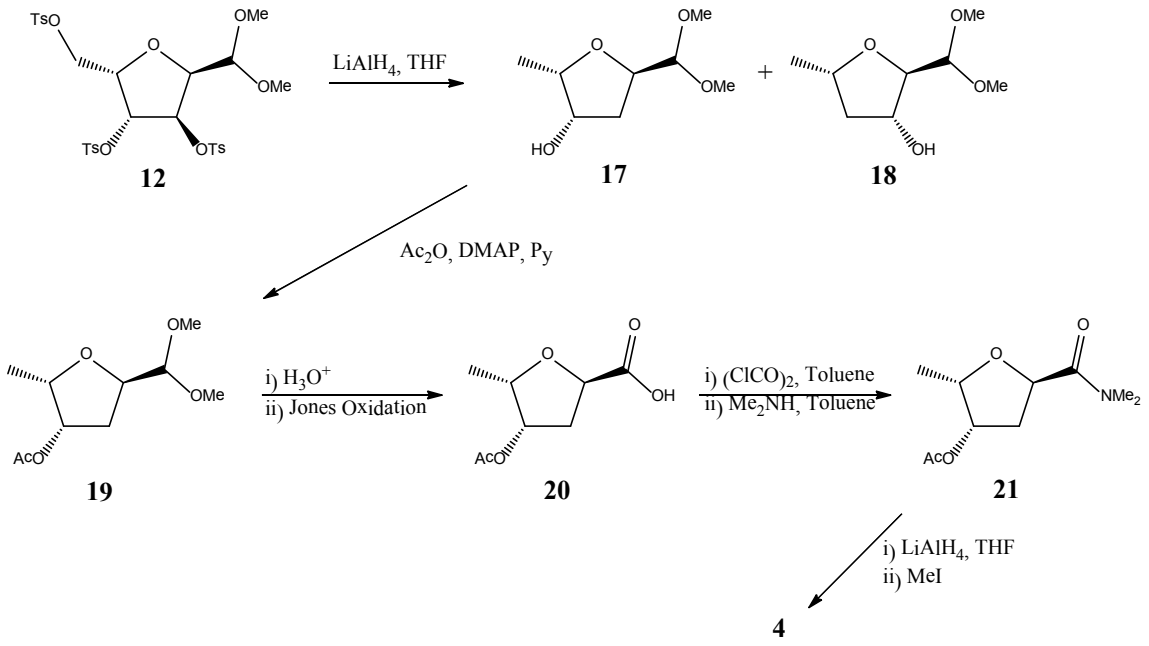
The syntheses of **4** and **11** required the acetal **12** as a precursor to the desired muscarinic products (Scheme 1.2.1.2). This was achieved *via* a method discovered by Defaye[3], whereby D-glucose **13** was treated with zinc chloride and 85% phosphoric acid in acetone to furnish glucofuranose **14**.[4] Mild acid hydrolysis of **14** selectively removes the isopropylidene group at C(5) and C(6) producing compound **15**.[4] Tosylation of **15** followed by reflux of **16** with methanol containing 2% concentrated HCl produced compound **12** in 64% overall yield from D-glucose.[5]



13 **14** **15** **16** **12**

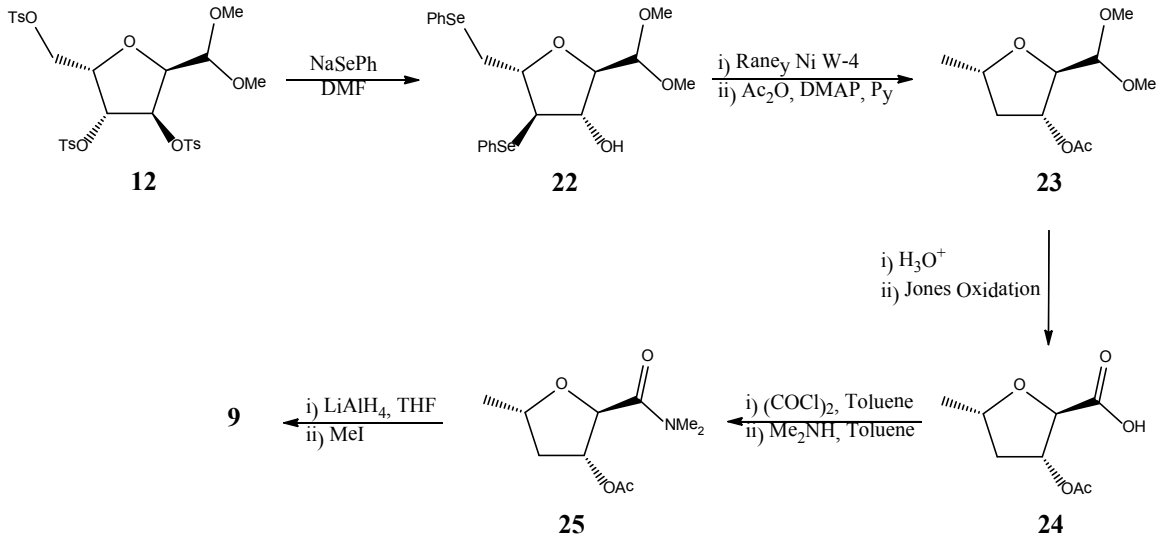
Scheme 1.2.1.2

Now that the desired precursor had been synthesised, reduction of **12** afforded a 3:2 mixture of alcohols **17** and **18** respectively. The desired alcohol **17** was isolated by chromatographic separation from **18** and acetylated with acetic anhydride and DMAP in pyridine. The resulting acetal **19** was hydrolysed and the aldehyde immediately oxidised to carboxylic acid **20** and then converted into amide **21**. The synthesis of **4** was completed by reduction followed by quaternisation with excess methyl iodide (Scheme 1.2.1.3).



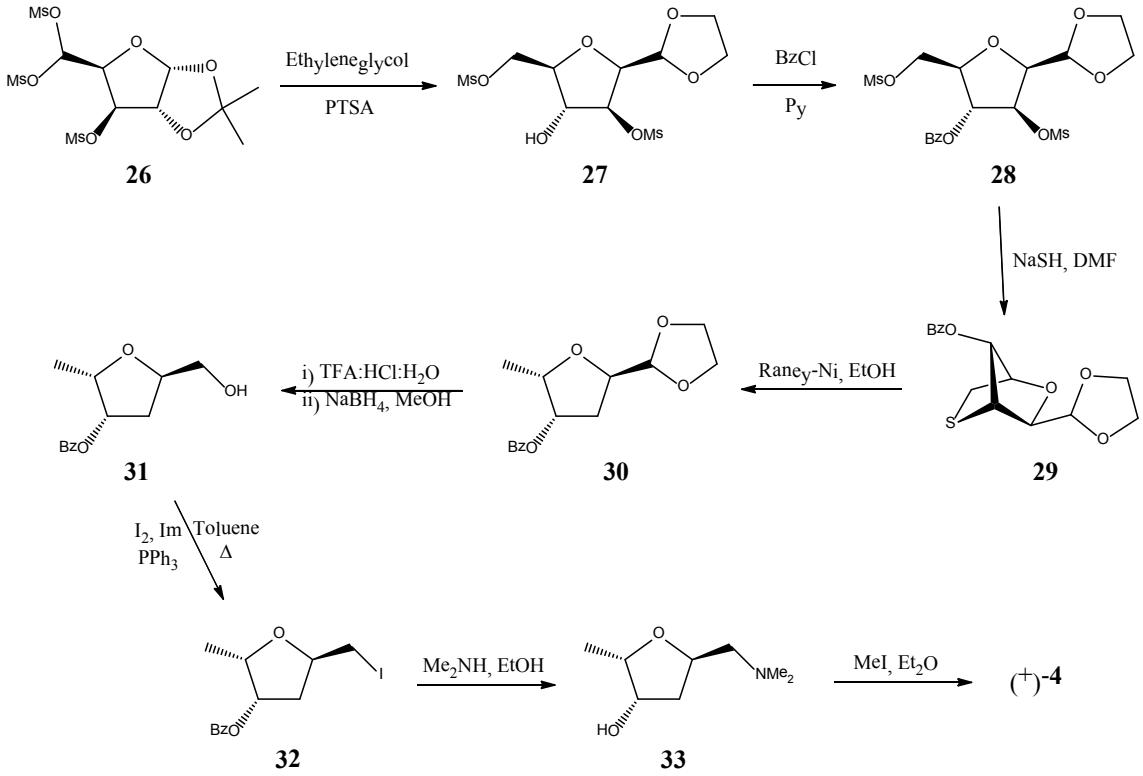
Scheme 1.2.1.3

(2*S*,3*R*,5*S*)-isoepiallomuscarine **11** was accessed (Scheme 1.2.1.4) from reaction of **12** with sodium phenylselenide in DMF to yield the bis-selenide **22**. Removal of the selenide groups was carried out with W-4 Raney nickel followed by acetylation to **23**. The rest of the synthesis followed the same method as the previous example where **23** was in sequence to the corresponding aldehyde and carboxylic acid **24**. The latter was in turn converted into an acid choride *via* oxalyl chloride followed by transformation to amide **25**. The synthesis was completed by reduction of **25** with lithium aluminium hydride and quaternisation to **11**.



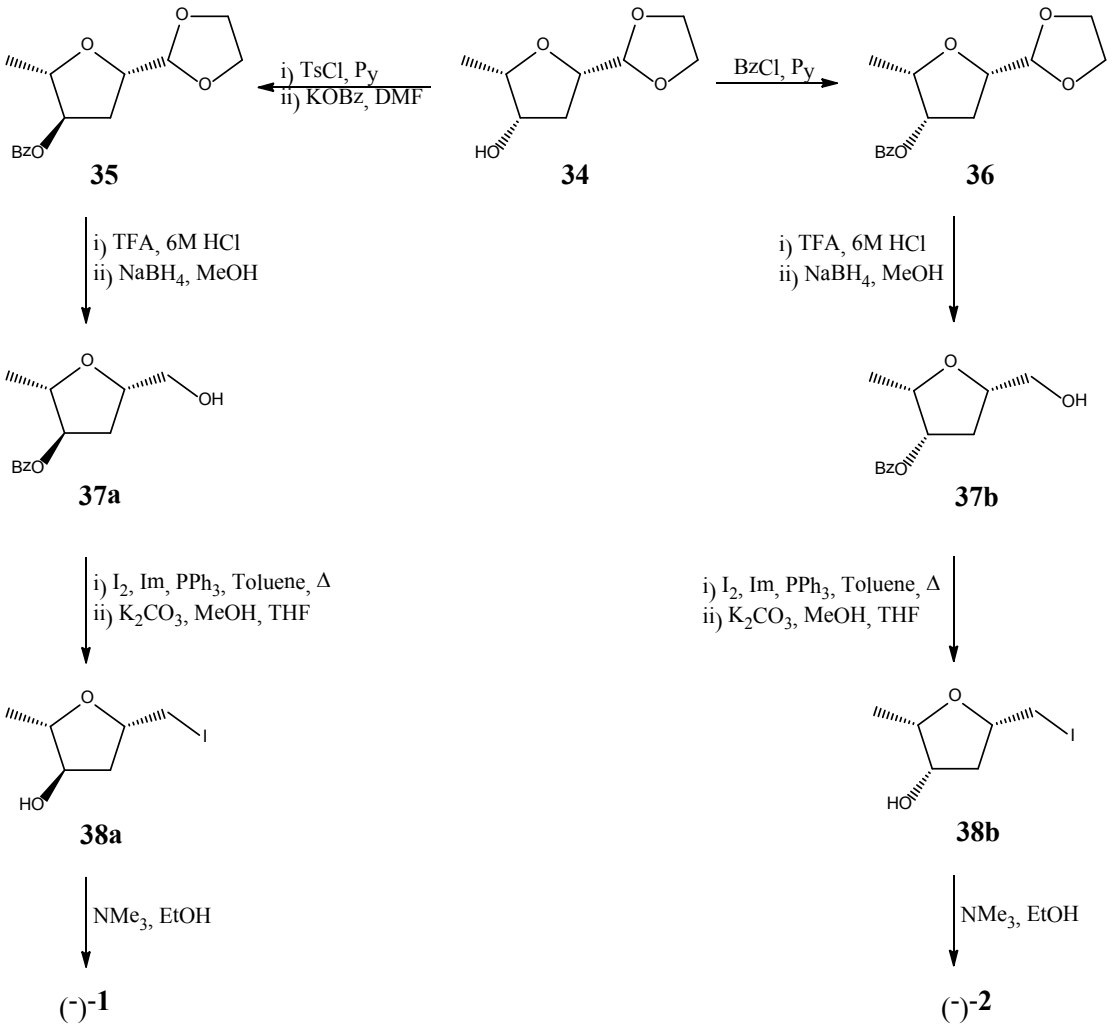
Scheme 1.2.1.4

Popsavin *et. al.*[6] proposed a modified synthesis of **4** from D-glucose. They addressed the limitation that the previous synthesis[2] contained a non-regiospecific step that required separation of structural isomers before completing the synthetic pathway. Trimesylate **26**, readily available from D-glucose,[7] was reacted with ethyleneglycol and catalytic PTSA to yield **27**. Benzoylation of **27**, followed by inter- and intra-molecular attack of hydrogensulfide anion on **28** led to the formation of the bicyclic oxathiane **29**. Desulfurisation with Raney nickel in ethanol afforded key intermediate **30**. Treatment of **30** with 18:1:1 TFA:HCl:H_2O mixture, was followed by immediate reduction to primary alcohol **31**. The synthesis was completed by iodination of **31**, followed by treatment of **32** with dimethylamine and subsequent debenzoylation to yield the iodo-(+)-epiallomuscarine precursor **33**. Compound **4** was finally attained by reaction of **33** with excess methyl iodide in dry ether (Scheme 1.2.1.5).



Scheme 1.2.1.5

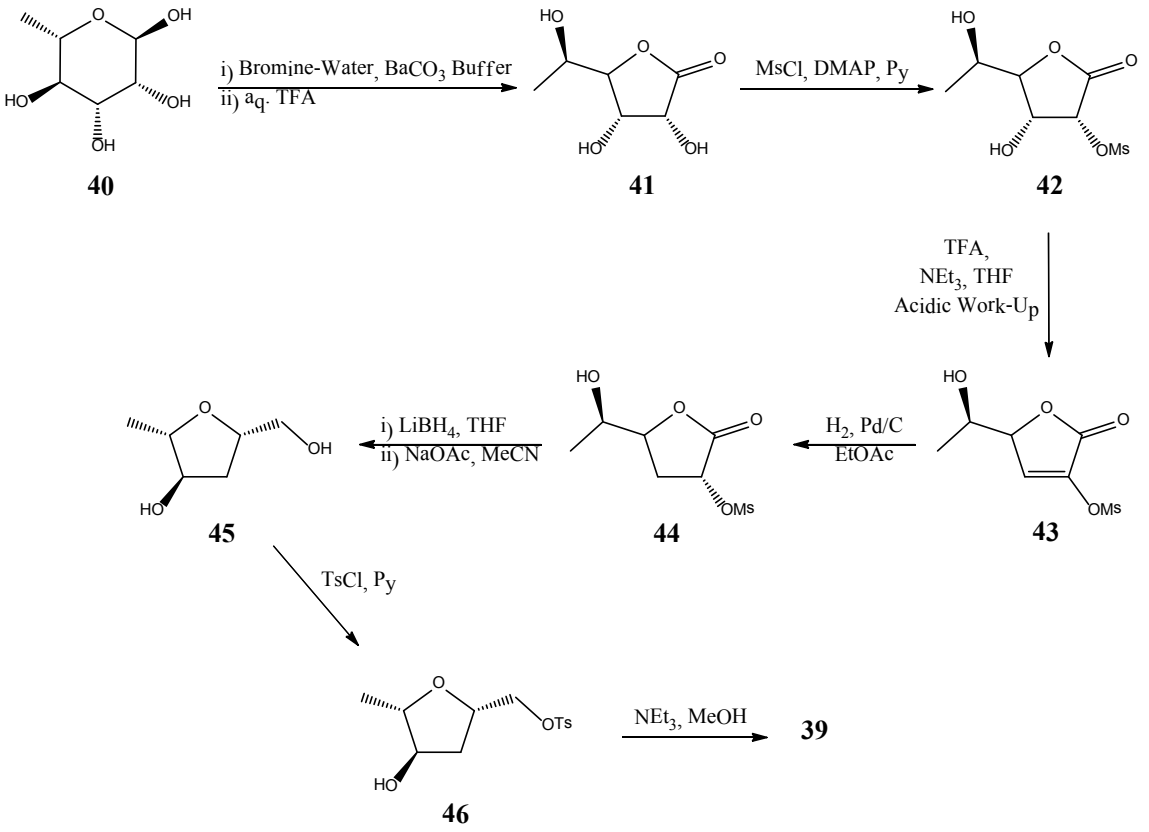
Not satisfied with this method, Popsavin returned in 2000 to publish a divergent synthesis of both **1** and **2**, again utilising the many structural features of D-glucose.[8] The key intermediate **34** from which **1** and **2** are accessed is shown in Scheme 1.2.1.6. To complete the synthesis of **1**, it was necessary to tosylate **34** followed by benzoylation, resulting in chiral intermediate **35** containing the desired stereocentres necessary for completion of the synthesis of **1**. To access **2**, intermediate **34** was reacted with benzoyl chloride in pyridine to furnish the complementary chiral compound **36**, necessary for completion of the synthesis of **2**. Both epimers were processed using the same chemistry to yield the target desired target molecules. Acidic removal of the dioxolane group followed by immediate reduction of the unstable aldehyde results in the formation of a primary alcohols **37a** and **b**. Iodination of the respective primary alcohols, debenzoylation with potassium carbonate in methanol and subsequent reaction of **36a** and **b** with ethanolic trimethylamine produced **1** and **2**.



Scheme 1.2.1.6

Mantell *et. al.*[9] identified a synthesis of (+)-muscarine (as its tosylate **39**) without the need for protecting groups and separation of intermediate stereoisomers. The authors report a short, concise route from L-rhamnose **40**, chosen as it contains the necessary chirality and functionality, and can be easily converted from a pyranose to a furanose moiety *via* nucleophilic displacement at C(2) by the oxygen functionality at C(5) of the sugar (Scheme 1.2.1.7). The synthesis proceeds by treatment of **40** with bromine-water in the presence of barium carbonate, followed by treatment with aqueous TFA to give the γ-lactone **41**.[10] Mesylate **42** was furnished by selective esterification of the C(2)-hydroxyl group of **41**. Dehydration of **42** (trifluoroacetic anhydride and triethylamine in THF), and subsequent base catalysed elimination followed by acidic work-up resulted in elimination of the trifluoroacetate ester to produce the vinyl mesylate **43**. This mesylate was reduced to **44**, followed by a further reduction and sodium acetate induced cyclisation of the

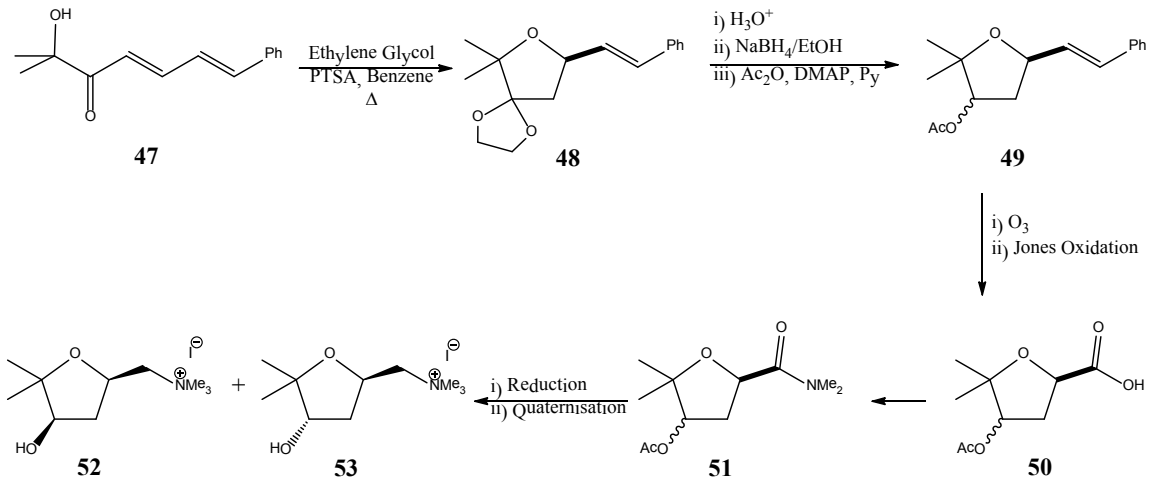
lactone to diol **45**. Tosyl chloride in pyridine selectively gave rise to tosylate **46**. Reaction of the latter with triethylamine in methanol gave the target compound **39**.



Scheme 1.2.1.7

1.2.2 Other Syntheses of Muscarines

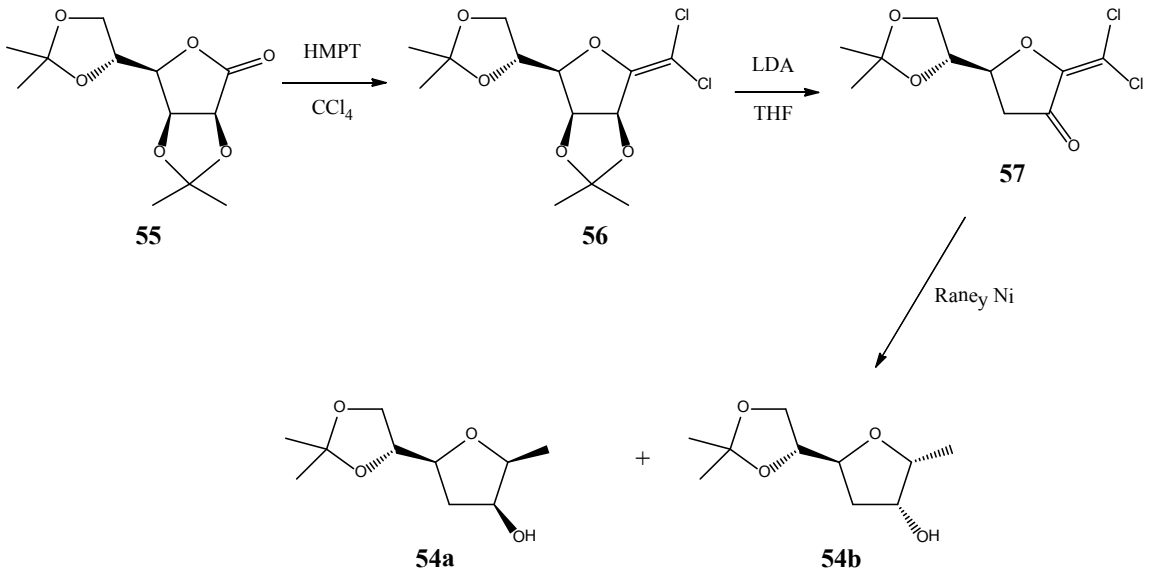
Semple *et. al.*[11] utilised inexpensive, acyclic and achiral starting materials in their 1980 synthesis of the 2,2-dimethyl analogues of 2-methylepimuscarine iodide and 2-methylmuscarine iodide (Scheme 1.2.2.1). Aldol condensation (NaOEt, EtOH, 0 °C) of 3-hydroxy-3-methylbutan-2-one with *trans*-cinnamaldehyde yielded α-hydroxyenone **47** in 71% yield. The cyclisation was effected when the enone was treated with ethylene glycol and PTSA in refluxing benzene to yield ketal **48**. The protecting group was removed, the resulting furanone reduced with an ethanolic sodium borohydride solution and subsequently acetylated to yield acetate **49** as a *ca* 1:1 mixture of isomers. This mixture was subjected to ozonolysis followed by Jones oxidation, producing **50**, which was then converted to amide **51** with retention of the above isomeric ratio. The respective isomers were separated and respectively reduced, followed by quaternisation of the corresponding amines produced the desired compounds **52** and **53** with excellent yields reported.



Scheme 1.2.2.1

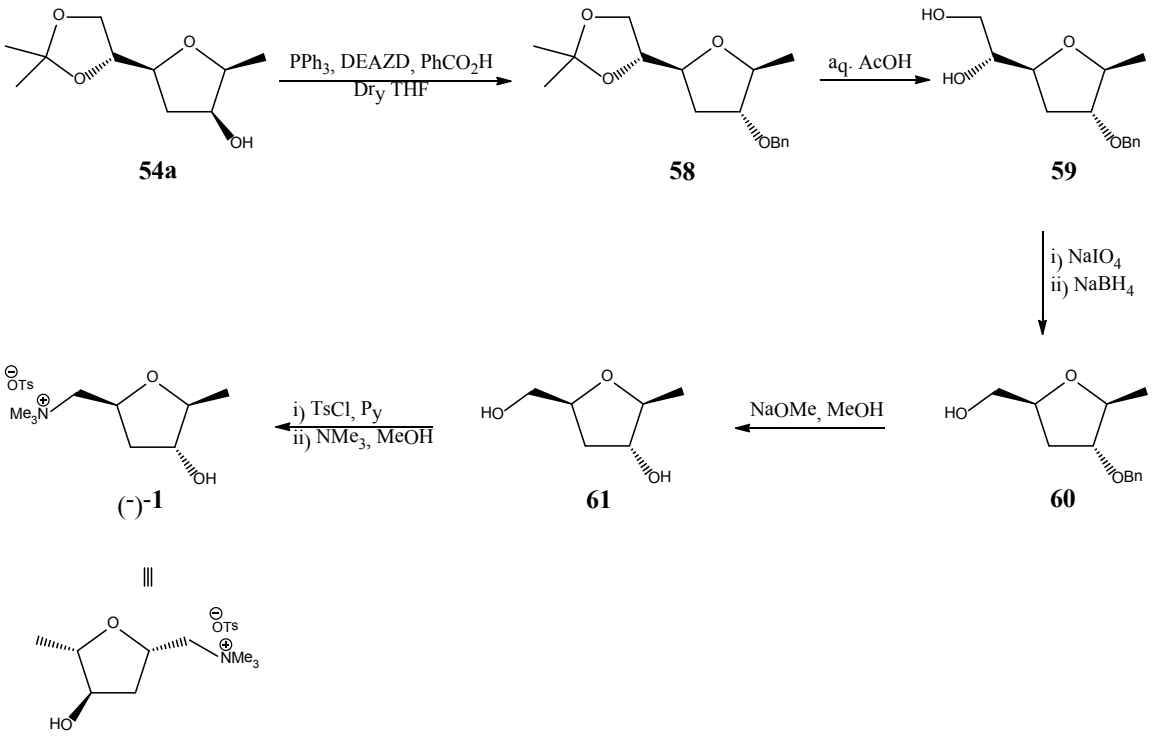
In 1987, Bandzouzi and Chapleur[12] reported a synthesis of (+)-**1** and (+)-**2** as their tosylate salts. They describe a synthesis involving dichloromethylenation of sugar γ-lactones. The synthesis to both muscarine analogues proceeds through a key 3-hydroxytetrahydrofuran intermediate **54** (Scheme 1.2.2.2), which contains all the key stereochemical features of muscarine. Production of this intermediate commences with reaction of **55** with HMPT and carbon tetrachloride to yield the dichloromethylene

compound **56** in high yield. **56** was treated with LDA to yield 57, and subsequent Raney nickel reduction of **57** followed by chromatographic separation furnished the desired alcohol intermediate **54a**.



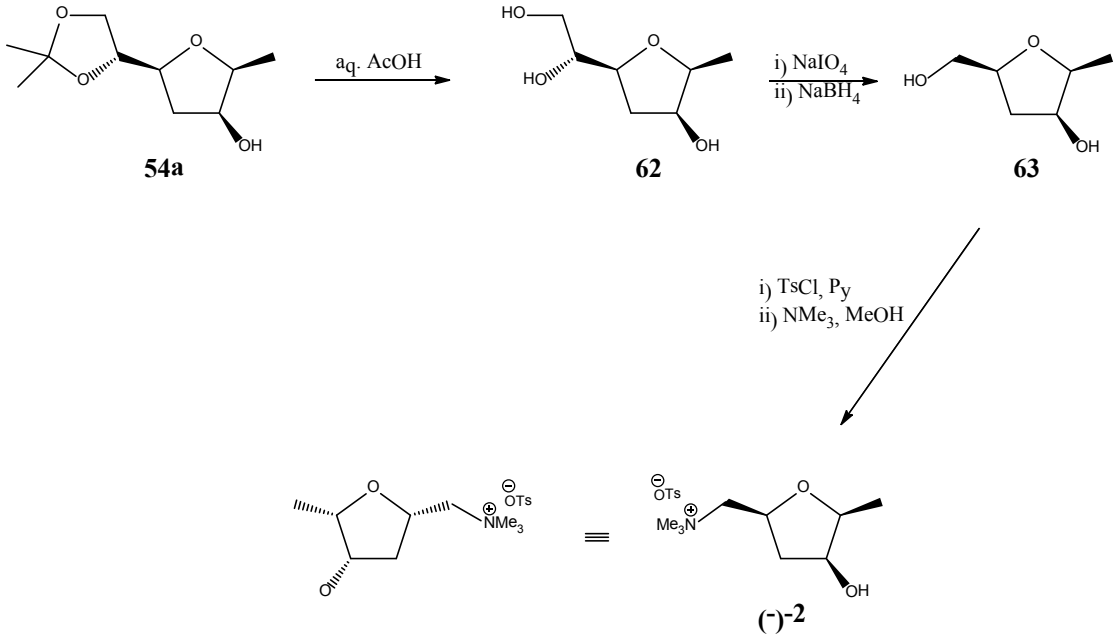
Scheme 1.2.2.2

The synthesis of L-(-)-muscarine-tosylate (Scheme 1.2.2.3) was progressed by Mitsunobu inversion of the hydroxyl group and conversion to its *O*-benzyl derivative **58** with triphenylphosphine, DEAZD and benzoic acid in dry THF. Acidic hydrolysis of **58** to **59**, followed by glycol cleavage and reduction, gave alcohol **60**. Methoxide-mediated ester cleavage enabled isolation of the crystalline diol **61**. The desired compound was attained using the procedure employed by Mubarek and Brown[1] *via* selective tosylation of the primary alcohol group, followed by reaction with methanolic trimethylamine.



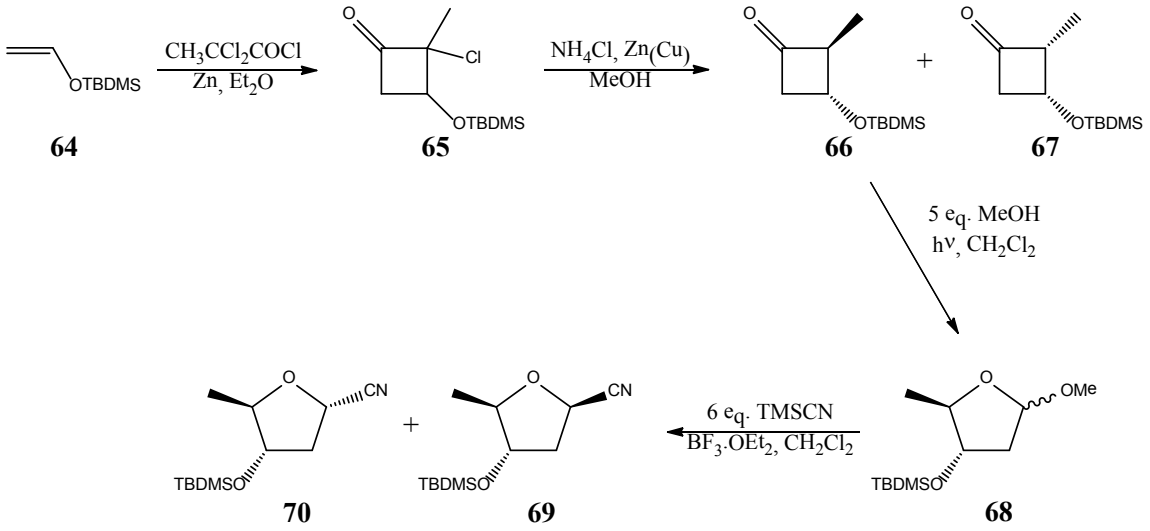
Scheme 1.2.2.3

Synthesis of L-(-)-epimuscarine was achieved by reaction of **54** with aqueous acetic acid, removing the isopropylidene protecting group to yield diol **62**. The glycol group was cleaved and the resulting compound reduced to **63**, before tosylation of the primary alcohol and subsequent reaction with trimethylamine in methanol resulted in the desired compound (Scheme 1.2.2.4).



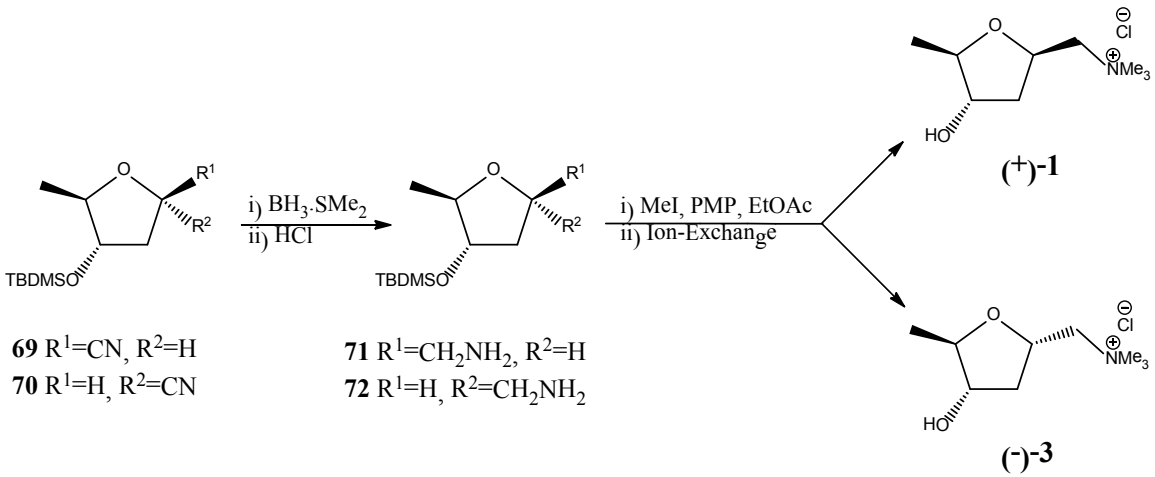
Scheme 1.2.2.4

Pirrung and DeAmicis'[13] total syntheses of **1** and **3** as their chloride salts were reported in 1988, where the key step was the stereospecific photochemical ring expansion of a cyclobutanone (Scheme 1.2.2.5). This particular synthesis commenced with cycloaddition of silyl enol ether **64** with methylchloroketene to yield **65** as a 4:1 mixture of isomers. The α-chloride was removed reductively with zinc-copper couple in methanol saturated with ammonium chloride to produce cyclobutanones **66** and **67** in a 3:1 mixture respectively, easily separated by flash chromatography. The desired cyclobutanone **66** was irradiated at -78 °C in dichloromethane containing 5 equivalents of methanol to yield the acetal **68** as a mixture of diastereomers. Reaction of these acetals with trimethylsilyl cyanide and borontrifluoride etherate in dichloromethane furnished a 1:1 mixture of nitriles **69** and **70**, separated by flash chromatography. These nitriles provide the key intermediates in completing the syntheses of the desired target molecules **1** and **3**.



Scheme 1.2.2.5

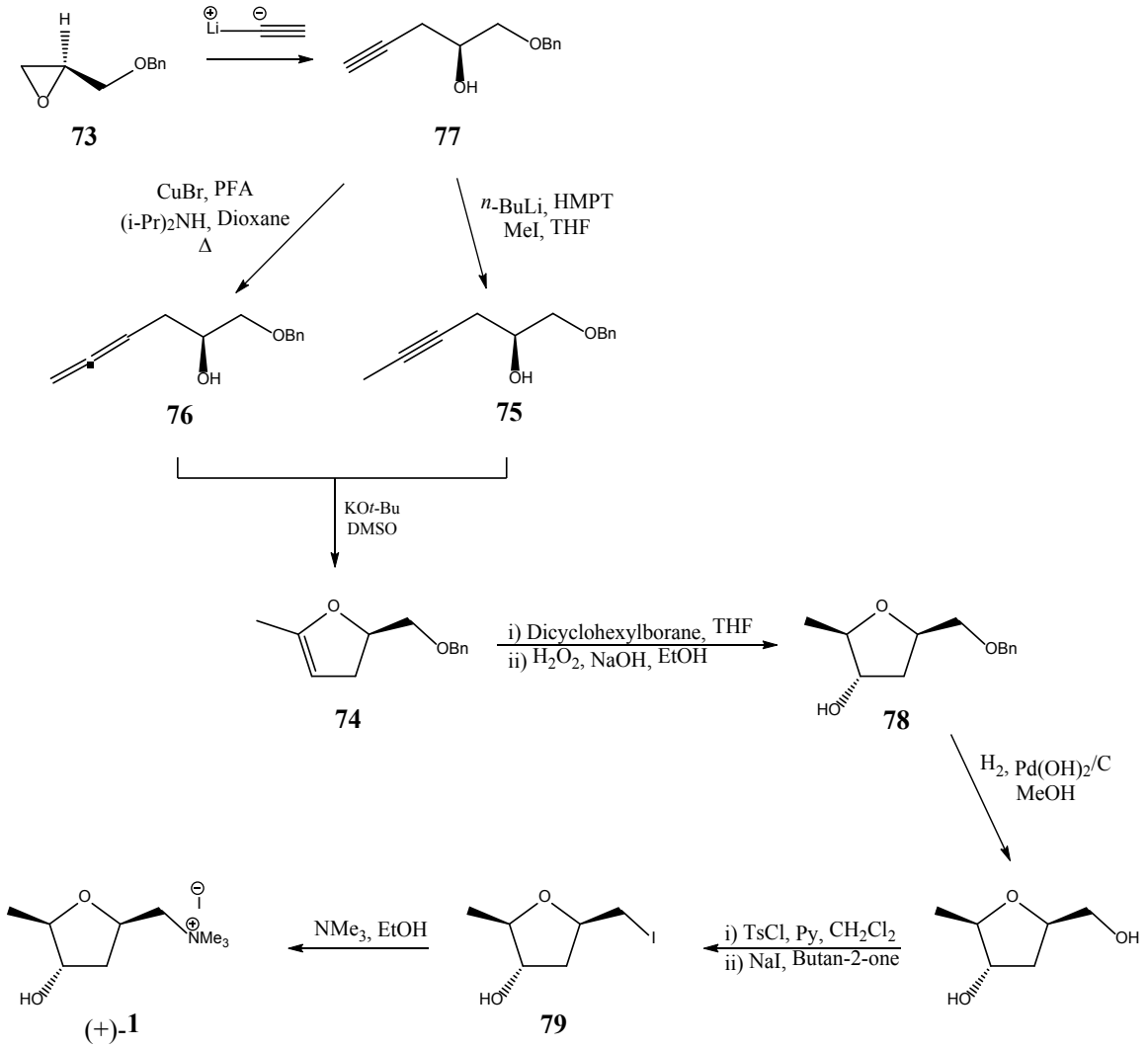
The synthetic path to both target molecules is identical from nitriles **69** and **70**, whereby treatment of the respective compounds with borane-dimethylsulfide complex followed by acid hydrolysis produces, almost quantitatively, the deprotected amines **71** and **72**. Quaternisation with excess methyl iodide and 1,2,2,6,6-pentamethylpiperidine (PMP) followed by ion exchange to the chloride furnishes **1** and **3** in 71% and 67% overall yields, from the respective nitriles (Scheme 1.2.2.6).



Scheme 1.2.2.6

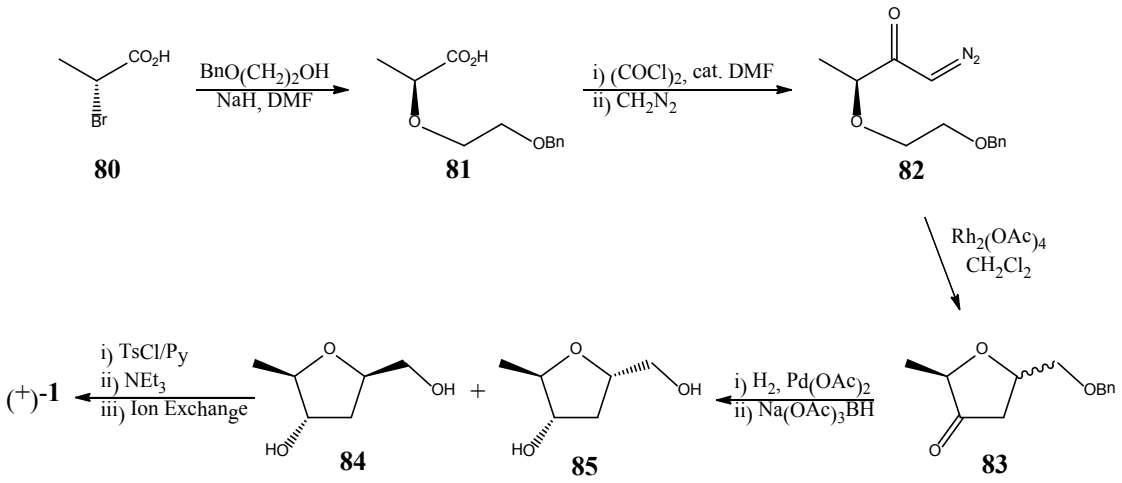
In 1989, Takano *et. al.*[14] reported a concise synthesis of (+)-**1**-iodide from an epoxide **73** (Scheme 1.2.2.7). This method allows for formation of a chiral 2,5-disubstituted-2,3-dihydrofuran **74** from both acetylenic **75** and allenic **76** precursors.

Alkylation of the acetylene alcohol **77** with methyl iodide and *n*-butyllithium gave rise to alkyne **75**. Treatment of **77** with paraformaldehyde and diisopropylamine in the presence of copper (I) bromide yielded the allenic alcohol **76**. Both the resulting allenic and acetylenic alcohols could be reacted separately with potassium *t*-butoxide in DMSO at 60 °C to furnish dihydrofuran **74**. Hydroboration[15]-oxidation stereoselectively introduced the necessary hydroxyl group on the furan ring **78**. Catalytic debenzylation of **78**, followed by tosylation and iodination to **79**. The synthesis was completed by reaction of **79** with ethanolic trimethylamine to produce (+)-muscarine-iodide **1** in 38% overall yield.



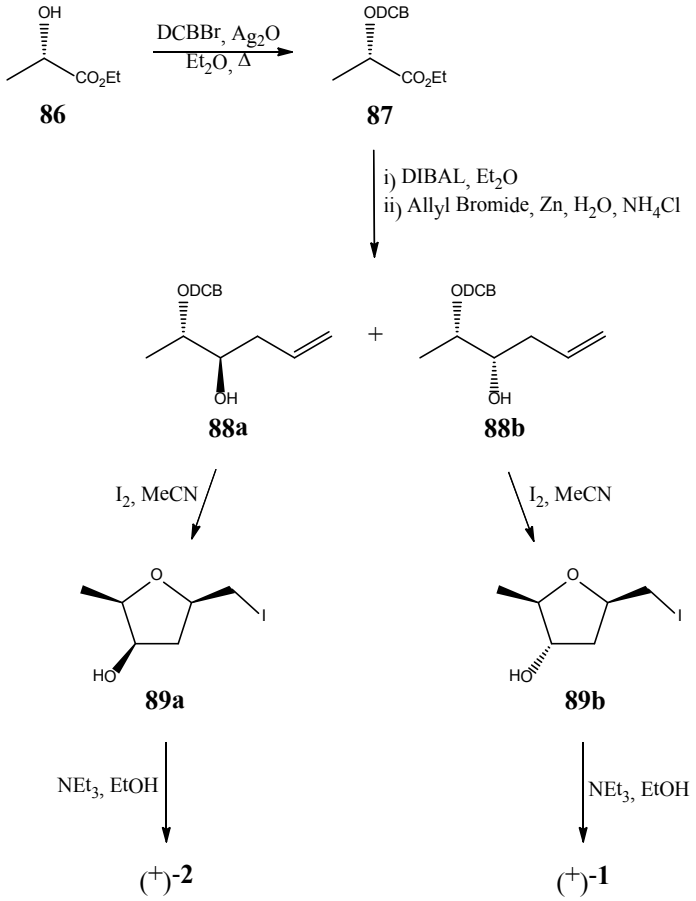
Scheme 1.2.2.7

Adams *et. al.*[16] reported a synthesis of (+)-muscarine-chloride **1** utilising the synthetically very useful and well studied rhodium catalysed carbenoid C-H insertion methodology (Scheme 1.2.2.8). The synthesis commenced with conversion of (*R*)-2-bromopropionic acid[17] **80** into acid **81**. The bromide was displaced with the sodium alkoxide of 2-benzyloxyethanol and the reaction proceeded with complete stereochemical inversion. Acid **81** was converted into its acid chloride derivative and subsequent reaction with diazomethane in dichloromethane afforded **82**. Rhodium (II) acetate cyclisation afforded furanone **83** and subsequent reduction produced a mixture of diols **84** and **85**, which were readily separated by flash chromatography. The synthesis was completed as per methods already outlined, from the diol **84**.



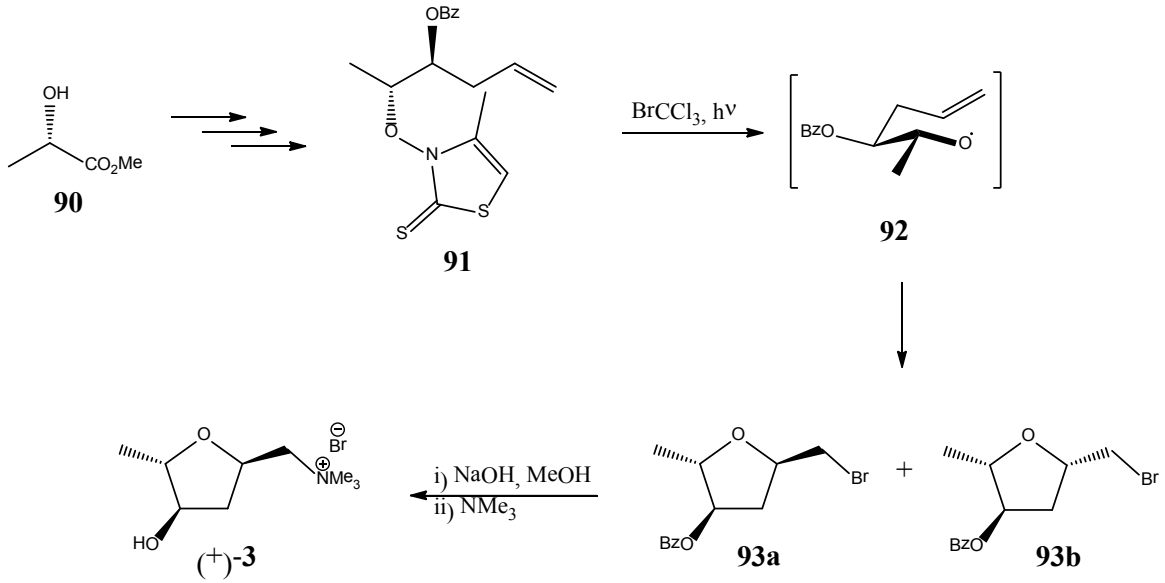
Scheme 1.2.2.8

Chan and Li, in 1992,[18] devised a five-step synthesis (Scheme 1.2.2.9) of **1** and **2** from *S*-(-)-ethyl lactate **86**, which was converted to its 2,6-dichlorobenzyl ether **87**. Subsequent reduction of the ester followed by reaction with allyl bromide and zinc powder/catalytic ammonium chloride in water resulted in a chromatographically separable 71:29 mixture of **88a** and **88b** respectively. Both diastereomers were then cyclised with iodine in acetonitrile before reaction of the respective iodo alcohols **89a** and **89b** with excess methyl iodide gave the desired natural products **1** and **32**.



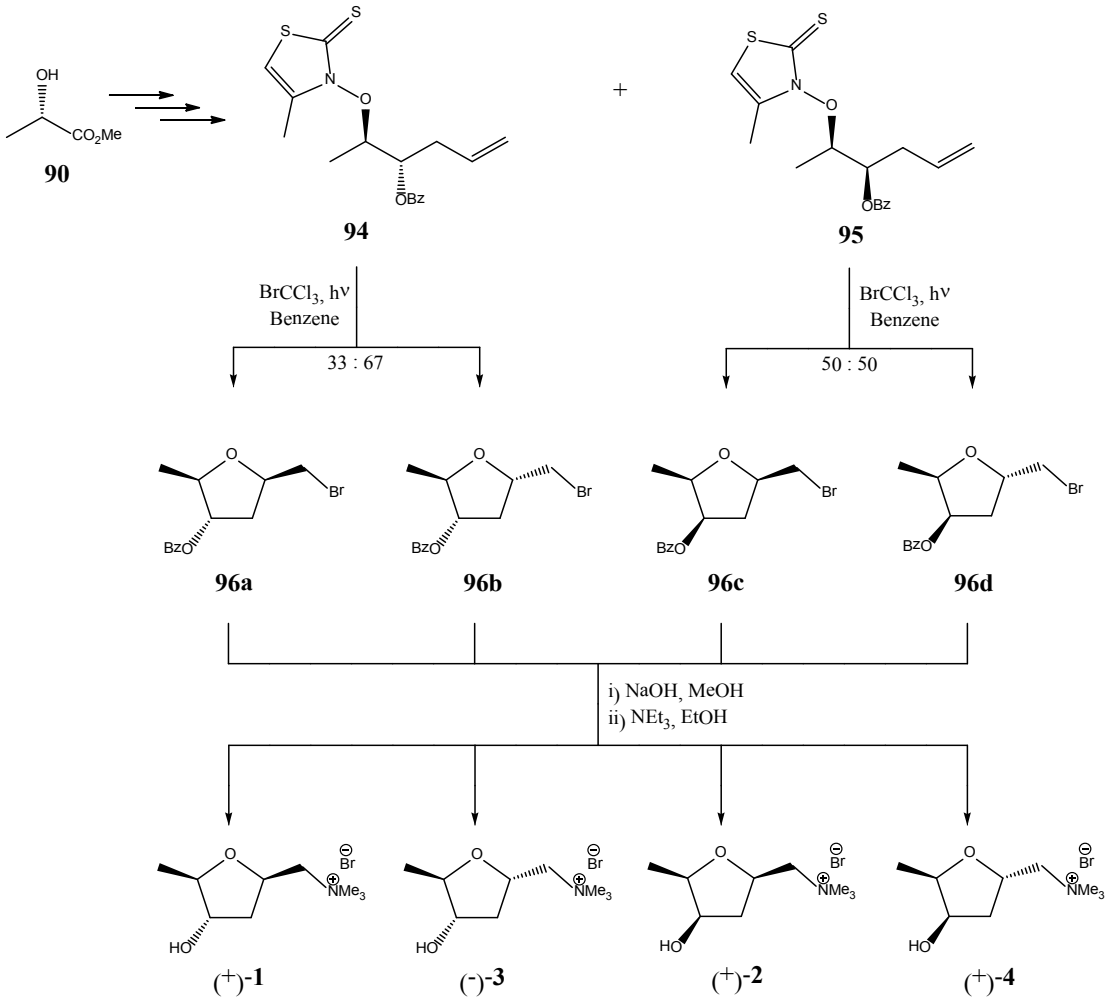
Scheme 1.2.2.9

Hartung and Kneuer[19] published a synthesis of (+)-**3**-bromide, starting from *S*-(-)-methyl lactate **90** and utilising ring closing reactions of disubstituted 4-penten-1-oxyl radicals **92** to form tetrahydrofurylmethyl radicals from its precursor **92**. These were subsequently trapped with bromotrichloromethane to afford a mixture of diastereomeric bromomethyl-substituted cyclic ethers **93a** and **93b**. The diastereomers were separated and **93a** was then converted to (+)-**3**-bromide by a two-step synthetic path (Scheme 1.2.2.10).



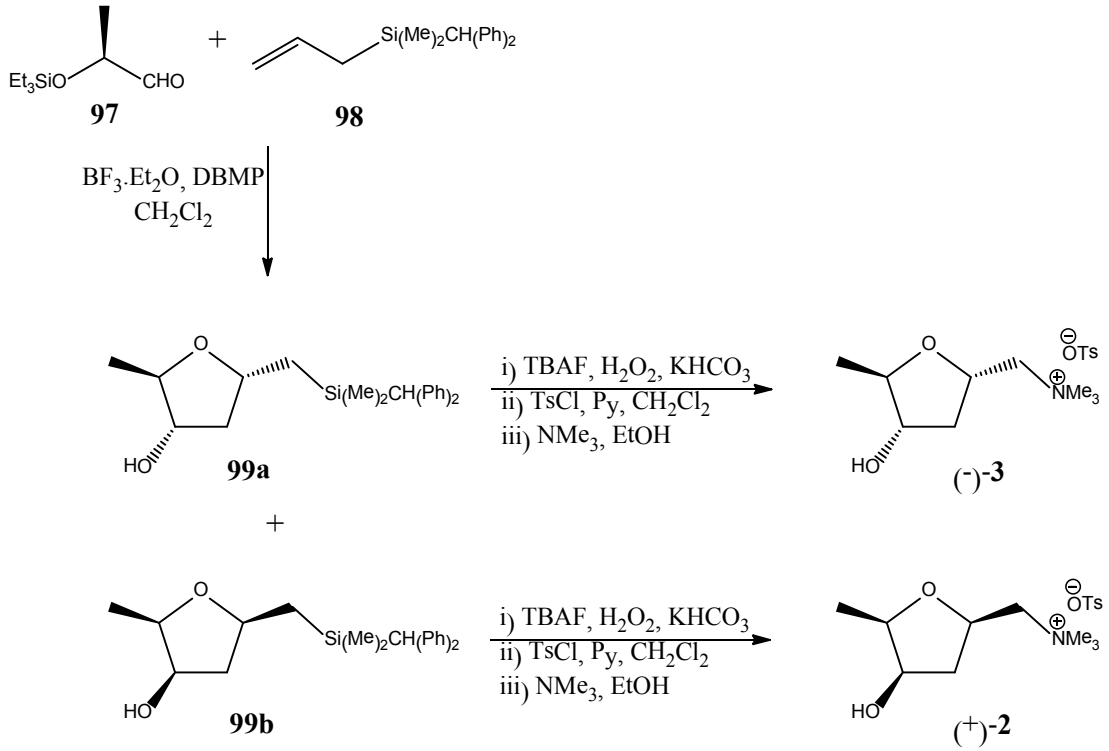
Scheme 1.2.2.10

With the above synthesis completed, the same researchers[20] extended the methodology to the syntheses of all four (2*R*)-configured muscarines *via* alkoxy radical cyclisation products. The synthesis commenced from *S*-(-)-methyl lactate **90** and several steps later the key thiazolethione intermediates **94** and **95** were formed. As can be seen in Scheme 1.2.2.11, *anti*-**94** undergoes radical cyclisation with bromotrichloromethane and benzene under photolysis to yield bromomethyl-substituted cyclic ethers **96a**:**96b** (33:67), chromatographically separated. Subsequent reaction of **96a** and **96b**, respectively, with methanolic sodium hydroxide followed by trimethylamine in ethanol produced muscarine analogues (+)-**1** and (-)-**1**. The synthesis of the remaining two muscarines (+)-**2** and (+)-**2** proceeded from *syn*-**94** *via* **96c**:**96d** (50:50).



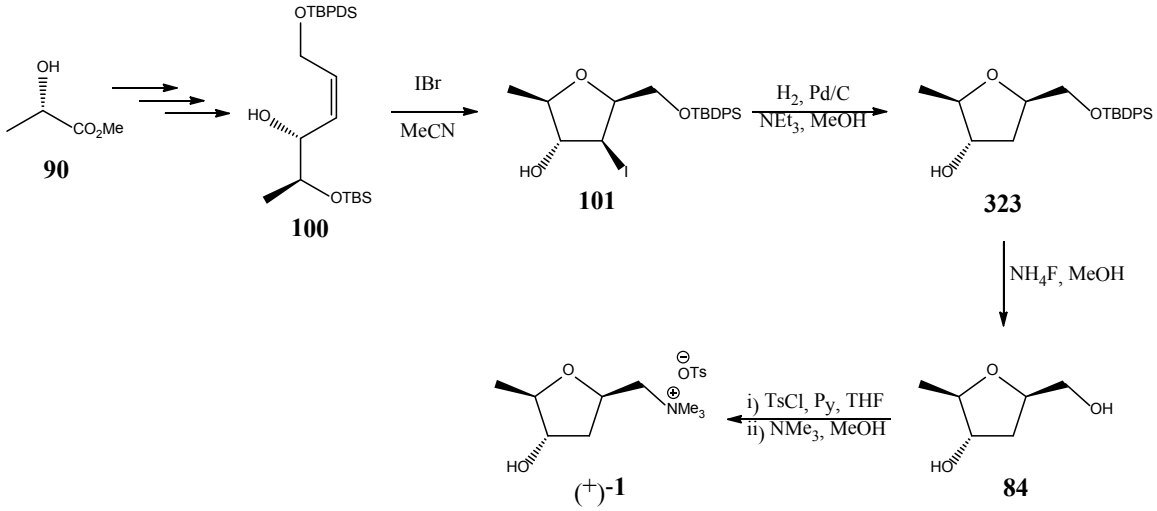
Scheme 1.2.2.11

Angle and Al-Said,[21] in 2002, published their synthesis of (-)-allomuscarine and (+)-epimuscarine *via* a formal cycloaddition of aldehydes with allylsilanes (Scheme 1.2.2.12). Aldehyde **97** and allylsilane **98** were reacted with boron trifluoride diethyletherate and 2,6-di-*t*-butyl-4-methylpyridine (DBMP) in dichloromethane to yield silyl substituted tetrahydrofurans **99a** and **99b**. The desired products were afforded by modified Tamao oxidation of the silyl group to a primary alcohol followed by previously reported conversion[9, 12, 14] of the respective primary alcohols into the muscarines.



Scheme 1.2.2.12

Knight and Staples,[22] reported a nine-step synthesis of (+)-**1**, as its *p*-toluenesulfonate salt, from *S*-methyl lactate **90** *via* 5-*endo*-trig cyclisations (Scheme 1.2.2.13). The key step in the reaction is the iodocyclisation[23] of **100** to iodotetrahydrofuran **101** as a single diastereomer[24] and in a stereochemical configuration that allows for completion of the synthesis of (+)-**1**. The iodo-moiety was removed by hydrogenolysis[3] before deprotection of **323** to the diol **84**. Conversion of **84** to (+)-**1** was achieved by selective tosylation of the primary alcohol group followed by heating with trimethylamine in methanol at 80 °C.[26, 27]

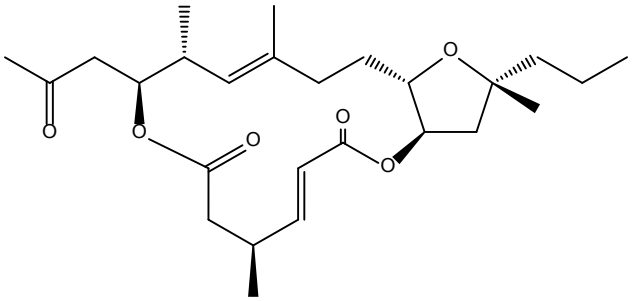


Scheme 1.2.2.13

1.3 Amphidinolides X and Y

Amphidinolides X **102** and Y **103a/b** are a novel class of cytotoxic macrodiolides from extracts of marine dinoflagellates of the *Amphidinium* spp. Both compounds were first isolated and characterised by the research group of Tsuda in 2003. These are a class of compounds that possess esterified hydroxytetrahydrofuran moieties in their molecular structures. Intramolecular lactone forming reactions involving 3-hydroxytetrahydrofurans are an established feature in the total syntheses of amphidinolides.

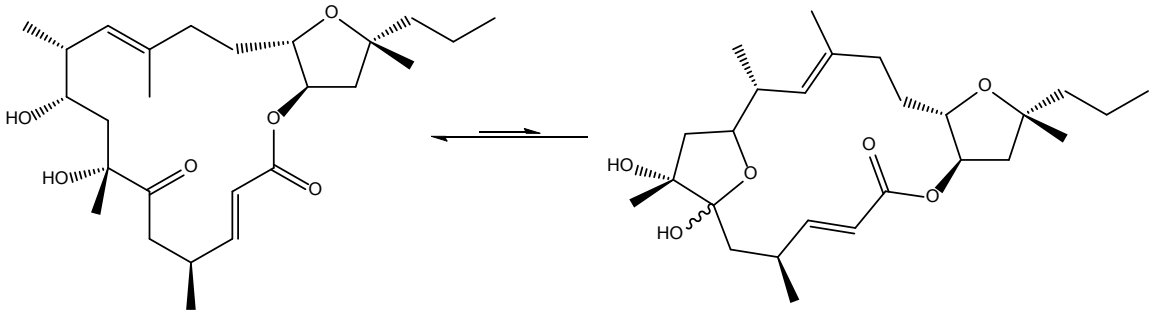
Macrolide **102** was found to be a 16-membered diolide consisting of polyketide derived diacid and diol units, the first of its kind. The structural properties were elucidated using various NMR techniques such as COSY, TOCSY and HSQC, with NOESY techniques employed to establish its relative and absolute stereochemistry.[28]



102

Figure 1.3.1 Structure of Amphidinolide X **102**

Amphidinolide Y was isolated as a 17-membered macrolide and is a plausible biogenetic precursor for **102**. The isolate of Amphidinolide Y was found to exist as a 9:1 equilibrium mixture of keto and hemiacetal forms (**103a** and **103b**, respectively), on the basis of 2D NMR studies.



103a **103b**

Figure 1.3.2 Structure of Amphidinolide Y **103a/b**

The first total synthesis of amphidinolide X **102** was published in 2004 by Fürstner *et. al.*[29] Retrosynthesis of the target molecule gave rise to three main fragments, leading to intermediates **105**, **106** and the hydoxytetrahydrofuran derivative **104**. The tetrahydrofuran segment was produced by a six-step synthesis from (*E*)-5-((*t*-butyldiphenylsilyl)oxy)pent-en-2-ol **107** *via* a propargyl epoxide to furnish a bromo-ester. The final step was bromine removal following standard protecting group manipulations.

Vinyl iodide segment **105** was accessed by palladium-catalysed addition of an enantiopure propargyl mesylate to an aldehyde ketal. Hydrozirconation/iodination of the resultant alkyne followed by cleavage of the OPMB group furnished **105.**

The final intermediate, carboxylic acid **106**, was derived from a known aldehyde.[30] Subsequent Wittig coupling was followed by Swern and Pinnick oxidations producing **106**.

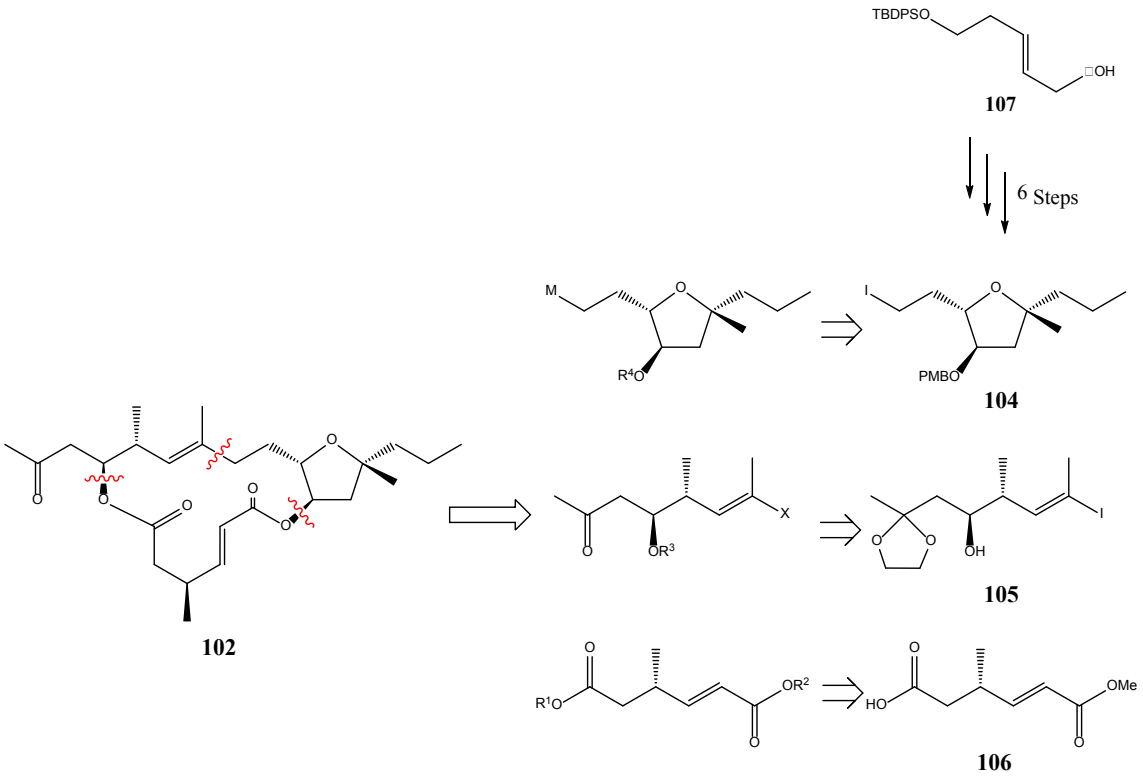
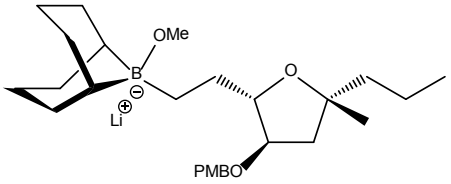


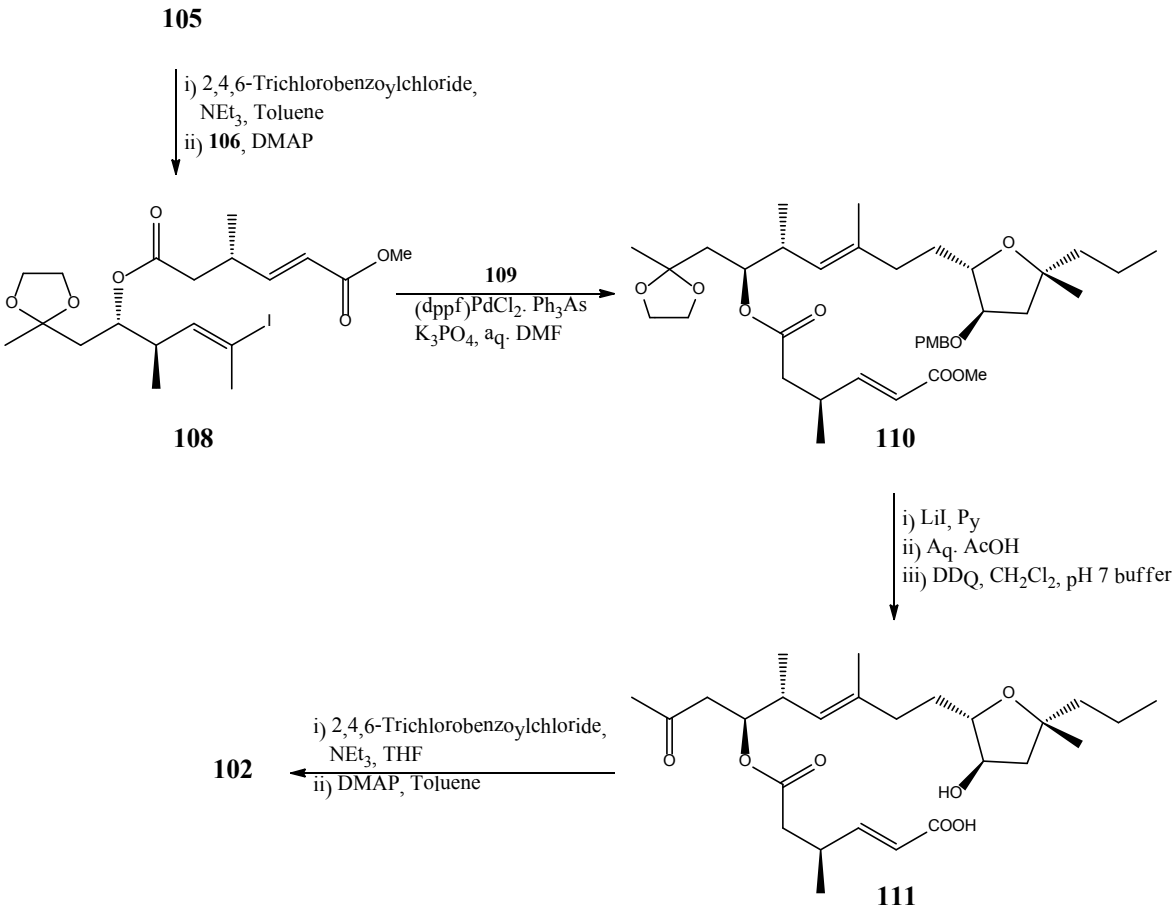
Figure 1.3.3 Retrosynthetic Analysis of **102**

Now that the relevant building blocks were in hand, the authors began the process of combining them to furnish **102** (Scheme 1.3.1). The first step involved Yamaguchi esterification of **105** and **106** to produce **108**. The next stage was combination of **108** with the tetrahydrofuran segment. This required the conversion of **104** to a borate using 9-methoxy-9-borabicyclononane, before palladium-mediated reaction of **108** with **109** to furnish methyl ester **110**. The synthesis of **102** was completed by cleavage of the methyl ester, successive removal of the ketal and PMB moieties and final cyclisation of **111** to give amphidinolide X **102** in 62% yield.



109

Figure 1.3.4 Borate **109**



Scheme 1.3.1

Fürstner *et. al.*[31] published the first reported synthesis of amphidinolide Y **103** in 2006. They took a similar retrosynthetic analysis approach to the previous example as the tetrahydrofuran scaffold **104** is common to both natural products. Fragment **112** required further disconnections to ultimately furnish aldehyde **113** and ketone **114** as the key synthetic intermediates, which the authors envisaged would be coupled *via* an aldol reaction.

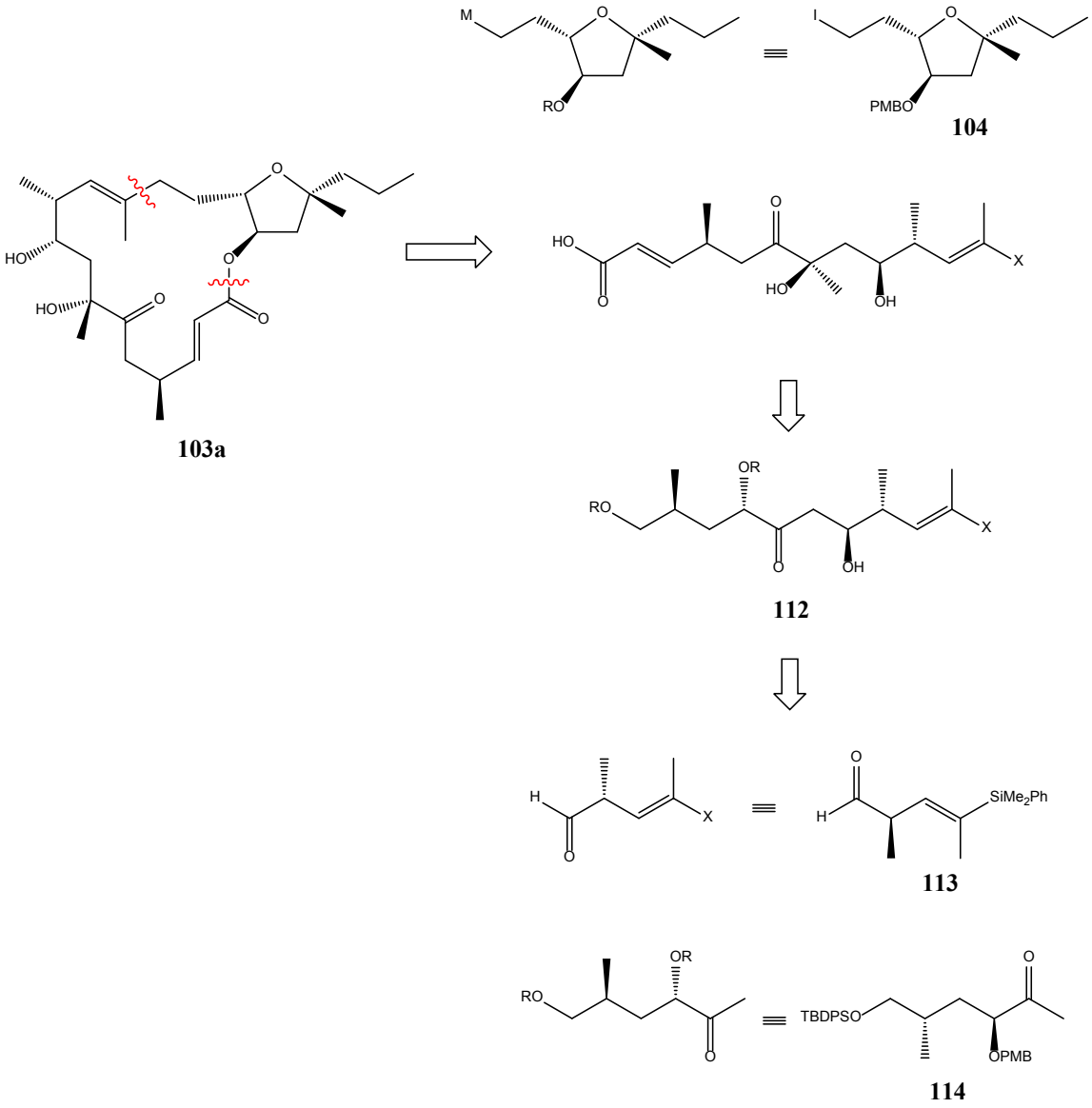
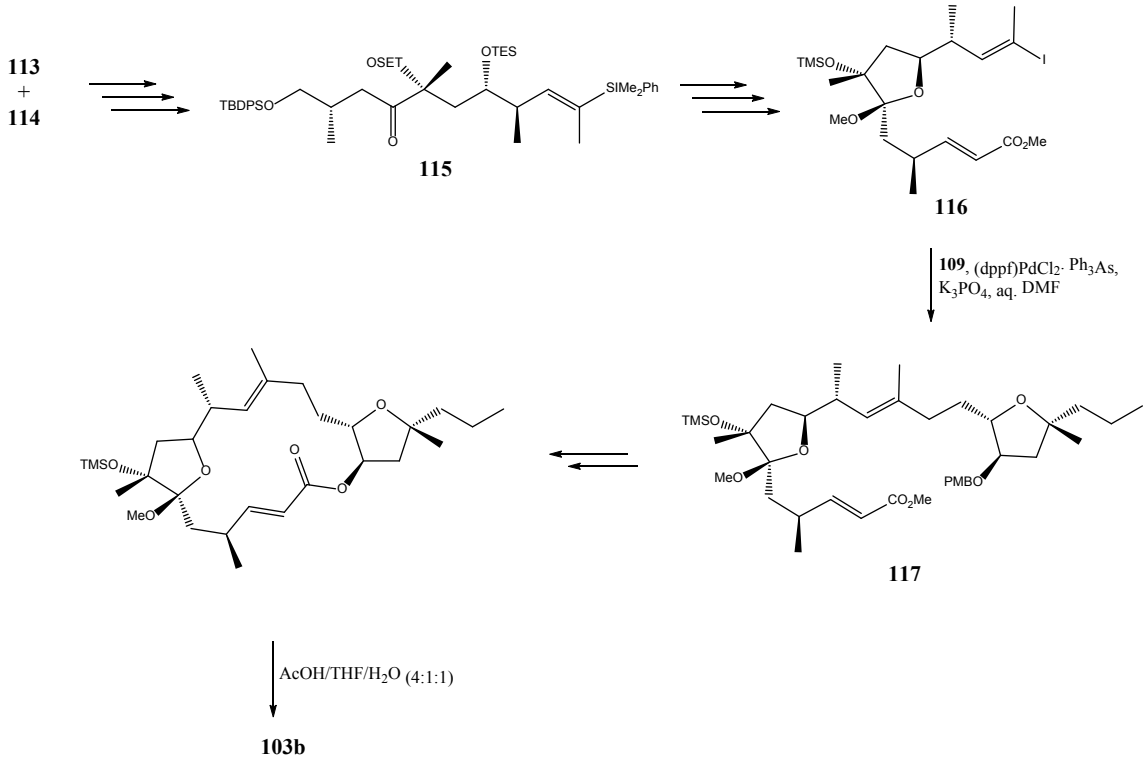


Figure 1.3.5 Retrosynthetic Analysis of **103a**

The aldol reaction of **113** with **114** was achieved by reaction with diethylboron triflate and diisopropylethylamine in toluene at -90 °C (Scheme 1.3.2). Conversion of **115** into enoate **116** occurred in four steps *via* camphorsulfonic acid-mediated cyclisation, iodination of the terminal vinylsilane group, primary alcohol oxidation and finally Horner-Wadsworth-Emmons reaction.

Attachment of the tetrahydrofuran segment **109** occurred as in the previous example[29] to produce **117**. The total synthesis of **103** was completed in four steps by removal of the PMB protecting group in **117**, conversion of the methyl ester to its

triethylammonium carboxylate salt, cyclisation to the hydroxytetrahydrofuran, and deprotection with dilute acetic acid in aqueous THF.



Scheme 1.3.2

There have been several publications in which alternative syntheses of **102** and **103** have been centered around altering the hydroxytetrahydrofuran-containing fragment.

Figure 1.3.6 shows two examples of such work; on the left-hand side Rodriguez-Escrich *et. al.*[32] identified **118** as the desired hydroxytetrahydrofuran with further retrosynthesis yielding *anti-Z*-diol **119** as the key intermediate. Diol **119** was accessed by a three-step reaction from combination of a vinyl iodide with an enantiopure aldehyde. The desired tetrahydrofuran framework was furnished through cyclisation of **119** with phenylselenylchloride, followed by removal of the phenylselenyl moiety with tris(trimethylsilyl)silane and azo-bisisobutyronitrile to produce **118**.

On the right-hand side of Figure 1.3.6, Doan's[33] synthetic plan is outlined. Further retrosynthesis of the desired hydroxytetrahydrofuran produced allylic alcohol **120** as the key intermediate. This alcohol is readily available in stereochemically-pure form from geraniol in four steps.[34, 35] What followed was a seven-step synthetic path to a vinyl

oxirane, that when treated with camphorsulfonic acid furnished **121** in 79% yield and 90% e.e.

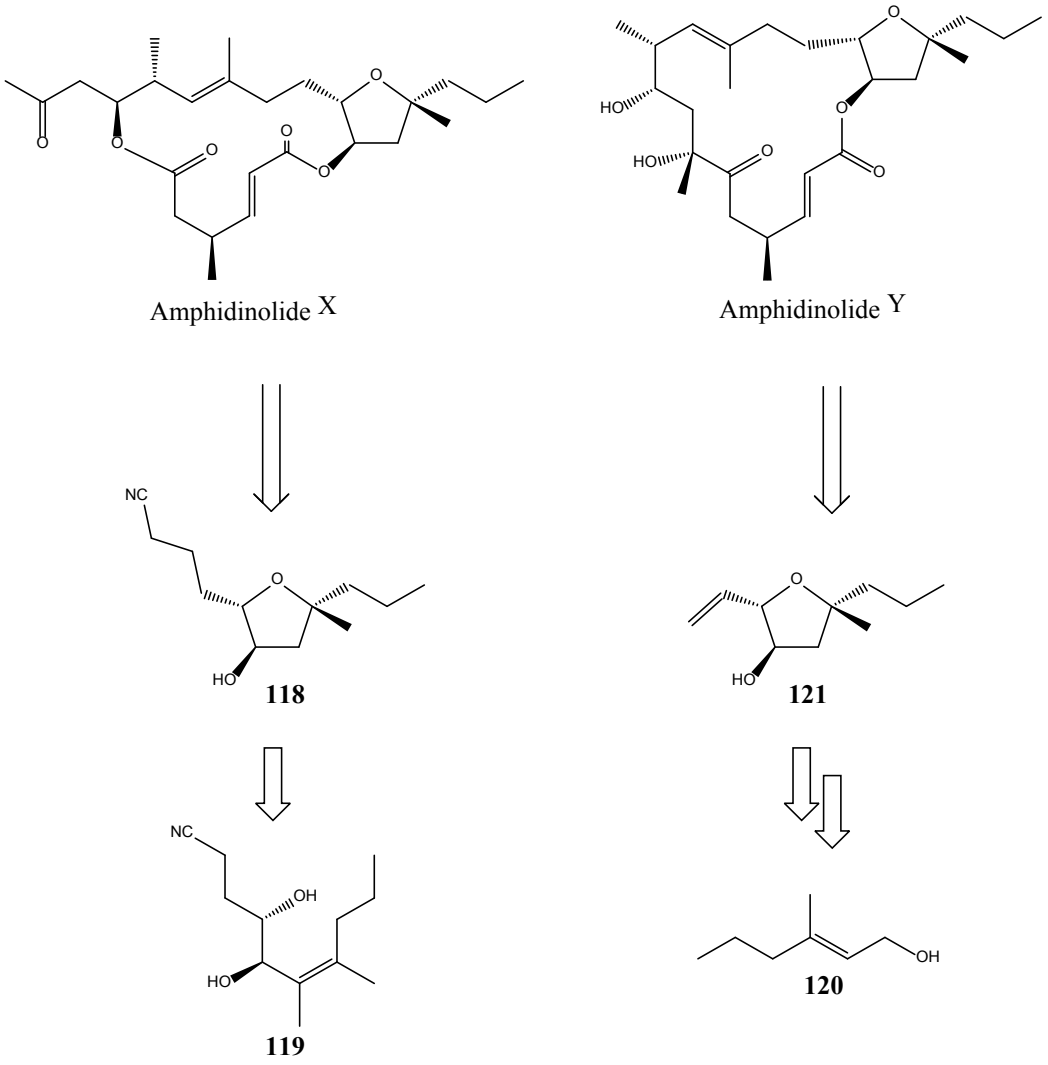
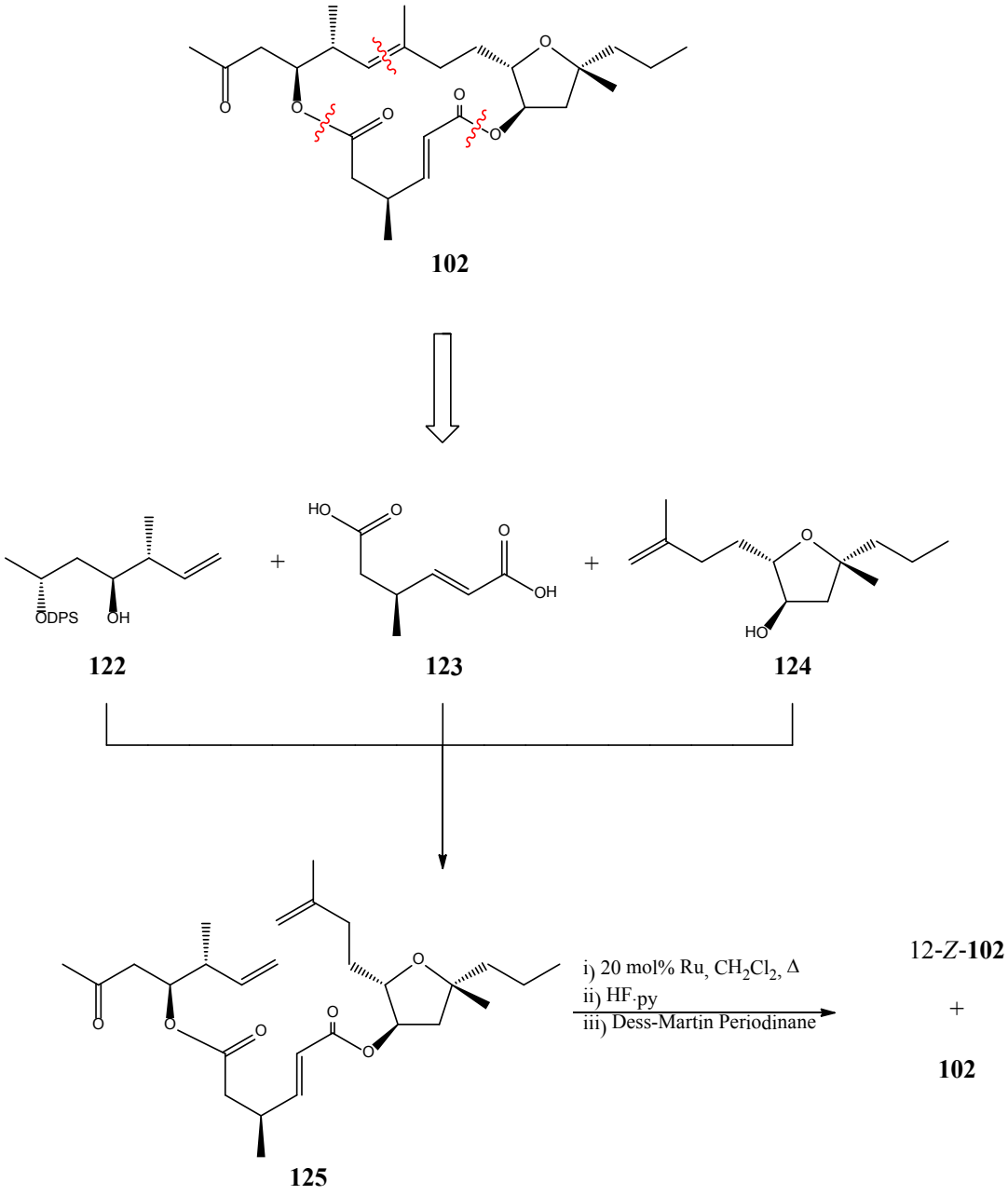


Figure 1.3.6 Synthetic plan for syntheses of **102** and **103**

Dai *et. al.*[36] have synthesised amphidinolide X and its 12-*Z*-isomer (12-*Z*-**102**) utilising ring-closing metathesis chemistry. This total synthesis followed on from their 2007 publication of a total synthesis of amphidinolide Y.[37] Their retrosynthesis identified fragments **122**, **123** and hydroxytetrahydrofuran **124** as the desired building blocks in the synthesis (Scheme 1.3.8). They were coupled together *via* an eight-step synthesis to furnish the tetrahydrofuran-containing compound **125**, then cyclised in the presence of a second generation Grubbs catalyst to produce **102** and its 12-*Z*-isomer in a 71:29 (*E*:*Z*) ratio. Both the *E*- and *Z*- isomers were subjected to testing against several cancer cell

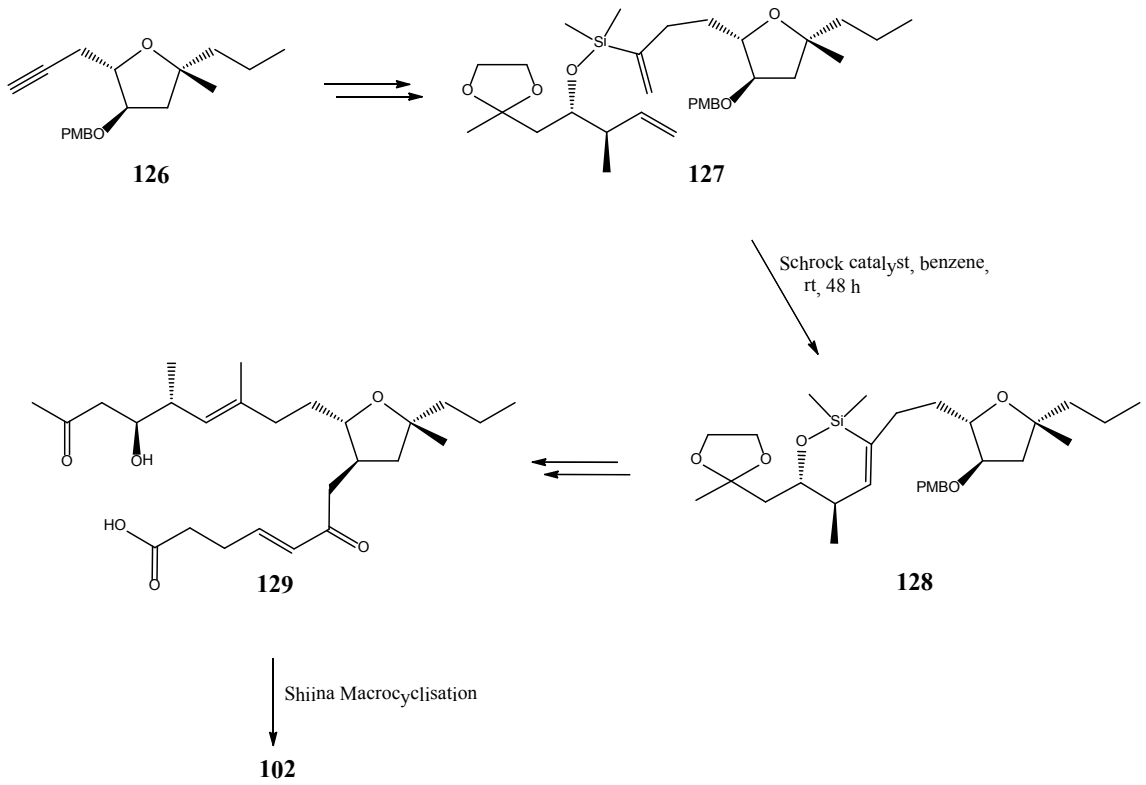
lines. Both isomers exhibit similar cytotoxicity, (IC_{50}: 7.6-13.9 μg/mL), indicating that the geometry of the trisubstituted alkene is not essential for cytotoxic activity.



Scheme 1.3.3

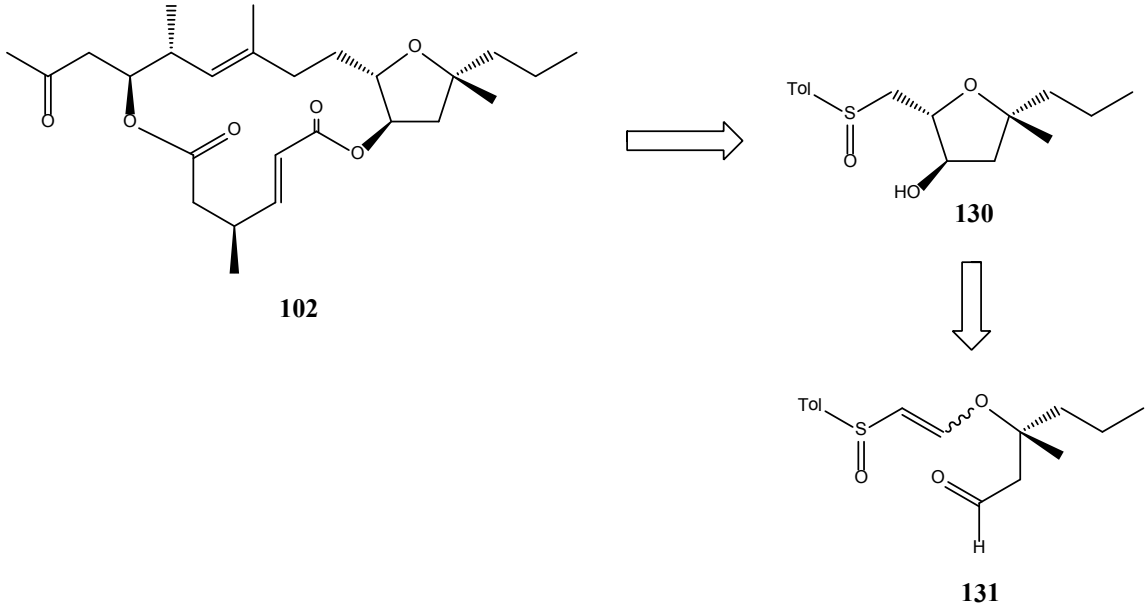
In the previous example for total synthesis of **102**, it was observed that there was no reaction when Schrock's catalyst was employed in the ring-closing metathesis reaction and a mixture of the *E*/*Z* isomers was observed when using ruthenium-based Grubbs catalysts. Rodriguez-Escrich *et. al.*[38], however, reported a stereocontrolled total synthesis of **102** *via* a silicon-tethered metathesis reaction that produced **102** exclusively as the

desired *E*-isomer (Scheme 1.3.4) from the tetrahydrofuran **126** via intermediates **127**, **128** and **129**.



Scheme 1.3.4

Jung and Lee's synthesis[39] of **102**, contained many synthetic features of previous total syntheses of the natural product. However, they took a novel approach to the synthesis of the tetrahydrofuran-containing segment of **102**. Retrosynthesis identified the sulfinyl hydroxytetrahydrofuran **130** as the key structural element, obtained by 5-*exo*, samarium-mediated cyclisation of aldehydo-β-alkoxyvinyl sulfoxide **131** (Figure 1.3.7). Synthesis of **102** was achieved through combination of the various required fragments and final macrocyclisation was again carried out *via* ruthenium-catalysed ring closing metathesis.



102 **130** **131**

Figure 1.3.7 Retrosynthetic analysis of **102**

It is generally widely believed that the key aspect of the total synthesis of **102** is based on construction of the tetrahydrofuran-containing fragment in a stereocontrolled manner. In a recent paper, Gurjar *et. al.*[40] reported a carbohydrate-based route to the tetrahydrofuran core of amphidinolide X. Retrosynthesis yielded two major fragments **132** and **133**, envisaged to arise *via* a Julia coupling[41, 42] (to form the C12-13 double bond) and Yamaguchi lactonisation, as described in previous examples. Further retrosynthesis of **132**, gave the desired carbohydrate based starting point in the synthesis, L-sorbose **134**. This publication did not report the full synthesis of the natural product, only the synthesis of the tetrahydrofuran fragment that could be subsequently utilised in a total synthesis of **102**.

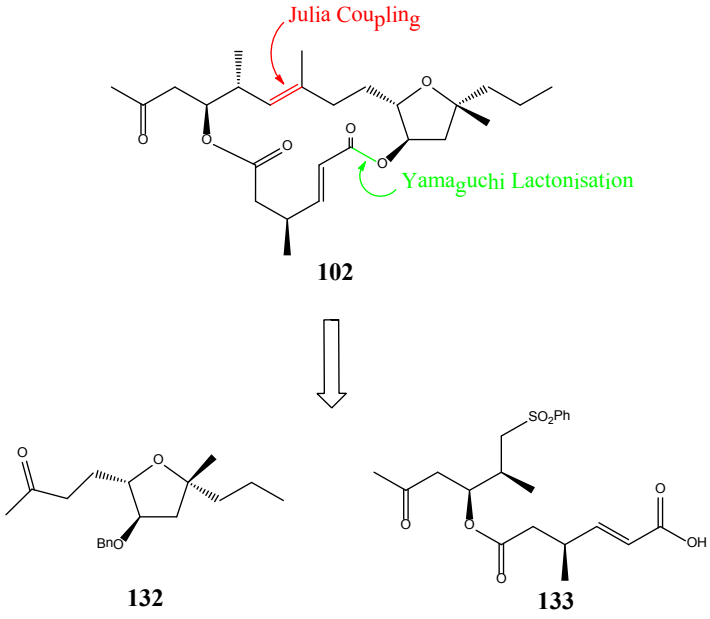
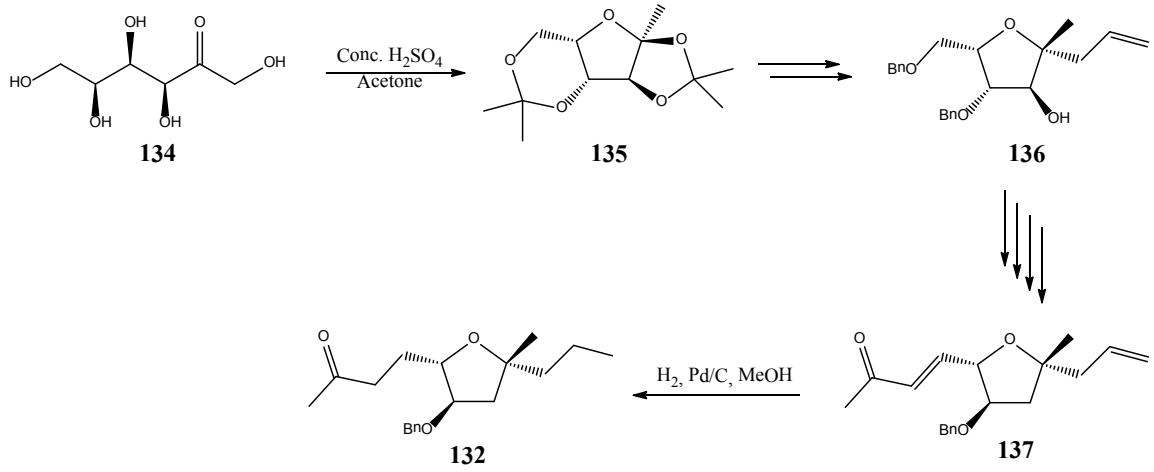


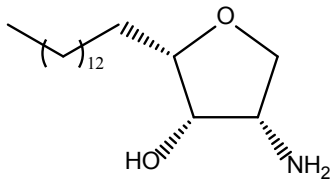
Figure 1.3.8 Retrosynthetic analysis of **102**

What followed to synthesise the tetrahydrofuran-containing fragment **132** was an eleven-step reaction sequence from **134** (Scheme 1.3.5). Various classical organic reactions were involved along the way through intermediates **135** and **136**; including protecting group chemistry, Barton-McCombie deoxygenation, Mitsunobu inversion, Dess-Martin oxidation to reach compound **137**, the precursor to the desired fragment **132**. This fragment was delivered through reduction of both alkene groups of **137** without cleavage of the benzylether group.



Scheme 1.3.5

1.4 Pachastrissamine (Jaspine B)

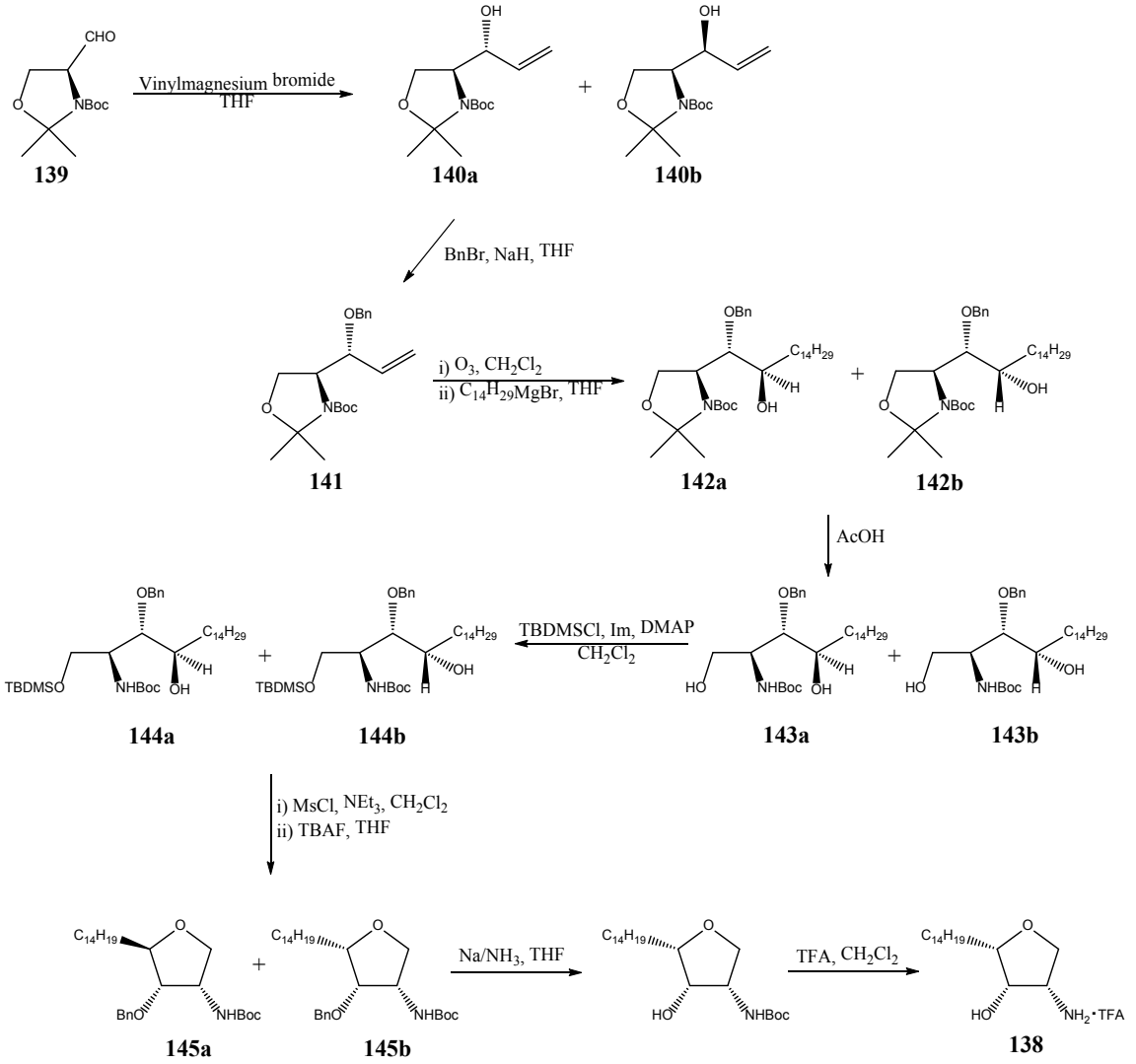


138

Figure 1.4.1 Structure of Pachastrissamine (Jaspine B) **138**

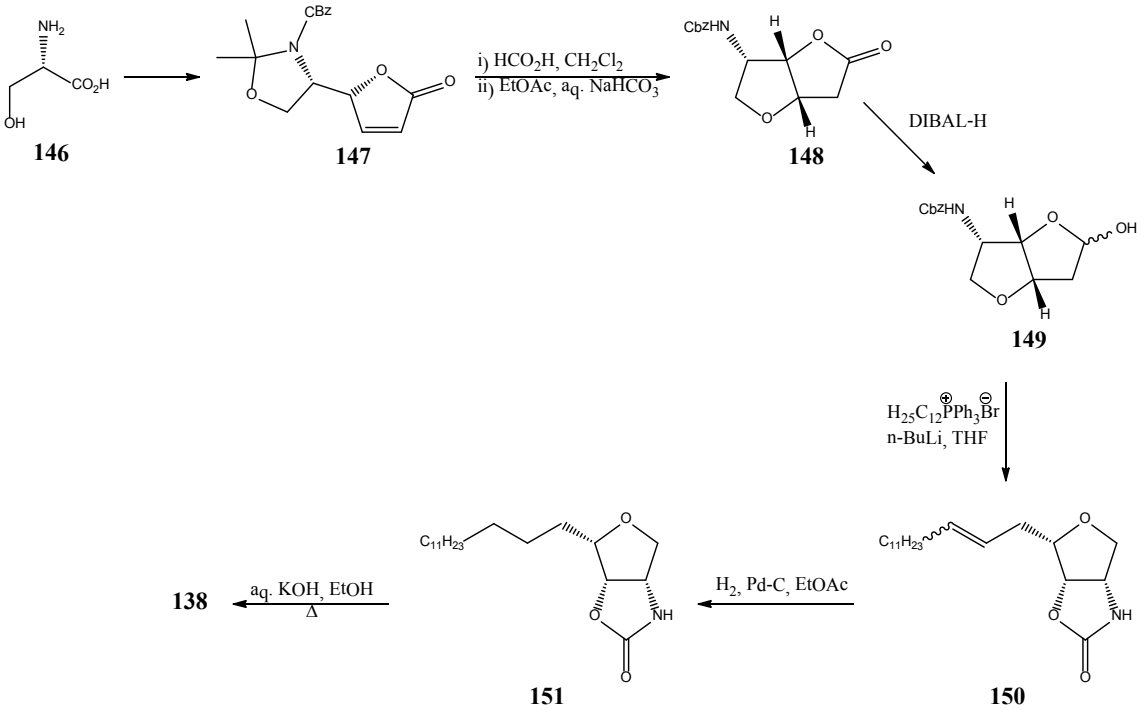
In 2002, Pachastrissamine **138** was isolated from the Okinawan marine sponge *Pachastrissa* spp.[43] In 2003, research carried out by Ledroit[44] led to the isolation of the same natural product from a different marine sponge, *Jaspis* sp., leading to the name Jaspine B. The all-*syn* trisubstituted hydroxytetrahydrofuran framework and its absolute configuration was assigned on the basis of NMR, mass spectrometry and chemical derivatisation studies. This natural product is reported as being the first containing anhydrosphingosine structural features and was tested against several human cancer cell lines and exhibited submicromolar cytotoxic activity leading to many research groups investigating total synthesis and structure-activity relationship studies of this natural product.

The first total synthesis of Jaspine B (as its TFA salt) was reported in 2005 by Sudhakar *et. al.*[45] using Garner's aldehyde[46] **139** as the starting material. Stereoselective addition of vinylmagnesium bromide to **139** produced the allylic alcohols **140a** and **140b** in a 6:1 mixture, separated by column chromatography. Isomer **140a** was protected as its benzyl ether **141** before oxidative degradation with ozone followed by Grignard addition afforded **142a** and **142b** as an inseparable 7:3 mixture of diastereomers. The acetonide group was subsequently deprotected with 80% acetic acid (**143a** and **143b**), before conversion to silyl ethers **144a** and **144b**. Reaction of these silyl ethers with methanesulfonyl chloride followed by treatment with TBAF produced the five-membered heterocycles **145a** and **145b** in a 7:3 ratio, separable by chromatography. To complete the synthesis the *O*-benzyl ether of **145b** was cleaved with sodium in liquid ammonia before treatment with 50% TFA-DCM furnished the natural product **138** as its trifluoroacetate salt (Scheme 1.4.1).



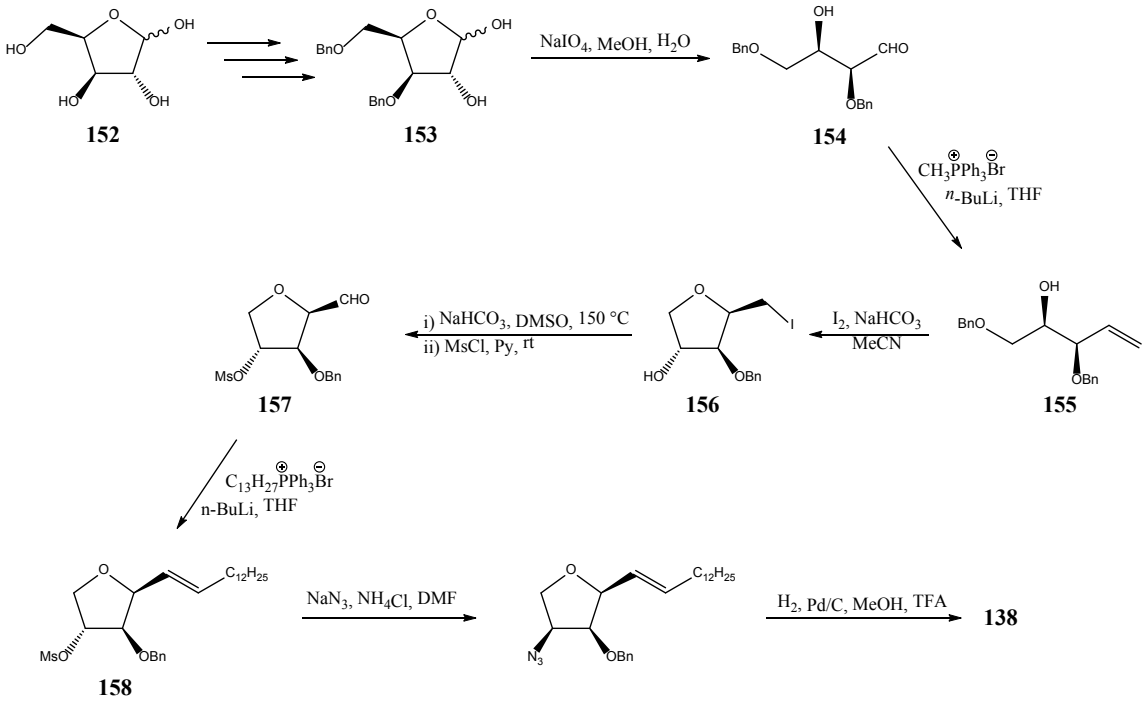
Scheme 1.4.1

Later that year, Bhaket and co-workers[47] reported their total synthesis of **138** from L-serine **146** (Scheme 1.4.2). Chiral lactone **147** was prepared from **146** using a protocol developed by the same authors before conversion into lactone **148**. Reduction to the lactol derivative **149** followed by Wittig olefination with the desired C-12 alkyl donor resulted in the formation of **150** as an inseparable mixture of *E*- and *Z*-isomers. The alkene group of the alkyl side chain was removed by catalytic hydrogenation to **151** before alkaline hydrolysis of the cyclic carbamate yielded **138**, with all relevant spectral and analytical data concurrent with the reported data.[44]



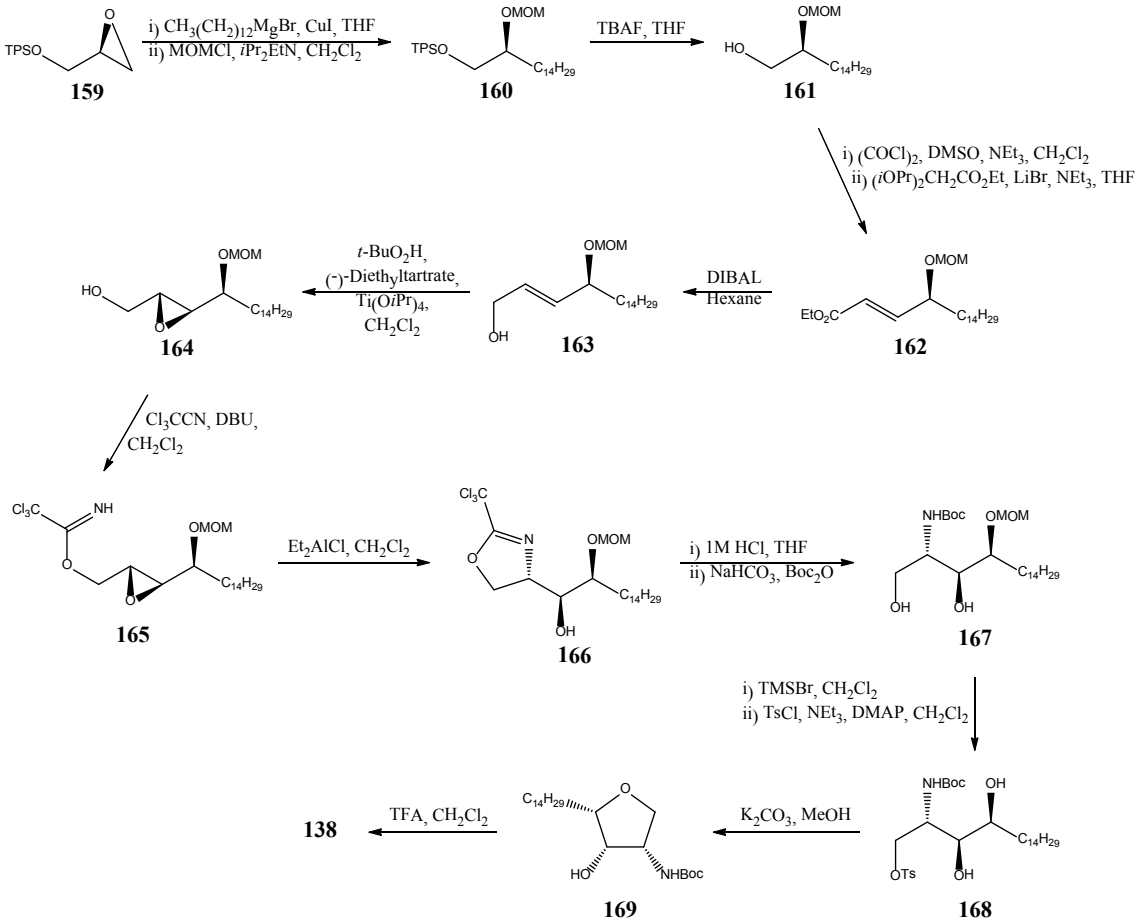
Scheme 1.4.2

Liu and co-workers,[48] in 2006, published a stereoselective total synthesis of **138**. However, upon scale-up of this particular synthesis several issues arose. This led to development and, ultimately, publication of their eleven step synthesis later that same year (Scheme 1.4.3).[49] The synthesis commenced with selective dibenzylation of D-xylose **152** in a three-step reaction[50, 51] to furnish furanose derivative **153**. Reaction of **153** with sodium periodate in methanol[52] produced acyclic aldehyde **154** that was directly subjected to Wittig olefination, yielding terminal alkene **155**. Next, the iodohydroxytetrahydrofuran **156** was accessed *via* an iodine-induced consecutive cyclisation/benzyl deprotection[53-56] and then subsequently transformed into aldehyde **157** with DMSO.[57] Mesylation of **157**, followed by further Wittig olefination furnished **158** as a mixture of isomers (>10:1, Z:E). S_N2 substitution of **158** with sodium azide followed by catalytic hydrogenation produced **138** as its TFA salt in 24% overall yield.



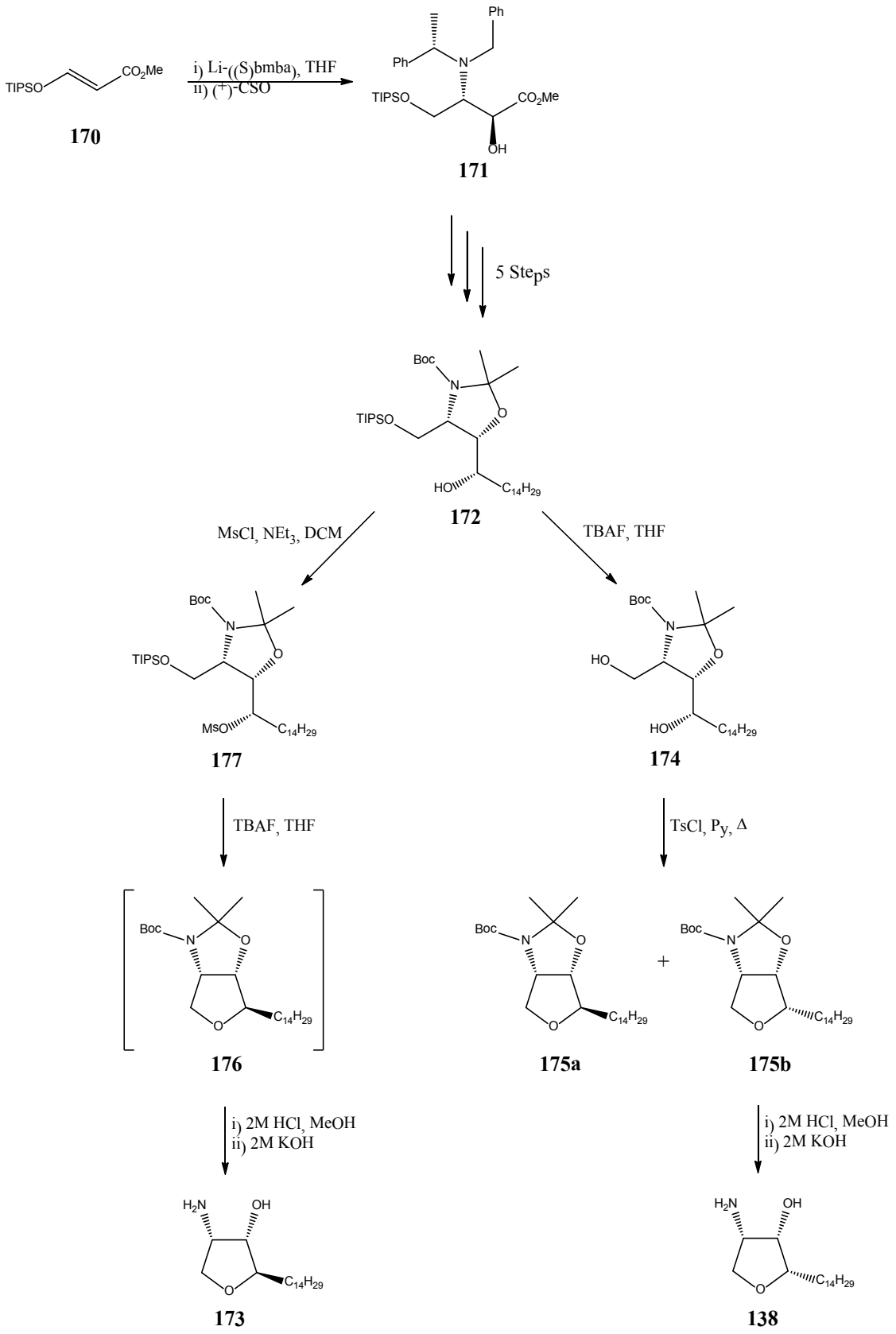
Scheme 1.4.3

Around this time, there was widespread interest in the synthesis of **138** and the publication of Ribes *et. al.*[58] described a synthesis from commercially available (*R*)-glycidol, converted into its known[59] TPS ether **159** (Scheme 1.4.4). Epoxide opening with an *n*-tridecyl cuprate reagent[60] followed by protection of the alcohol as its MOM ether[61] furnished **160**. Desilylation with TBAF yielded alcohol **161**, which was subsequently transformed into the *E*-unsaturated ester **162** *via* Swern oxidation and Horner-Wadsworth-Emmons olefination.[62] DIBAL reduction to **163** followed by Sharpless asymmetric epoxidation[63] afforded the epoxy alcohol intermediate **164**. Imino ester derivative **165** was accessed by reaction with trichloroacetonitrile in the presence of DBU[64] before nucleophilic intramolecular epoxide opening to oxazoline **166** was achieved through the use of diethylaluminium chloride.[65] Acid hydrolysis of **166**, followed by *N*-Boc protection produced diol **167**. The MOM protecting group was removed[66] before selective tosylation of the resulting primary alcohol furnished compound **168**. Intramolecular tosylate displacement with potassium carbonate in methanol produced tetrahyrofuran **169**, that was subsequently treated with TFA, removing the *N*-Boc protecting group to produce the desired natural product **138** as trifluroacetate salt.



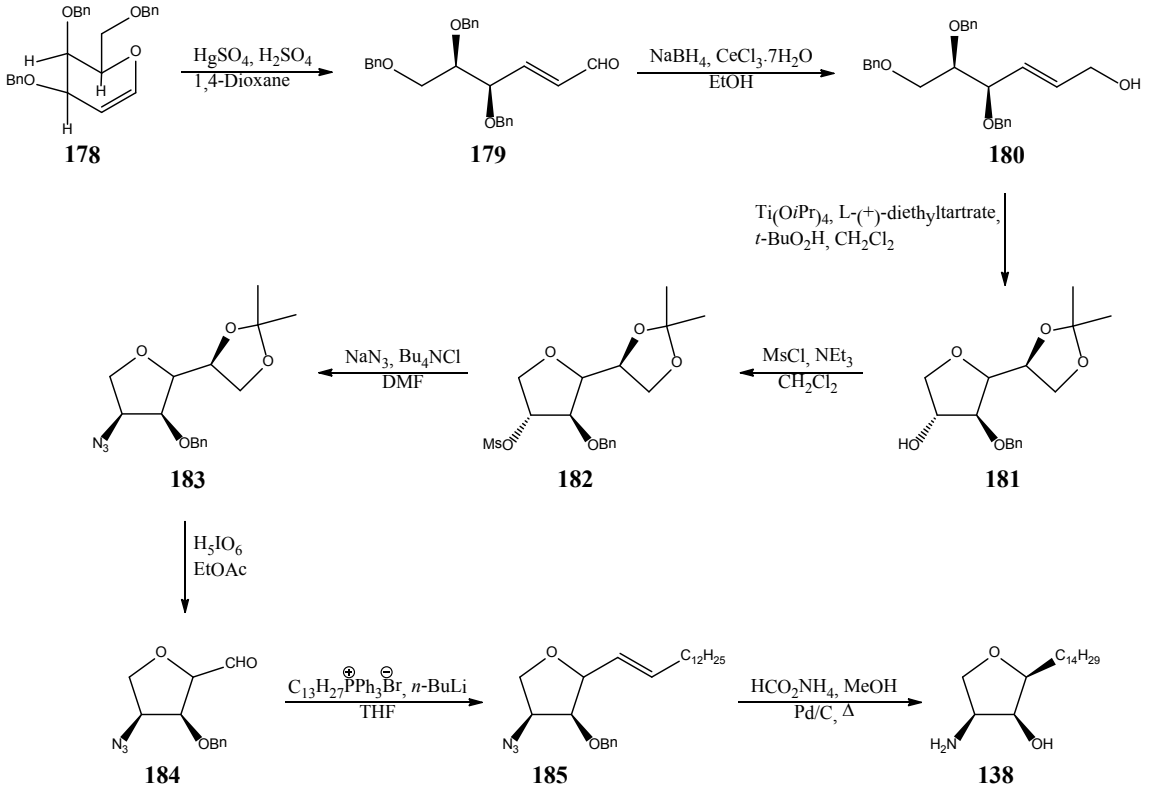
Scheme 1.4.4

Davies *et. al.*[67] published a synthetic route to **138**, and its C(2)-epimer through utilisation of a highly diastereoselective conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (Li-(*S*)-bmba) to a γ-silyloxy-α,β-unsaturated ester **170** and *in-situ* enolate oxidation with (+)-camphorsulfonyloxaziridine ((+)-CSO) as the key step to form **171**. The key intermediate in the synthetic scheme is alcohol **172**, accessed in five steps from **171**. It is through this compound that both Jaspine B and its C(2)-epimer **173** are accessed. For the desired natural product **138**, disilylation **172** of with TBAF followed by tosylation of primary alcohol **174** promoted intramolecular cyclisation to a chromatographically separable mixture of diastereomers **175a** and **175b**. The major diastereomer was basified and recrystallised to furnish **138** in 79% yield. The epimer of **138** was produced by mesylation of **172**, promoting an analogous intramolecular cyclisation to **176** following treatment of **177** with TBAF. Basification followed by recrystallisation produced, **173**, the C(2)-epimer of **138** (Scheme 1.4.5).


TIPSO
CO2Me
170
i) Li-((S)bmba), THF
ii) (+)-CSO
Ph
Ph
N
TIPSO
CO2Me
OH
171
5 Steps
Boc
N
O
TIPSO
HO
C14H29
172
MsCl, NEt3, DCM
TBAF, THF
MsO
177
HO
174
TBAF, THF
TsCl, Py, Δ
176
175a
175b
i) 2M HCl, MeOH
ii) 2M KOH
H2N
OH
173
138

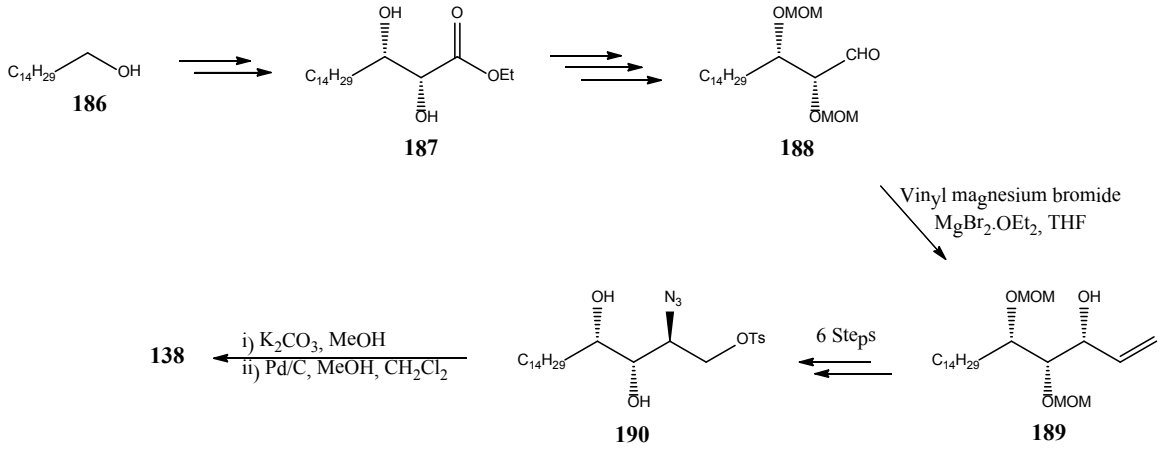
Scheme 1.4.5

Reddy *et. al.*[68] developed a method for the stereoselective synthesis of trisubstituted tetrahydrofuran derivatives, from enantiopure glycal derived 2,3-epoxyalcohols.[69] This research group utilised that approach in their eight-step synthesis of Jaspine B, using benzylated galactal **178** as the starting point (Scheme 1.4.6). This was subjected to Perlin hydrolysis[70], producing α,β-unsaturated aldehyde **179**, which underwent subsequent Luche[71] reduction to **180**. The tetrahydrofuran domain **181** was constructed from **180** by a previously established procedure[69], before mesylation of this compound resulted in **182**. Azide **183** was furnished *via* reaction with sodium azide in DMF, employing tetra-butylammonium chloride as a phase-transfer catalyst due to the poor solubility of sodium azide in DMF. This also resulted in stereochemical inversion, necessary for accessing the desired natural product. The alkyl side-chain was attached using sequential hydrolysis-oxidation-Wittig olefination. Hydrolysis-oxidation of **183** using periodic acid and Wittig olefination of **184** with tridecanylidene triphenylphosphorane produced the unsaturated terahydrofuran derivative **185**. The target **138** was produced in 72% yield by catalytic transfer hydrogenolysis[72] with palladium/carbon and ammonium formate in refluxing methanol.



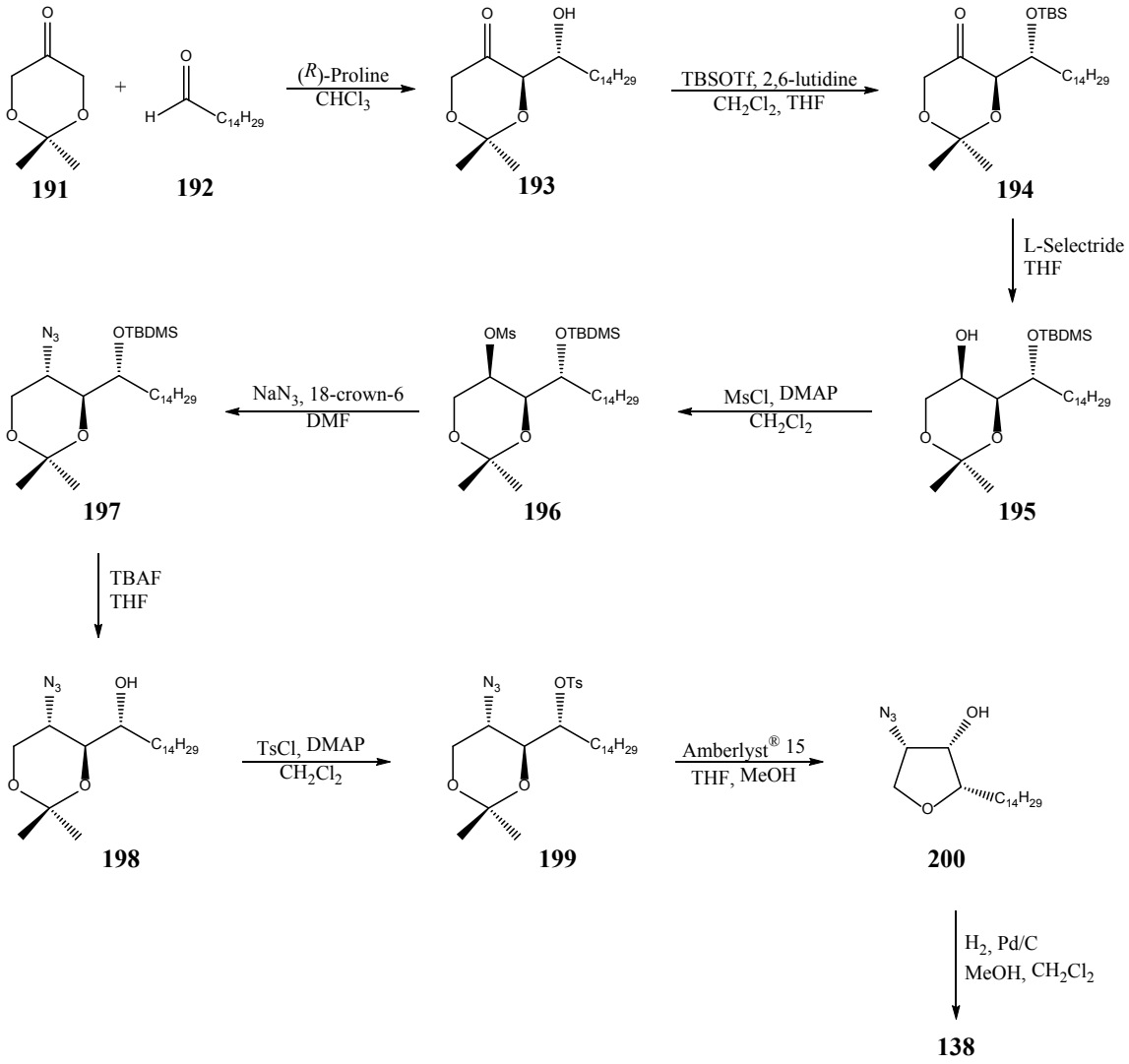
Scheme 1.4.6

A novel synthesis of **138** emanated from the laboratory of Srinivasan[73] where the starting material was achiral pentadecanol **186**. Scheme 1.4.7 shows the synthetic path employed, commencing with PCC oxidation of **186**, followed by Wittig olefination of the resulting aldehyde. The unsaturated ester produced from this olefination was reacted with osmium tetroxide and potassium ferricyanide, as co-oxidants, in the presence of a $(DHQ)_2PHAL$ ligand under asymmetric dihyroxylation[74] conditions to furnish **187** in 88% yield and 97% e.e. Aldehyde **188** was accessed in three steps from **187** following protection of the diol with MOMCl, DIBAL reduction of the ester and iodoxybenzoic acid (IBX) oxidation of the resultant primary alcohol. Allylic alcohol **189** was accessed *via* chelation controlled Grignard chemistry. **188** was reacted with vinyl magnesium bromide and magnesium bromide deithyletherate in THF at -78 °C to furnish **189** *via* a chelation controlled Grignard reaction.[75] What followed was a six-step process to reach the penultimate step of the synthesis. These six-steps included various protections, removal of protecting groups, the insertion of an azide group with an inversion of stereochemistry at that carbon and the conversion of the primary alcohol to tosylate **190**. Jaspine B was finally produced by cyclisation, followed by reduction according to the literature procedure prescribed by Prasad.[76]



Scheme 1.4.7

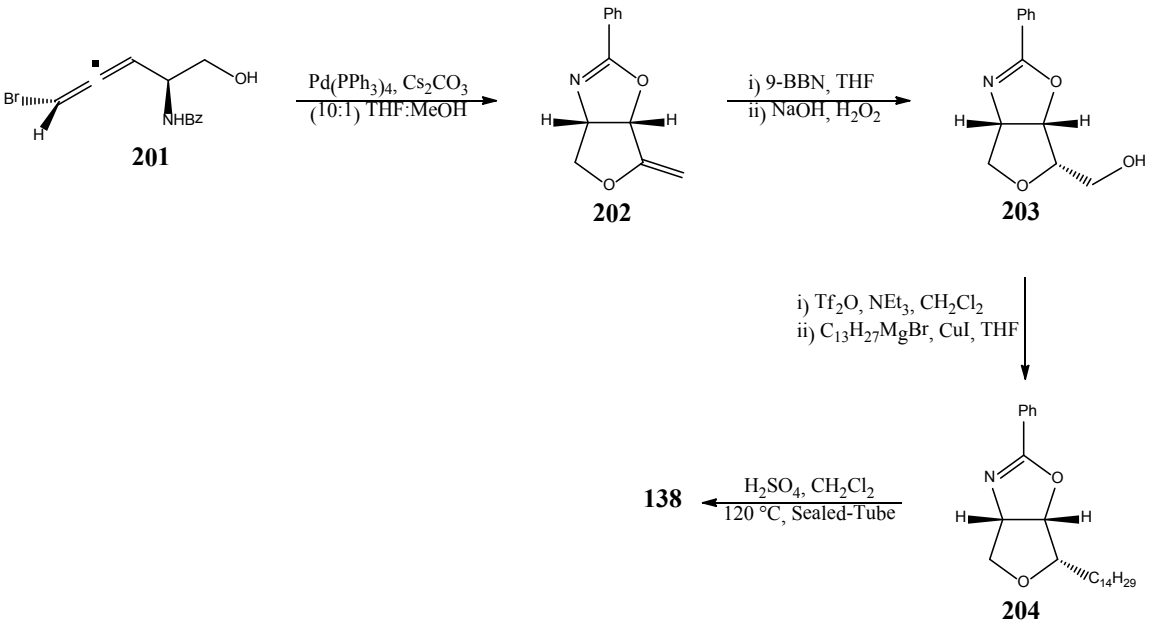
Later in 2008, Enders[77] reported a synthesis of Jaspine B where the key step in the total synthesis employed an organocatalytic aldol reaction as the key step (Scheme 1.4.8). The first step in the synthetic plan is the aforementioned aldol reaction where **191** and **192** were reacted with (*R*)-proline to yield **193**. This compound was protected to form **194**, which was subsequently reduced diastereoselectively to *anti*-1,3-diol **195**. The free hydroxyl of **195** was then converted to its mesylate derivative **196** before introduction of an azide group at this position using sodium azide in the presence of 18-crown-6 to produce the desired TBS-protected *syn*-1,3-azido alcohol **197**. Deprotection of **197** with TBAF to **198** followed by tosylation yielded **199**. Treatment of this tosylate in a methanol/THF solution with Amberlyst® 15 at room temperature installed the desired tetrahydrofuran ring before catalytic hydrogenation of **200** afforded Jaspine B.



Scheme 1.4.8

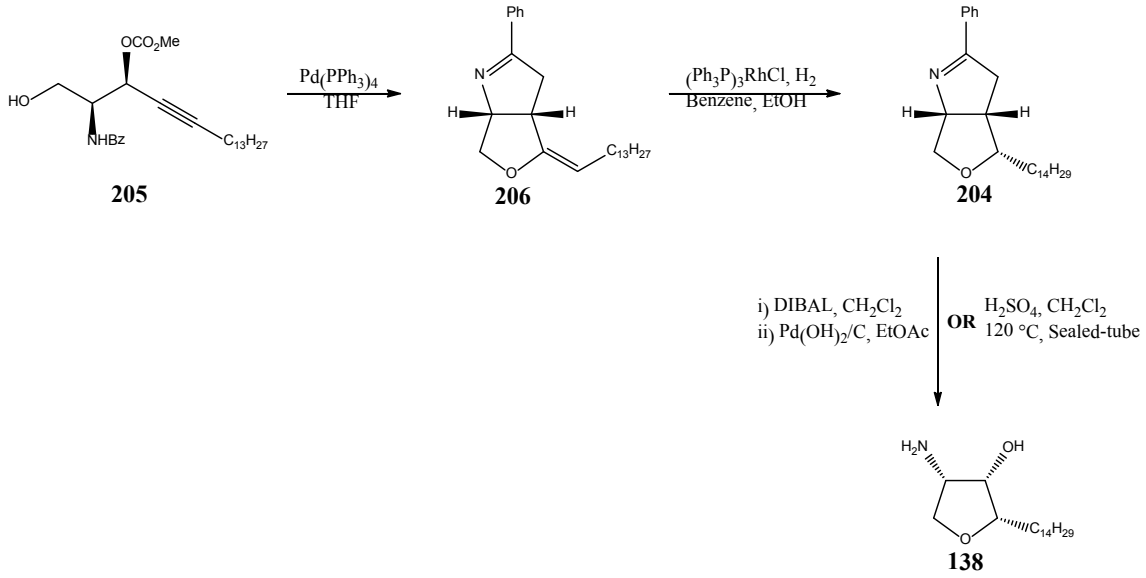
There have been many reported methods and synthetic plans employed in the total synthesis of Jaspine B. Inuki *et. al*.,[78] have produced several publications on the synthesis of this natural product with the first reported in 2009, where palladium-catalysed *bis*-cyclisations of bromoallenes were employed to access the 3-hydroxytetrahydrofuran containing natural product (Scheme 1.4.9). Bromoallene **201** was accessed in three steps from Garner's aldehyde. The key cascade step was performed on **201** in the presence of a palladium (0) catalyst to produce bicyclic product **202**. Hydroboration-oxidation of the terminal alkene moiety in the presence of 9-BBN furnished the primary alcohol **203** with the desired configuration as a single diastereomer.[79] Tetrahydrofuran **204** was accessed by treatment of **203** with triflic anhydride and triethylamine followed by displacement with a cuprate derived from the required alkyl magnesium bromide/copper iodide.[80] The final

step is an acidic hydrolysis of **204** with 20% aqueous sulfuric acid to furnish the desired natural product **138** (Scheme 1.4.9).



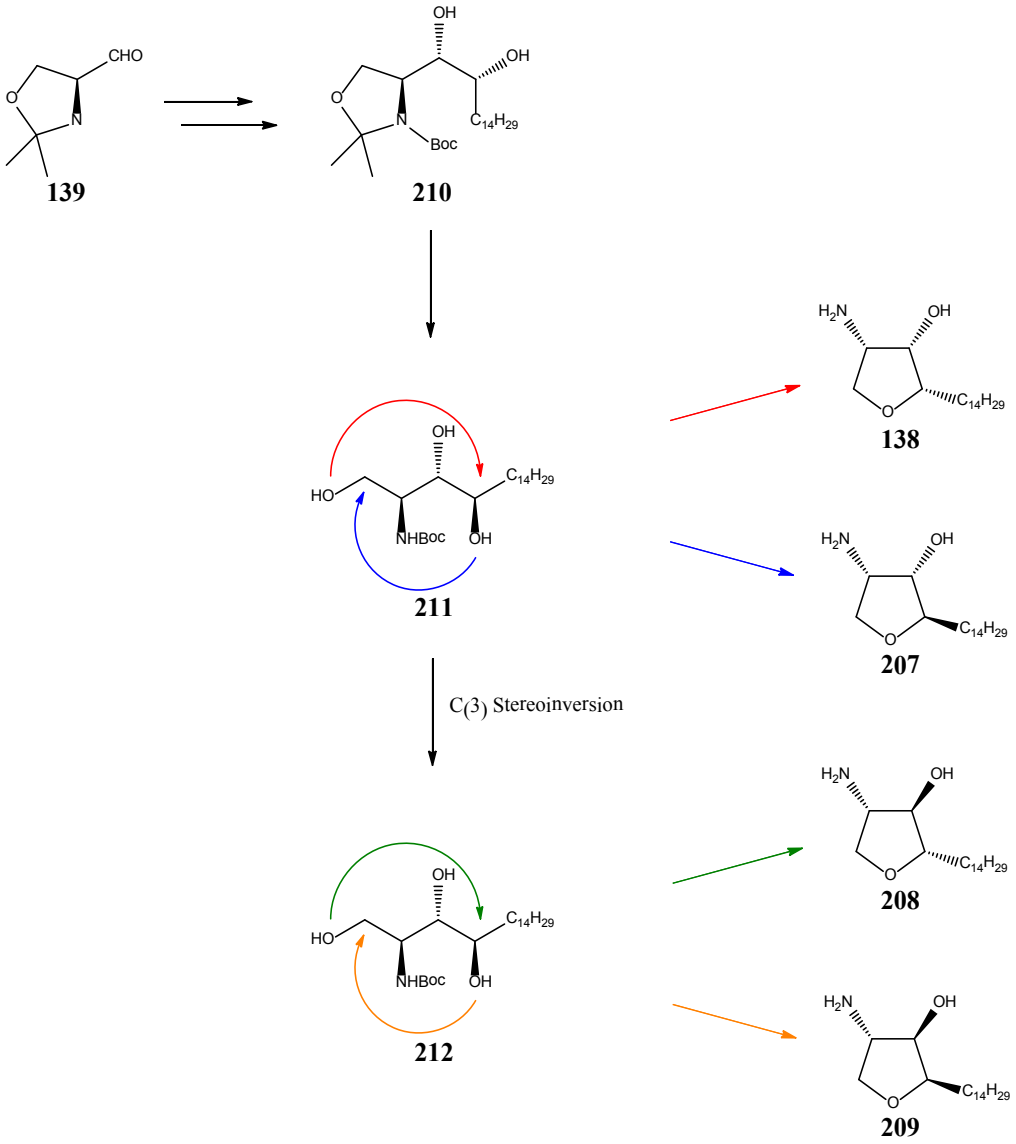
Scheme 1.4.9

In 2010, another synthesis of **138** was reported using palladium-catalysed *bis*-cyclisations of propargyl chlorides and carbonates (Scheme 1.4.10).[81] It is actually quite a similar synthesis to the previous example, but for the use of an alkyne as a synthetic equivalent of a bromoallene. Propargylic carbonate **205** was accessed in three steps from Garner's aldehyde before reaction of **205** in the presence of $Pd(PPh_3)_4$ furnished the bicyclic olefin **206**. To access the alkyl side-chain, **206** was subjected to hydrogenation in the presence of 10 mol% of $(Ph_3P)_3RhCl$ in benzene and ethanol. This also had the effect of creating the necessary C(2) stereogenic centre as a single diastereomer. To complete the synthesis, there are two potential routes to Jaspine B. The first method, previously reported in their 2009 publication[78] (20% aqueous sulfuric acid, 120 °C, sealed-tube), furnished the final product in 80% yield. Alternatively, treatment of **204** with DIBAL successfully produced the benzyl-protected pachastrissamine,[82-86] followed by removal of the benzyl group by catalytic hydrogenation furnished **138** in 86% yield.



Scheme 1.4.10

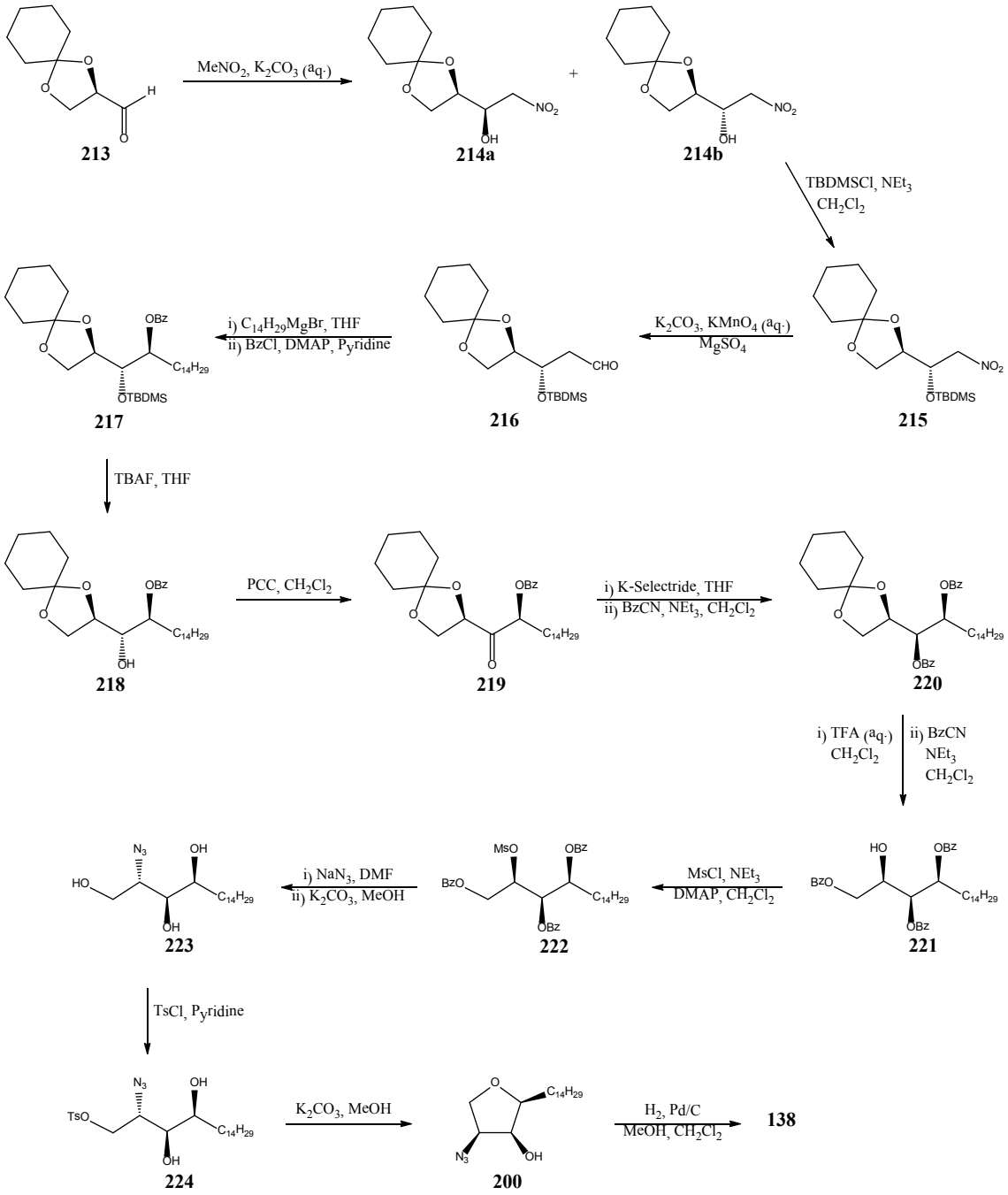
At the very same time in 2010, the same research group released a publication detailing the stereoselective syntheses of four diastereomers of Jaspine B; natural pachatrissamine **138**, 2-*epi*-pachatrissamine **207**, 3-*epi*-pachatrissamine **208** and 2,3-*epi*-pachatrissamine **209**. The synthesis of each diastereomer originates from Garner's aldehyde **139** as the chiral pool (Scheme 1.4.11).[87] This is easily converted by a procedure reported by Azuma *et. al*.[88] into Boc-protected diol **210**, which will serve as a common intermediate for the synthesis of all four diastereomers. The synthetic plan next required the removal of the acetonide group of **210** to yield the D-*ribo*-phytosphingosine derivative **211**, which could be converted to **212** by stereoinversion at C(3). It was envisaged that these amino-triol derivatives would serve as good precursors of the required pachastrissamine derivatives. Conversion of the C(4) hydroxy group of **211** and **212** to a leaving group would lead to nucleophilic attack by the C(1) hydroxy group to produce **138** and respectively **208**. Conversely, nucleophilic cyclisation using the C(1) hydroxyl group as the leaving group would furnish **207** and **209** respectively. The syntheses of the respective diastereomers were completed in a very efficient manner (two to three steps) from their respective amino-triol precursors, typically in good to excellent yields.



Scheme 1.4.11

The research group of Chattopadhyay have been exploiting stereoselective reactions of (*R*)-2,3-cyclohexylideneglyceraldehyde **213** for the synthesis of different classes of biomolecules. What is reported in their 2010 publication[89] is a stereoselective synthesis of Jaspine B (Scheme 1.4.12) from **213**, subjected to nitroaldol reaction with potassium carbonate to give 91% yield and 2:98 (**214a**: **214b**) selectivity. These diastereomers were easily separated by chromatography and the hydroxyl group of the *anti*-diastereomer was protected as a silyl ether to furnish **215** before a Nef reaction[90] with potassium carbonate and aqueous potassium permanganate to produce aldehyde **216**. Incorporation of the alkyl chain was achieved by reaction of **216** with the Grignard derivative of *n*-tetradecylbromide at -50 °C and with absolute 1,2-*anti*-selectivity before

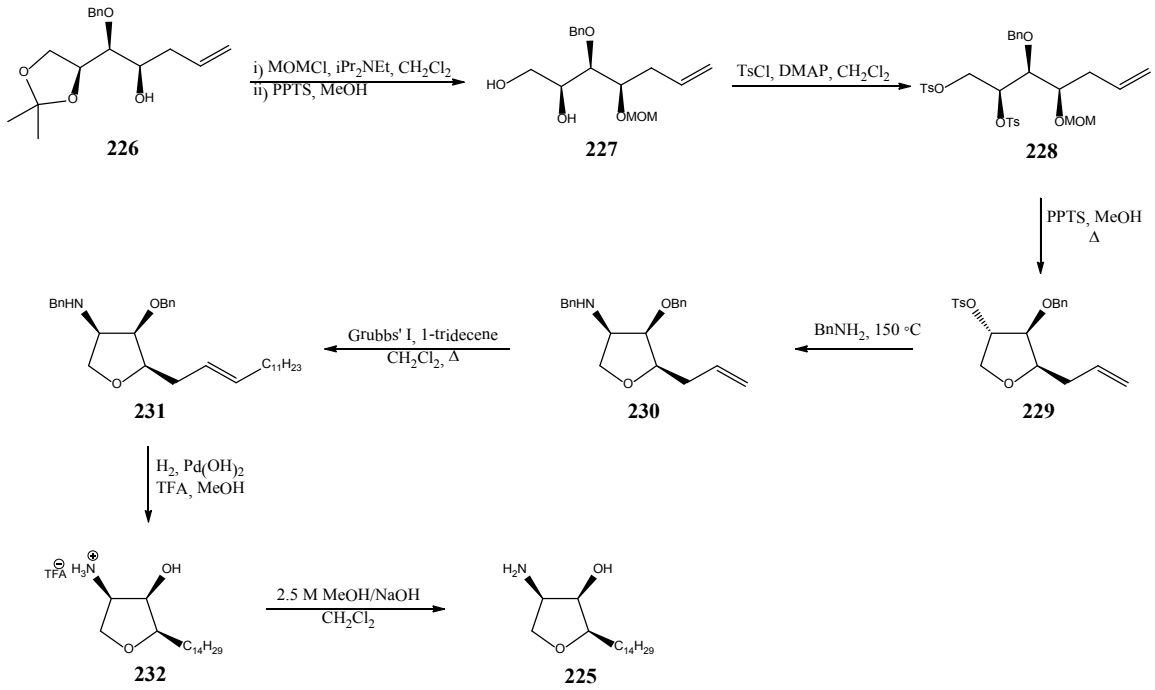
benzoylation yielded **217**. Desilylation to **218**, followed by chromium (VI) oxidation[91] to **219**, subsequent reduction of the ketone by K-Selectride[92] and benzoylation of the resulting alcohol produced **220** in good yield. The ketal moiety was removed with aqueous TFA before regioselective monobenzoylation of the primary alcohol furnished **221**. Mesylation of **221** to **222**, which underwent subsequent azidation (as in previous examples resulted in sterechemical inversion at the site of azidation) and hydrolysis to furnish triol **223**. Tosylation of this triol to **224**, resulted in a substrate that could now undergo base-mediated intermolecular cyclisation to the desired tetrahydrofuran framework **200**.[76, 93] Catalytic hydrogenation then afforded the natural product in high yield.



Scheme 1.4.12

Synthetic pathways are not only restricted to producing natural pachastrissamine but can also be applied to its epimeric forms. A synthesis of (-)-*ent*-pachastrissamine **225** was reported by Prasad[94] starting from conversion of the known homoallylic alcohol **226**[95], to its MOM ether derivative with subsequent removal of the acetonide group to furnish **227** (Scheme 1.4.13). Ditosylation of the resultant diol produced compound **228**. The tetrahydrofuran core was afforded by reaction of **228** with PPTS before stereospecific

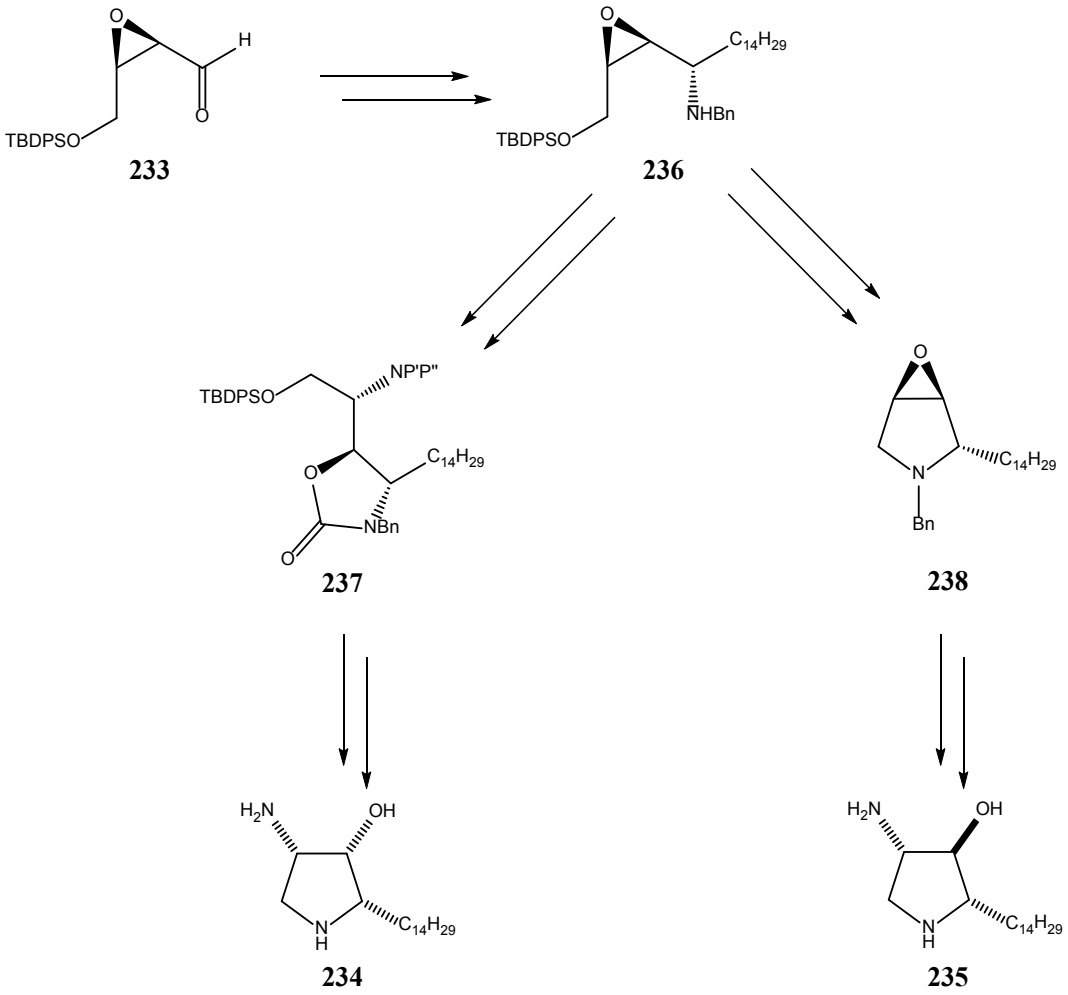
S_N2 displacement of tosylate **229** with benzylamine produced **230** as a single diastereomer in 86% yield. The side-chain was attached by cross-metathesis of **230** with 1-tridecene using Grubbs' first generation catalyst to furnish **231**. Hydrogenation of this compound in the presence of TFA cleanly produced the TFA salt of *ent*-Jaspine B **232** in 93% yield. The final product **225** was isolated in 95% yield by treatment of **232** with methanolic sodium hydroxide.



Scheme 1.4.13

It has also been found that the nitrogen-containing heterocyclic analogues of Jaspine B display marked pro-apoptotic behaviour in melanoma cells, correlated with an increased intracellular ceramide concentration. Rives *et. al.*[96] reported in 2010 that they accessed a number of aza-Jaspine B analogues using protected *cis*-epoxyaldehyde **233**.[97] Scheme 1.4.14 shows the general outline that the authors used to access the *cis*- and *trans*-aza-Jaspine B analogues **234** and **235**, respectively. The general route began with conversion of **233** to **236**, by treatment with benzylamine, and the resulting amine was reacted with tetradecyl magnesium bromide,[98] thus introducing amine functionality, while also incorporating the alkyl side-chain characteristic of pachastrissamine analogues. Introduction of nitrogen functionality with stereochemical inversion at this position would lead to oxazolidinone **237**, and subsequently lead to construction of the all *cis*- pyrrolidine

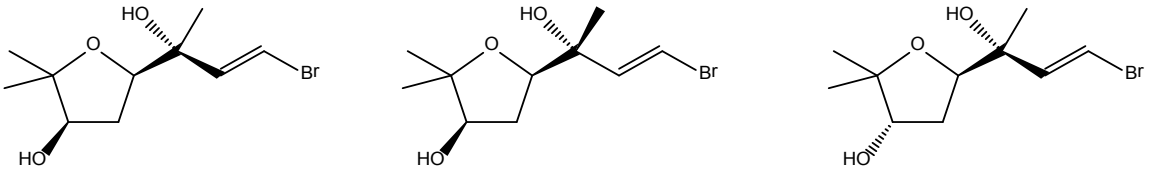
ring of **234**. This route could also be varied by epimerisation at C(2), giving access to *trans-cis* aminopyrrolidine derivatives.[99] Preparation of the all *trans*- analogues **235** would rely on the regioselective epoxide ring opening of **238**.



Scheme 1.4.14

1.5 Pantofuranoids

Pantoneura plocamioides is a red alga native to the Antarctic. Darias and Cueto,[100] in 1996, isolated six new oxygenated monoterpenes, called pantofuranoids A-F. Each of the six analogues contain a tetrahydrofuran ring, however, only pantofuranoids D, E and F (**239**, **240** and **241**) contain the 3-hydroxyl moiety relevant to this review. (For information purposes, pantofuranoids A-C possess a bromine atom, or substituent, in place of the alcohol at the C(6)).

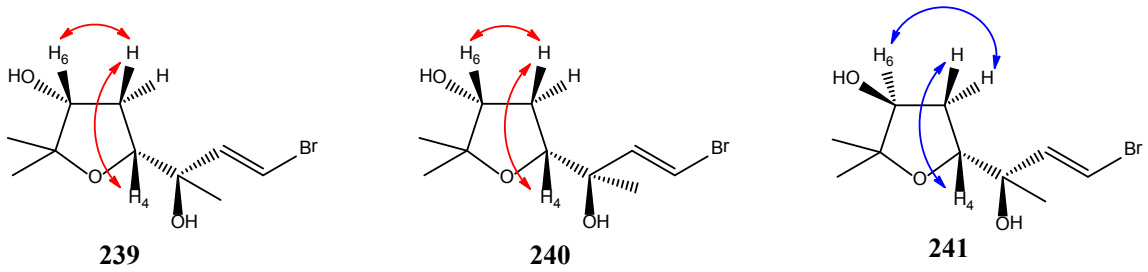


239 **240** **241**

Figure 1.5.1 Pantofuranoids D-F

Pantofuranoids D-F are also characterised by the fact that the number of oxygen atoms they contain exceeds that of the halogen substituents. The authors utilized NMR spectroscopy, in particular two-dimensional methods including NOE, HMBC and HMQC, to ascertain the structure and the relative stereochemistry of **239**-**241**.

Firstly, an NOE effect was observed in **239** between H(6), $H_{\beta}(5)$ and H(4), suggesting that H(4) and H(6) are on the same side of the plane of the ring. Structure **240** shows the exact same NOE correlations concluding that **239** and **240** possess the same stereochemistry around the C(4) and C(6) centres and that the difference between the two must lie at C(3). The NOE spectrum of **241** does not show the same correlations as the previous two compounds, with correlations occurring between H(6) and $H_{\alpha}(5)$ and between H(6) and H(4). These correlations can be seen below in Figure 1.5.2.

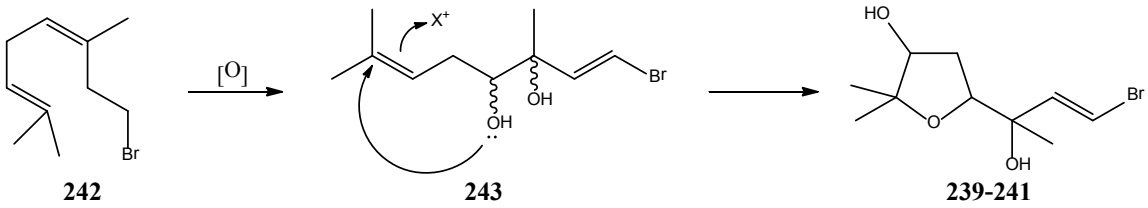


239 **240** **241**

Figure 1.5.2 NOE Correlations of **239-241**

All that was left to ascertain was the relative stereochemistry around the C(3) stereogenic centre. Analysis of HMBC and HMQC experiments returned similar chemical shifts for C(10)**C**H3 for compounds **239** and **241**, which suggests that these compounds have the same stereochemistry on C(3). Compound **240**, however, shows a highfield value for C(10)**C**H3, meaning that it is more hindered than in the other two pantofuranoids. The authors proposed an *S* configuration at C(3) for pantofuranoids D and F (**239** and **241**) and and *R* configuration for pantofuranoid E **240**, as can be seen in Figure 1.5.2.

Biogenetically, the authors have reported that the origin of compounds **239-241** can be explained beginning with the oxidation of a common precursor **242**, generating **243**, followed by the nucleophilic attack of a hydroxonium ion on the terminal isopropylene bond, thus inducing cyclisation of the C(4) alcohol to produce the skeleton of the desired pantofuranoids **239-241** (Scheme 1.5.1).



242 **243** **239-241**

Scheme 1.5.1

Cueto *et. al.*[101] managed to isolate a further novel marine monoterpenoids, pantoisofuranoids, from *Pantoneura ploamiaceae* containing a hydroxytetrahydrofuran ring, and isomeric with those isolated previously. In the case of the pantofuranoids mentioned above, the authors assigned the relative structure and stereochemistry of the three compounds (**244**, **245** and **246**) by NMR spectroscopy as shown by Figure 1.5.3.

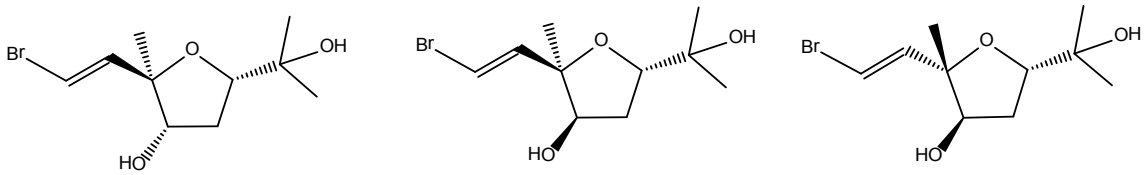


Figure 1.5.3 Pantoisofuranoids **244**, **245** and **246**

The same reseach group[102] investigated the biogenetic precursors of these isolates of *Pantoneura ploamiacea*. What they discovered was two acyclic polyhydroxylated monoterpenes, pantoneutriols **247a** and **247b**, as the most probable biogenetic precursors of panto- and panto-isofuranoids.

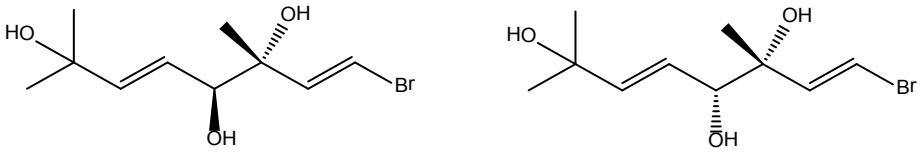
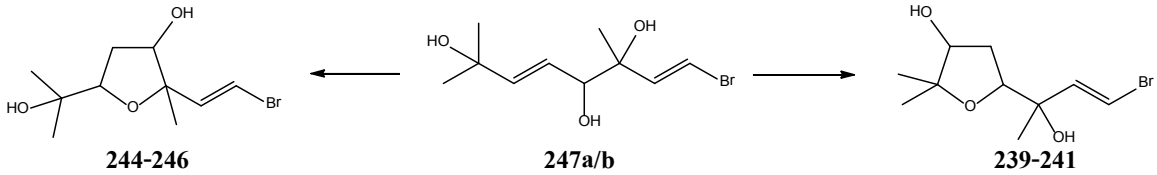


Figure 1.5.4 Pantoneutriols **247a** and **247b**

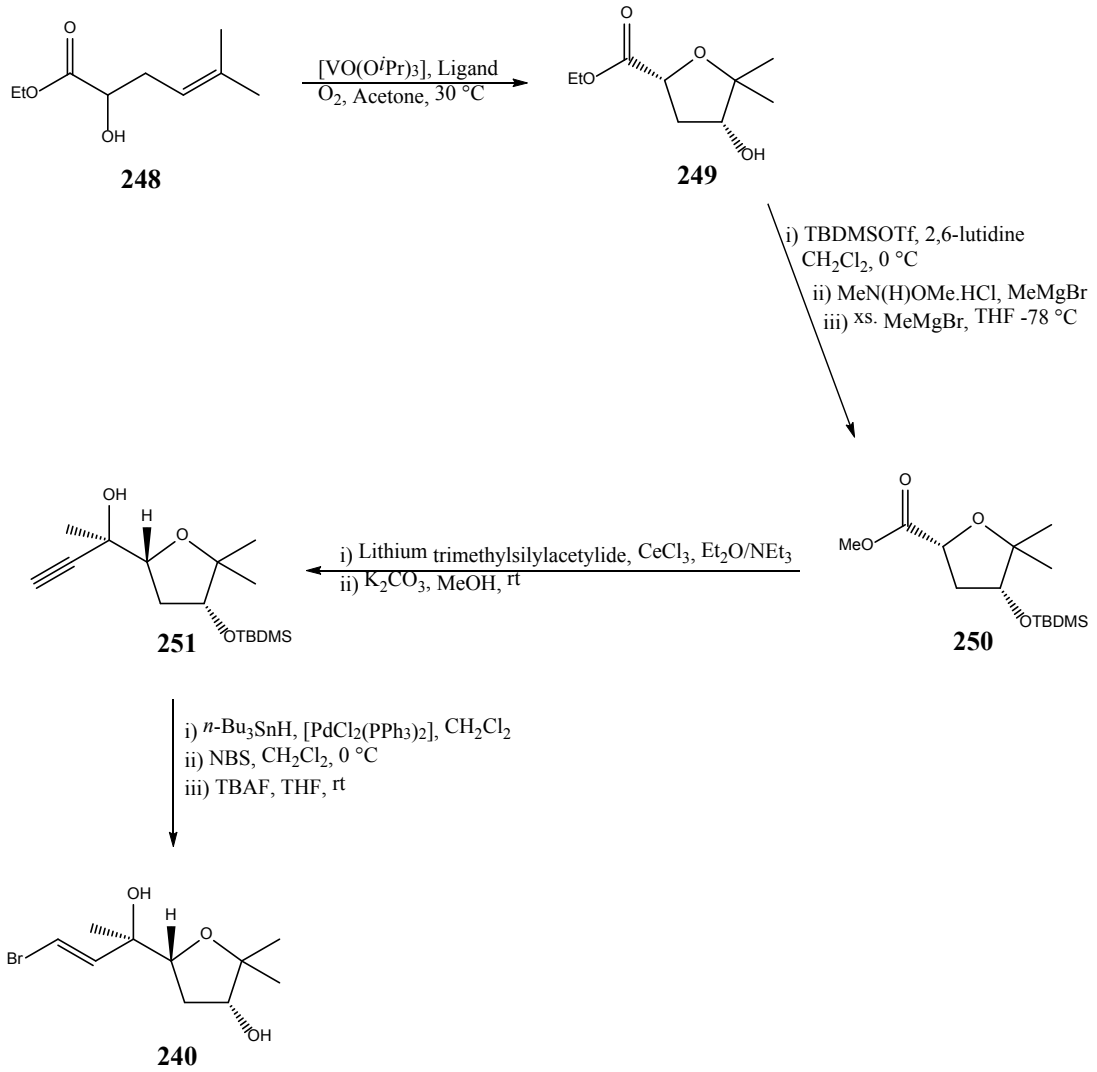
The general origin construction of the cyclic structure is outlined in Scheme 1.5.2. Either pantofuranoids or pantoisofuranoids can be formed from a pantoneutriol precursor.



Scheme 1.5.2

Toste and Blanc[103] reported a synthesis of Pantofuranoid E **240** as an application of their publication outling an enantioselective synthesis of cyclic ethers using vanadium catalysis (Scheme 1.5.3). The synthesis began with **248**, which underwent tandem vanadium catalysed resolution/cyclisation to the 2,4-*cis*-substituted tetrahydrofuran, *i.e.* compound **249**. The alcohol of **249** was protected as a silyl ether and the ester group was

subsequently converted into the methyl ketone **250** by *in situ* formation of a Weinreb amide followed by treatment with excess methyl magnesium bromide.[104] Propargylic alcohol **251** was achieved by addition of lithium trimethylsilylacetylide to **250** in the presence of anhydrous cerium (III) chloride.[105, 106] Installation of the vinyl bromide was achieved in two steps from **251**; palladium-catalysed hydrostannation[107] of the alkyne followed by tin-bromide exchange with NBS before deprotection of the TBS group with TBAF yielded (-)-pantofuranoid E **240** in high yield. This total synthesis and X-ray structural studies allowed assignment of the absolute configuration of **240**, which was in agreement with that previously published by Cueto.[100]



Scheme 1.5.3

1.6 Nucleosides

3-Hydroxytetrahydrofurans have also found a niche in the field of antiviral agents. Their presence within the structure of nucleosides and deoxynucleosides is evident in the form of the furanose ring of the structure bonded to a nitrogenous base. Nucleoside analogues have emerged as important and successful therapeutic agents in the battle against AIDS and its retrovirus, HIV. Their mode of action is blockage of the virally encoded reverse transcriptase,[108] which causes cessation of the virus proliferation. Nucleoside analogues generally differ in two areas, the heterocyclic base or the furanose ring. Variations on the furanose ring include expulsion of hydroxyl group(s) from the ring to be replaced by methylene groups. Where one of the hydroxyl groups is removed, the

nucleoside becomes a deoxynucleoside, similarly a nucleoside where both hydroxyl groups are lost is termed a dideoxynucleoside. Compound **252** is an example of a benzoxazinone *C*-nucleoside, a family of compounds that possess potent antiviral, anticancer and antitumour activity. An advantage of these nucleosides is their resistance to enzymatic hydrolysis associated with the C-C glycosidic linkage, which eliminates the potential for degradation of the nucleoside.[109] Structure **253**, a deoxynucleoside, is an ethynyl derivative of AZT, a known agent in anti-HIV therapy. Although AZT is effective, there are concerns over its toxicity[110] which led to research into a nontoxic nucleoside analogue exhibiting a resistance profile similar to AZT. One common structural feature found in recent anti-HIV nucleoside analogues, such as **253**, is a 4'-ethynyl substituent on the ribose moiety. The 4'-ethynyl group affords a good combination of potency and low cytotoxicity relative to other structural changes investigated at the 4'-position.[111] A_3 Ado-receptor agonists such as **254**, are nucleosides with the capability to act as drugs in the treatment of asthma,[112] cancer,[113] as anti-inflammatories[114] and are also believed to act as cardio[115] and cerebro-protective[116] agents. Extensive research into these compounds found that the introduction of a methoxy substituent at the N^6-position greatly improves the selectivity and affinity of A_3 receptor agonists,[117] hence enabling a full recovery without the risk of drug toxicity and side-effects.

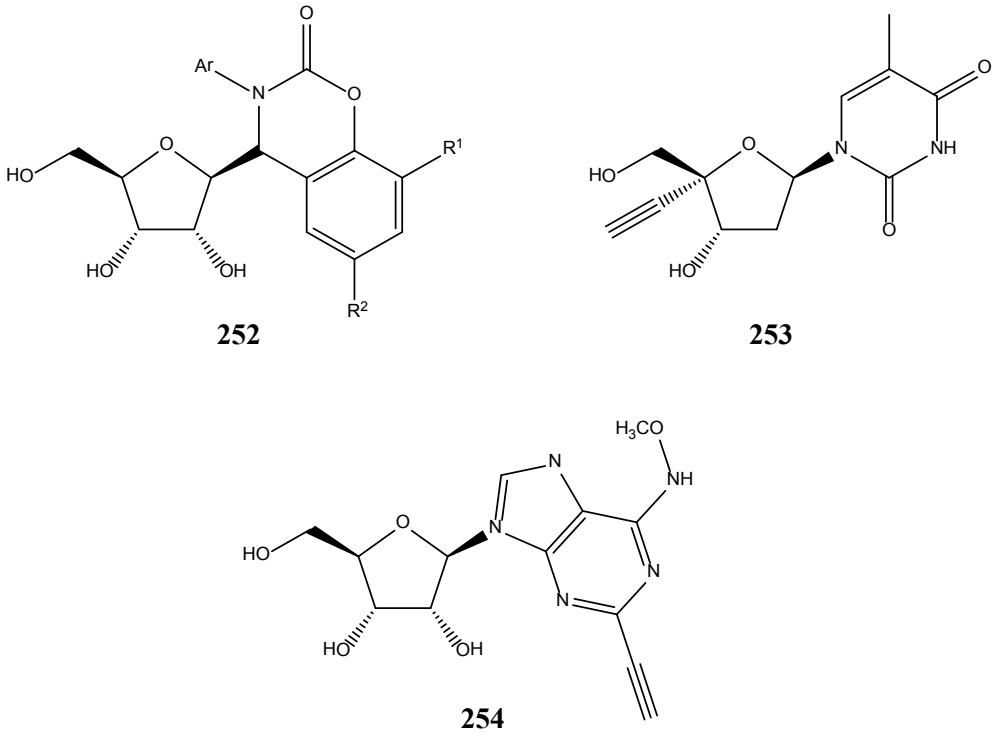
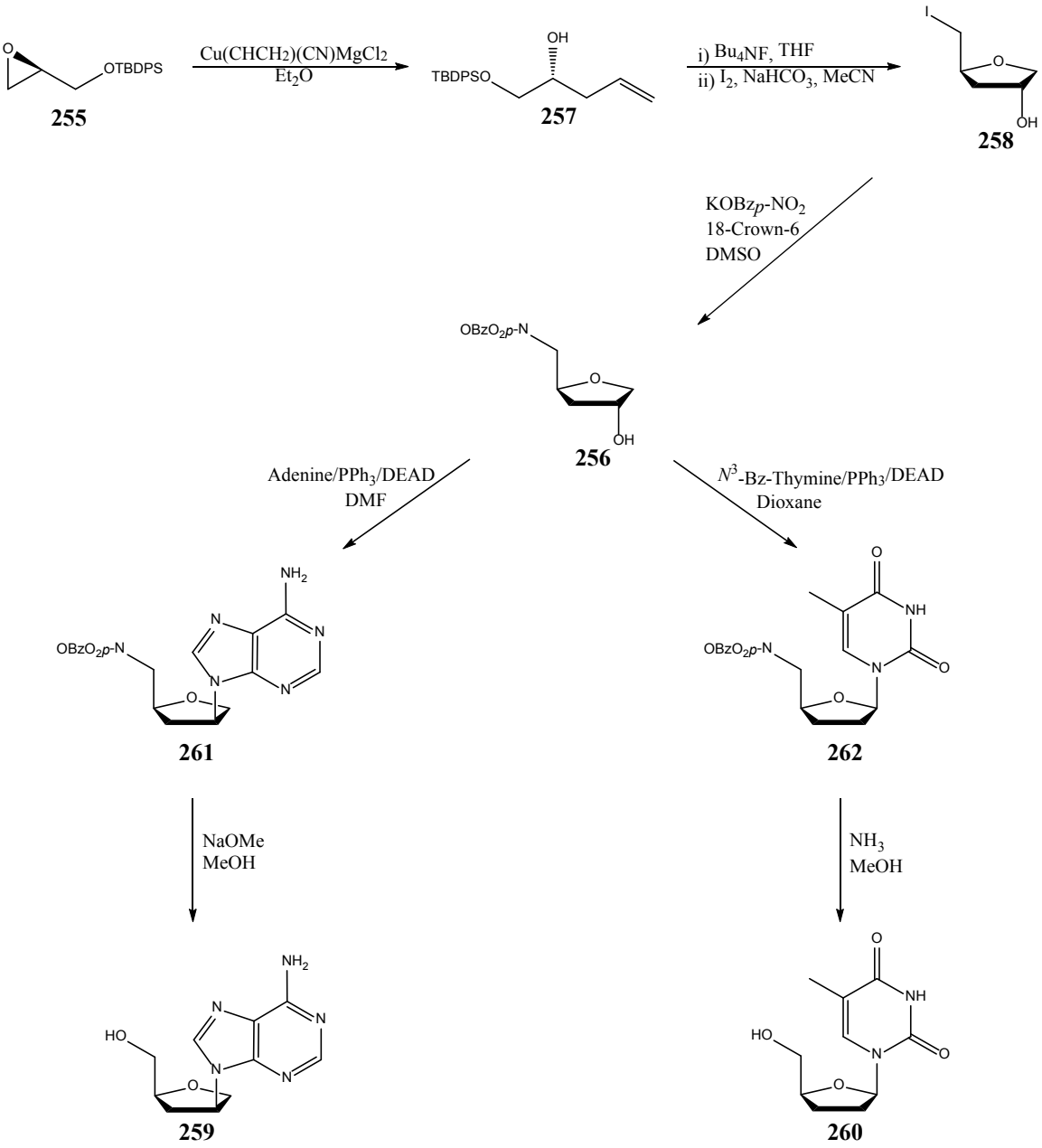


Figure 1.6.1 Examples of Nucleosides Containing 3-Hydroxytetrahydrofurans

In 1999, Diaz and co-workers[118] published an asymmetric synthesis of purine and pyrimidine isodideoxynucleosides from *S*-glycidol **255** using iodoetherification as the key step in the sequence, this led to the construction of **256** which is the key intermediate in the synthesis of the desired nucleosides (Scheme 1.6.1). Epoxide **255** is treated with an ethereal solution of an organocuprate reagent to afford homoallyl alcohol **257**. Iodoetherification of the fully deprotected homoallyl alcohol *via* a 5-*exo*-*trig* cyclisation[119] resulted in the formation of key intermediate **256** *via* **258** in 73% yield.[120] It was at this point that the authors used **256** to synthesise iso-ddA **259** and isonucleoside **260**. Treatment of **256** with adenine in dioxane under Mitsunobu conditions[121] with added DMF, led to **261** in 62% yield. Subsequent deprotection with sodium methoxide in methanol[122, 123] furnished isonucleoside **259** in 31% overall yield from *S*-glycidol. Coupling of **256** with N^3-benzoylthymine[124] under Mitsunobu conditions using dioxane[125] as solvent furnished **262** in 63% yield. Deprotection with methanolic ammonia produced **260** in 95% yield.[126]


OTBDPS
255
Cu(CHCH2)(CN)MgCl2
Et2O
TBDPSO
OH
257
i) Bu4NF, THF
ii) I2, NaHCO3, MeCN
I
O
OH
258
KOBzp-NO2
18-Crown-6
DMSO
OBzO2p-N
256
Adenine/PPh3/DEAD
DMF
N3-Bz-Thymine/PPh3/DEAD
Dioxane
NH2
261
262
NaOMe
MeOH
NH3
MeOH
HO
259
260

Scheme 1.6.1

Maddaford *et. al.*[127] released a publication detailing the use of stereoselective chelation control to form key intermediate **263**, that is subsequently transformed into **253**, **264** and **265**.

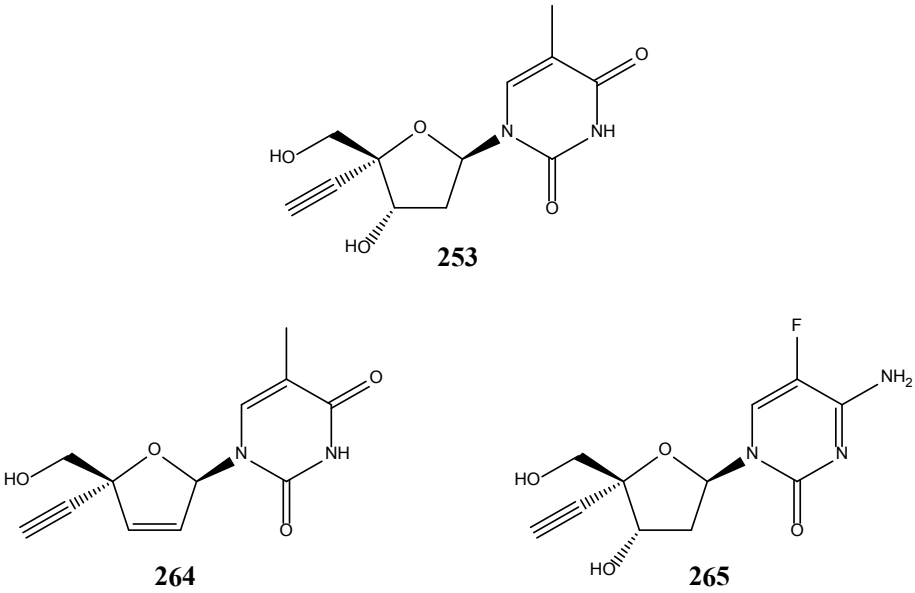
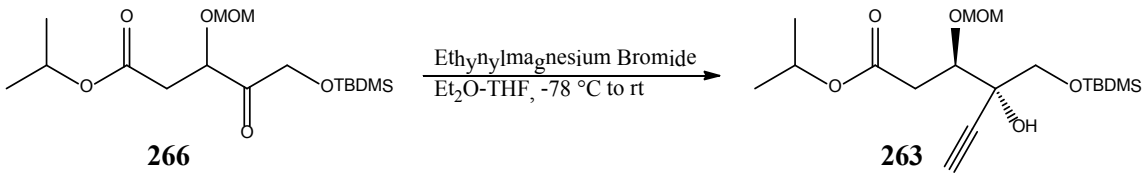


Figure 1.6.2 Structures of **253**, **264** and **265**

The key reaction is the chelation-controlled addition of ethynylmagnesium bromide to **266** to afford tertiary alcohol **263**, in 98% yield (Scheme 1.6.2 and Figure 1.6.3). **263** is reduced using DIBAL and the cyclic motif is formed *via* spontaneous cyclisation.[128] Thymidine-based nucleosides **253** and **264** along with cytosine-based **265** are formed in moderate yield by silyl Hilbert-Johnson coupling[129, 130] followed by successive deprotections.



Scheme 1.6.2

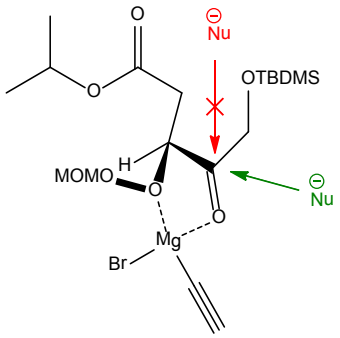
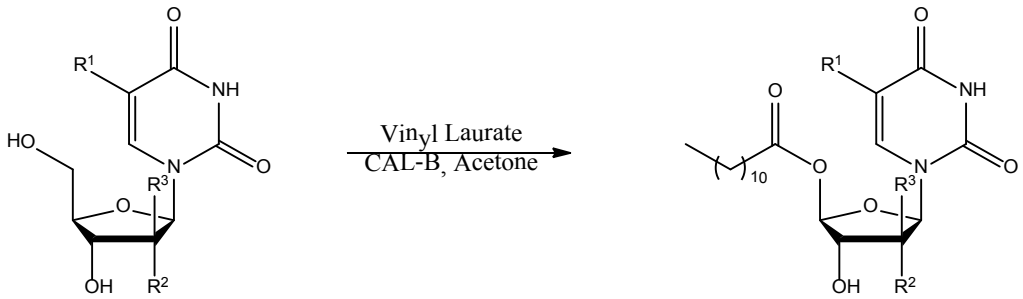


Figure 1.6.3 Diagrammatic Representation of Chelation-Controlled Addition

Biocatalytic methods have also found their place within the selective synthesis of nucleosides. Li *et. al.*[131] published a communication that looked into the regioselective acylation of nucleosides catalysed by CAL-B from an enzyme-substrate recognition point of view. They screened a variety of nucleosides against CAL-B and vinyl laureate as the acyl donor as per Scheme 1.6.3.



267 a-m **268 a-m**

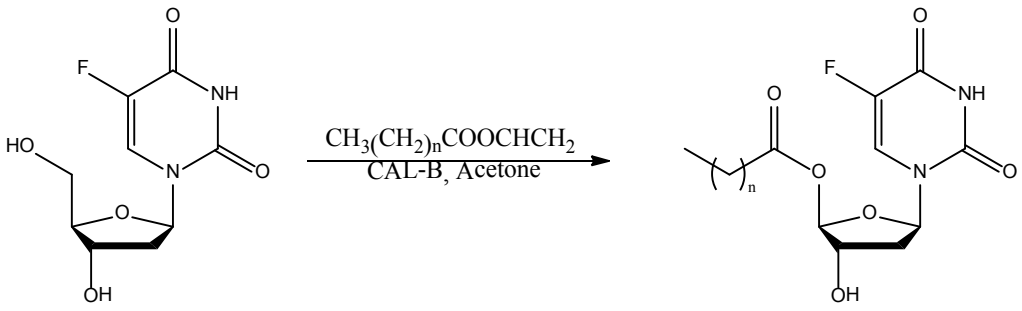
Scheme 1.6.3

The results of the initial screening protocol are summarised in Table 1.6.1, below. What is evident from the results is that CAL-B displayed high activities and moderate 5'-regioselectivities (71-83%) in the acylation of 2'-deoxynucleosides **267a-e**. On the other hand for ribonucleosides **267f-j**, the 5'-regioselectivities (94 to >99%) were excellent, while the activites of these substrates were comparable to the earlier examples.

Structure 268	R^1	R^2	R^3	Time (h)	% Conversion	% 5'-Regioselectivity
a	H	H	H	2	99	83
b	F	H	H	5	99	77
c	CH_3	H	H	3	99	80
d	Br	H	H	3	>99	71
e	I	H	H	4	99	77
f	H	OH	H	3	99	>99
g	H	OH	H	8	99	94
h	CH_3	OH	H	5	99	97
i	Br	OH	H	12	99	94
j	I	OH	H	12	99	95
k	H	F	H	2	99	98
m	H	H	OH	8	99	97

Table 1.6.1

The authors also explored the acyl chain-length specificity of CAL-B with **267b** as a model acyl acceptor (Scheme 1.6.3).



267b

Scheme 1.6.3

The results show that the enzyme is more selective for the introduction of 5'-butanoyl groups relative to other continuous chain alkanoyl groups. Also evident from the results is that the initial reaction rate dropped off with the elongation of the chain from C_4 to C_8 and then remained constant. This is not, however, overly surprising as it has been shown that

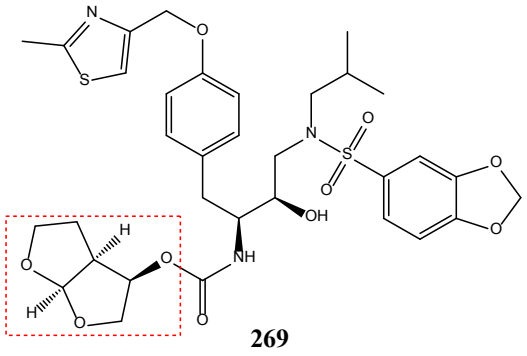
CAL-B is more specific towards acyl donors in the synthesis of glucose esters and in the acylation of β-thymidine.[132, 133]

Acyl Chain Length	n	v_0	Time (h)	% Conversion	% 5'-Regioselectivity
C2	0	44.6	2	99	65
C4	2	48.5	2	99	80
C6	4	38.2	3	99	77
C8	6	22.0	4	99	76
C10	8	19.6	5	99	75
C12	10	18.9	5	99	76
C14	12	19.1	5	99	77
C16	14	18.8	5	98	77
C18	16	19.0	5	98	77

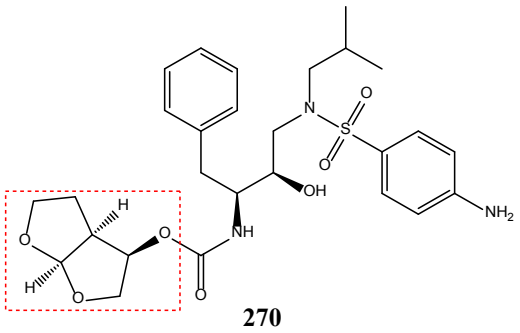
Table 1.6.2

1.7 Other Systems Containing 3-Hydroxytetrahydrofuran-Based Structures

Acquired immunodeficiency syndrome (AIDS) is a chronic, life-threatening condition caused by the human immunodeficiency virus (HIV). Since the first reports of AIDS, it has become a global epidemic. HIV protease inhibitors are important components of the current drug regimens to treat HIV infection. Their mode of action is to interrupt HIV replication at a later stage in its life cycle by interfering with the HIV protease enzyme. Two examples of such drugs are Brecanavir **269** and Darunavir **270**.



269



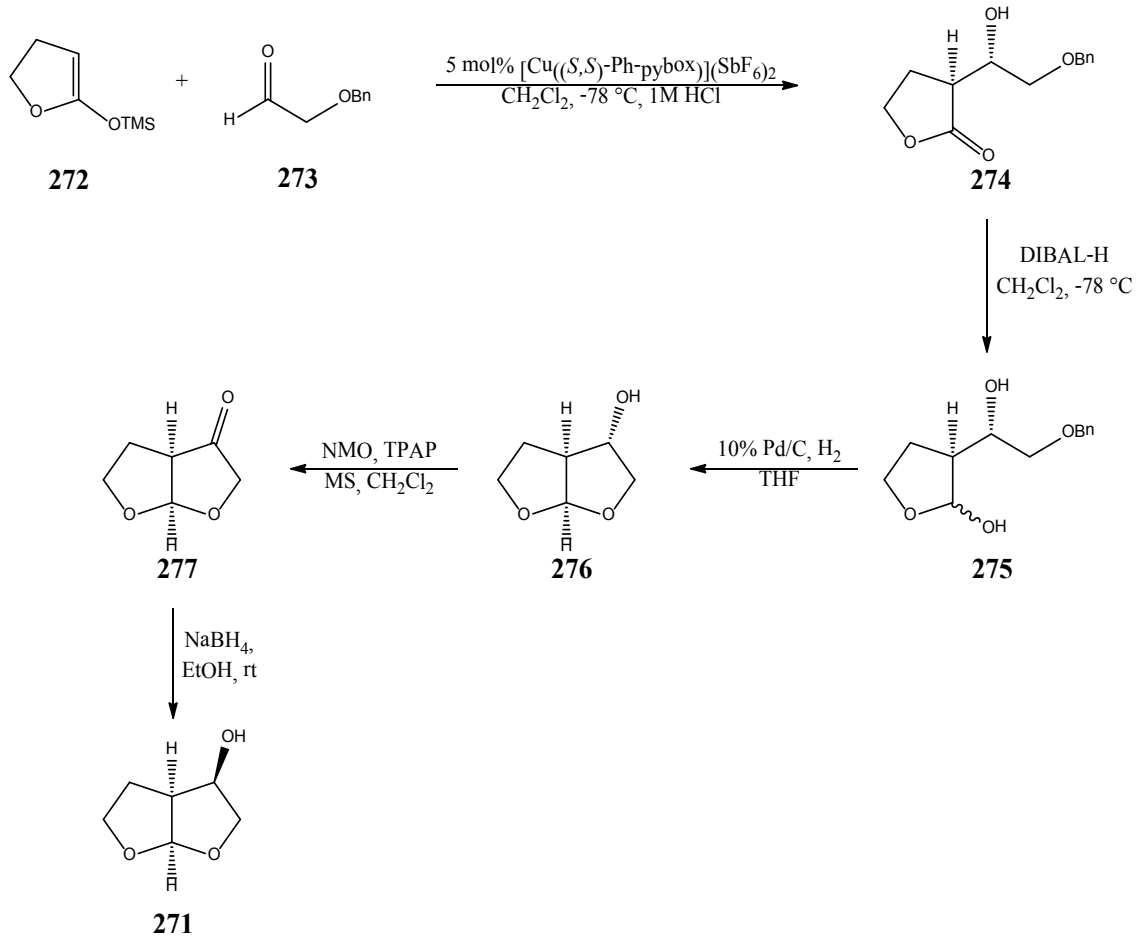
270

Figure 1.7.1 Structures of Brecanavir **269** and Darunavir **270**

The notable feature to these two drugs is that they both contain a bicyclic hydroxytetrahydrofuran (or *bis*-tetrahydrofuran) desired moiety, included within the structure as its significance as a nonpeptide P_2 ligand for outstanding potency against drug-resistant HIV is well documented.[134, 135]

Black *et. al*.[136] published a route to accessing the important *bis*-THF moiety **271** utilising the Mukaiyama-Evans aldol reaction and inversion of an alcohol stereocentre to furnish the desired *bis*-THF in a highly diastereo- (98:2) and enantioselective (97:3) manner (Scheme 1.7.1). The synthesis of **271** commenced from the Mukaiyama aldol reaction of **272** and **273** as reported by Evans.[137] Catalysis with 5 mol% of the chiral copper catalyst produced a TMS intermediate, which upon acidic hydrolysis provided **274** in 87% yield. Lactone **274** was reduced to lactol **275** with DIBAL-H,[138, 139] with atmospheric hydrogenolysis of **275** furnishing the hydroxytetrahydrofuran **276**, the α-epimer of the target *bis*-THF **271**.

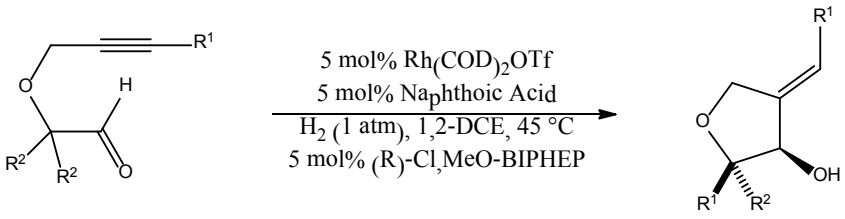
Hydroxytetrahydrofuran **271** was accessed in two steps, by oxidation of **276** with 4-methylmorpholine-*N*-oxide (NMO) in the presence of a catalytic amount of TPAP[140] before stereoselective reduction of **277** afforded the desired *bis*-hydroxytetrahydrofuran in 81% yield.



272 **273** **274** **275** **276** **277** **271**

Scheme 1.7.1

Krische and Rhee[141] reported a novel synthesis of a range of heterocycles that included 3-hydroxytetrahydrofurans **278**. The methodology was based around an enantioselective reductive cyclisation of acetylenic aldehydes **279** *via* rhodium catalysed asymmetric hydrogenation (Scheme 1.7.2). They report that hydrogenation of acetylenic aldehydes using chirally modified cationic rhodium catalysts enables formation of cyclic allylic alcohols in good yield and with very high levels of asymmetric induction. In the initial screening process, the authors carried out the reaction both in the presence and absence of the naphthoic acid additive. There was a small increase in the enantioselectivity, however a marked increase in yield was noted. This lead to the reaction conditions outlined in Scheme 1.7.2 with the rhodium based cationic catalyst precursor and the phosphine derived ligand.



279 **278**

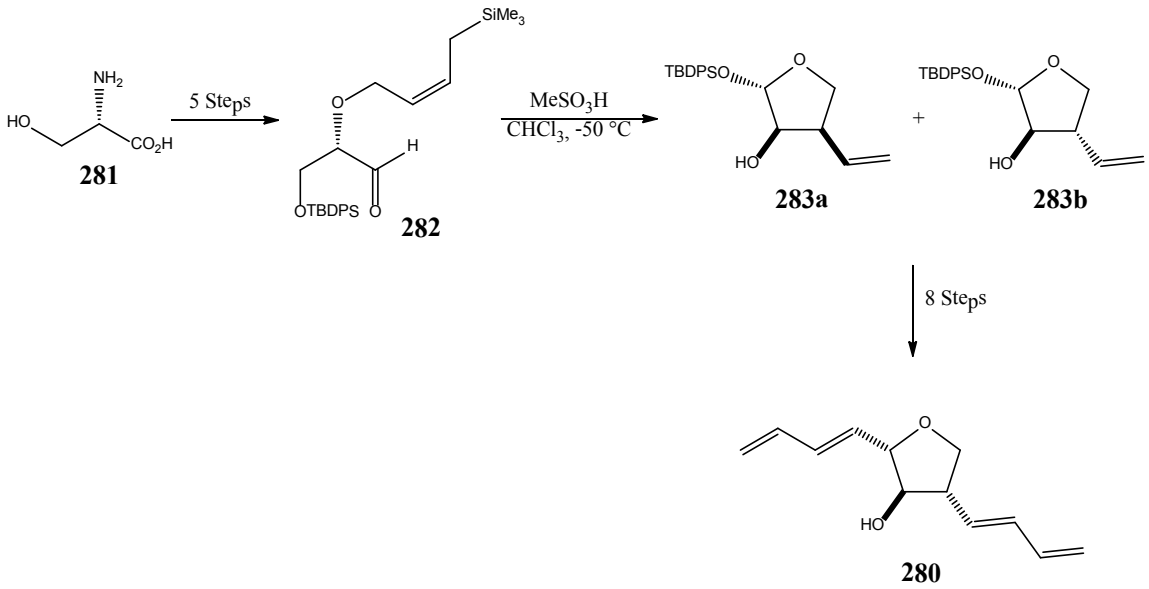
Scheme 1.7.2

Table 1.7.1 illustrates the results from Scheme 1.7.2. The yield and enantiomeric excess data for the three substrates investigated shows alkylidene furans form readily *via* hydrogen-mediated cyclisation. In fact, the publication shows that a broad range of heterocyclic compounds exhibiting a wide range of functionality can be accessed by this method.

R^1	R^2	R^2	% Yield	% ee
Ph	CH_3	CH_3	71	93
$CH_3(CH_2)_5$	CH_3	CH_3	86	99
CH_3	$(CH_2)_4$		73	99

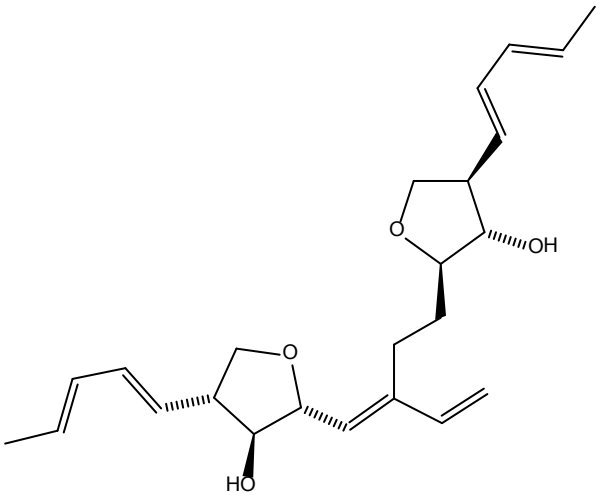
Table 1.7.1

Jervis and Cox,[142] synthesised two epimeric 3-hydroxytetrahydrofurans in their quest to establish the relative stereochemistry of aureonitol, and in the process reported the first known synthesis of (-)-aureonitol **280** (Scheme 1.7.3). Their synthesis originates from (*S*)-serine **281** and is a fourteen-step route to the desired compound. The key step in the synthetic pathway is the stereoselective intramolecular allylation of an allylsilane with an aldehyde, introducing three stereocentres to the tetrahydrofuran ring. Key intermediate **282**, an allylsilane aldehyde is accessed in five steps from **281**.[143, 144] The hydroxytetrahydrofuran framework is then constructed *via* an acid catalysed stereoselective intramolecular cyclisation, producing a diastereomeric mixture of products **283a** and **283b** in a ratio of 1:8 respectively. The final step is removal of the silyl protecting group with fluoride ion to furnish **280** in 91% yield.[145, 146]



Scheme 1.7.3

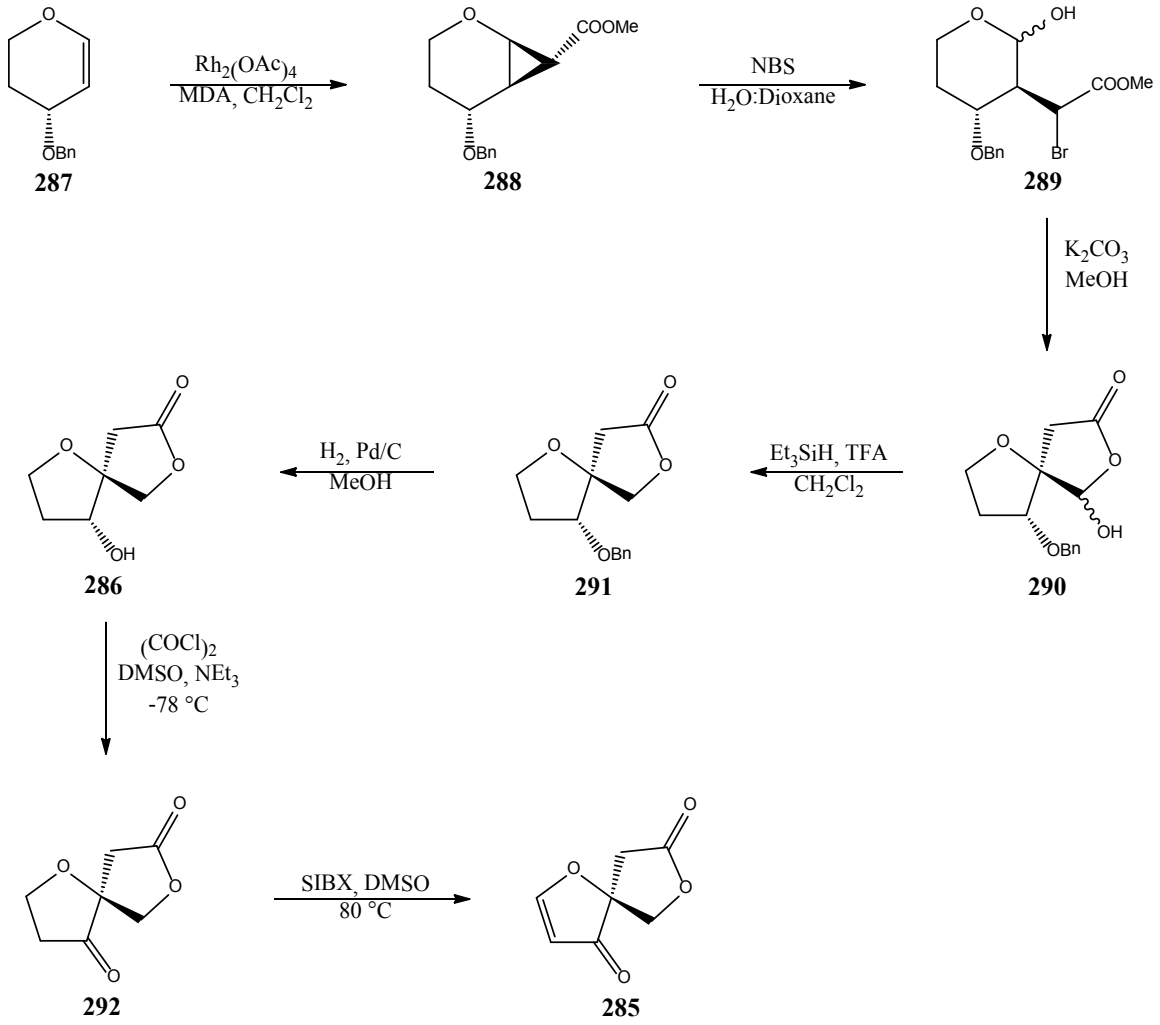
Another aureonitol-type metabolite is Musanahol **284**, an antibacterial furano-polyene isolated from the laboratory cultures of a *Chaetomium* sp. accessed from tomatoes. Chaetomium is an ascomycota of the family Chaetomiaceae. It is a large genus comprising of over one hundred species. Several strains of *Chaetomium* are found in soil, plants and endophytic habitats where they suppress the growth of bacteria and fungi through direct competition, mycoparasitism and antibiosis.[147] They are well known sources of bioactive compounds such as the antifungals chaetoatrosin A and fuscoatroside,[148] antitumour differensiole A and antibiotic chaetomin from *Chaetomium cochliodies*. Fatope *et. al*.[149] elucidated the structure of **284** using spectroscopic methods including extensive 2D-NMR experiments, double resonance experiments, Mosher's method and PM3 calculations.



284

Figure 1.7.2 Structure of Musanahol **284**

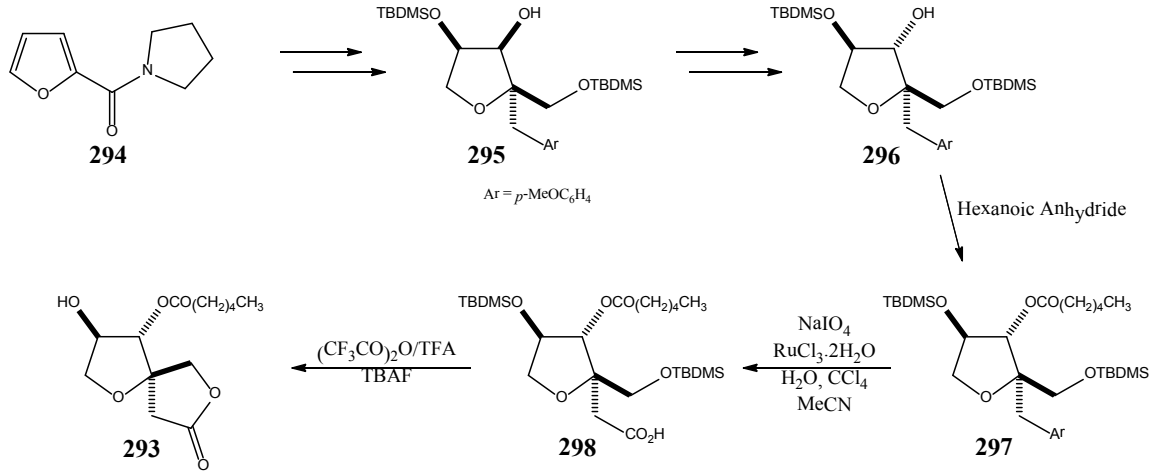
Perali and Kelapati[150] published the first enantioselective total synthesis of *S*-(-)-longianone **285** in 2012, synthesised *via* 3-hydroxytetrahudrofuran **286** (Scheme 1.7.4). The synthetic route commenced with rhodium catalysed stereoselective cyclopropanation of **287** (formed in five steps from 3,4,6-tri-O-acetyl-D-glucal[151-153]) to form 1,2-cyclopropanecarboxylate **288**. Subsequent ring opening *via* bromonium ion mediated electrophilic ring opening furnished compound **289** before treatment with methanolic potassium carbonate formed spirocyclic lactol **290** as a diastereomeric mixture. Dehydroxylation of **290** with triethylsilane/TFA in dichloromethane provided the enantiomerically pure spirolactone **291**. Hydrogenolysis to 3-hydroxytetrahydrofuran **286** followed by Swern oxidation yielded the saturated derivative of S-(−)-longianone **292**. Dehydrogenation[154] of **292** furnished the desired natural product **285**.



Scheme 1.7.4

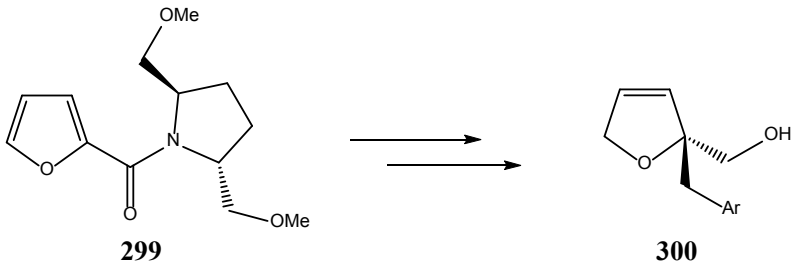
Another class of natural products containing a spiro-fused lactone 3-hydroxytetrahydrofuran are secosyrins. This family of compounds was isolated from *Pseudomonas syringae* and have been subject to widespread research in terms of synthetic studies. In a paper published by Donohoe and co-workers,[155] total synthesis of racemic Secosyrin 1 **293** was carried out before the authors then demonstrated an enantioselective total synthesis based on methodologies developed in the racemic synthesis (Scheme 1.7.5). Synthesis of the racemate began from electron deficient furan **294**, with conversion to **295** *via* Birch reduction, hydrolysis, reduction and dihydroxylation with osmium tetraoxide[156, 157]. Compound **296** was produced in three steps from **295** *via* hydroxyl-protection[158], alcohol oxidation and reduction. The synthesis was completed by conversion of alcohol **296** to its hexanoic ester **297** by means of

reaction with hexanoic anhydride followed by ruthenium-catalysed oxidation[159] to carboxylic acid **298**. Ultimate lactonisation to **293** was achieved by reaction of **298** with trifluoroacetic anhydride/TFA and TBAF mediated deprotection of the silyl group.



Scheme 1.7.5

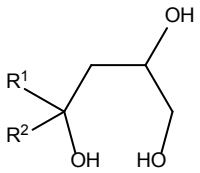
To achieve the asymmetric synthesis of (-)-**293**, the authors utilised the Birch reduction of a furan, employed in the racemic synthesis, with the major difference being the use of chiral furan **299** (Scheme 1.7.6). Alcohol **300** was prepared from **299** in ≥90% e.e., measured against its racemic counterpart, and subsequently transformed into (-)-**293** following the synthetic pathway used for production of the compound in racemic form.



Scheme 1.7.6

Another synthetic route to the formation of 3-hydroxytetrahydrofurans originates from the transformation of homoallylic alcohols in aqueous perchloric acid.[160] The transformation proceeds by hydrolysis of the epoxyalcohols in aqueous perchloric acid to the corresponding 1,2,4-triol followed by heating in the same reaction medium. This

induced cyclisation of the 1,2,4-triol into 3-hydroxytetrahydrofurans. This method, however, is restricted to substrates that can generate stable carbocations *via* elimination of the hydroxyl group from position 4 in intermediate 1,2,4-triols **301** (Table 1.7.2).

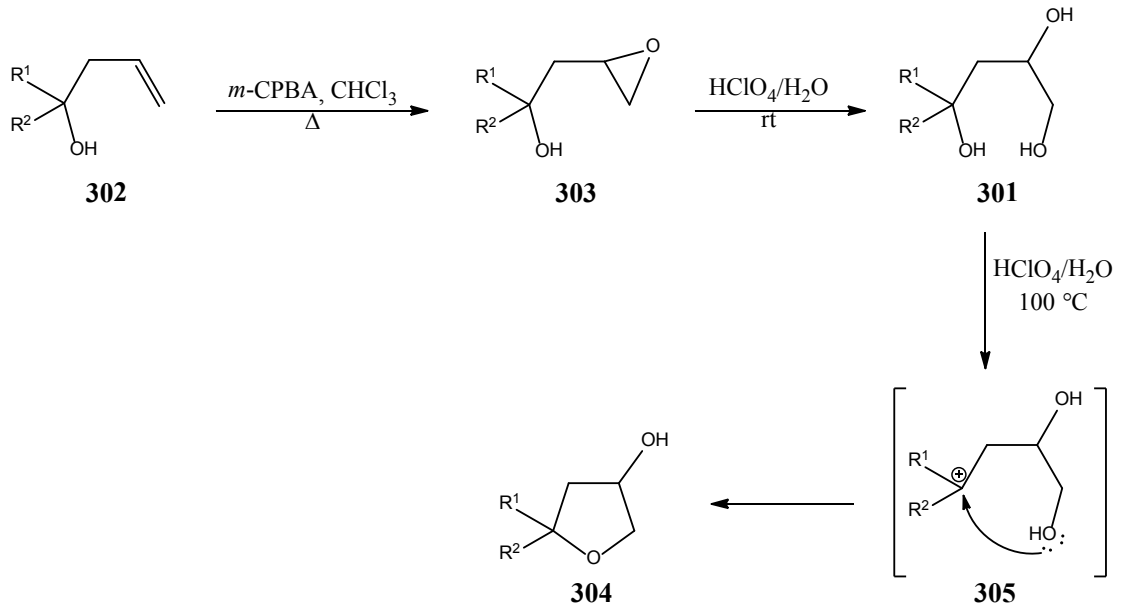


301

301	R^1	R^2
a	Ph	H
b	Ph	CH_3
c	$(CH_2)_5$	
d	Et	Et

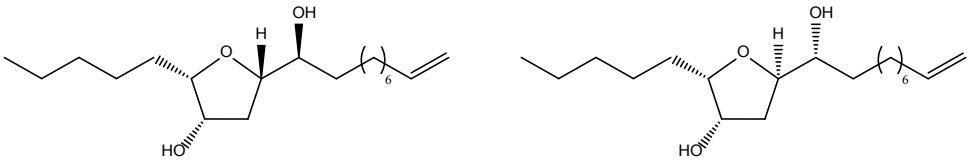
Table 1.7.2

Allyl carbinol **302** undergoes epoxidation of the terminal alkene to produce oxirane **303**, which was then reacted with aqueous perchloric acid at room temperature to produce 1,2,4-triols **301**. These triols were then cyclised to the desired 3-hydroxytetrahydrofuans **304** *via* **305** by heating **301** to 100 °C in aqueous perchloric acid (Scheme 1.7.7).



Scheme 1.7.7

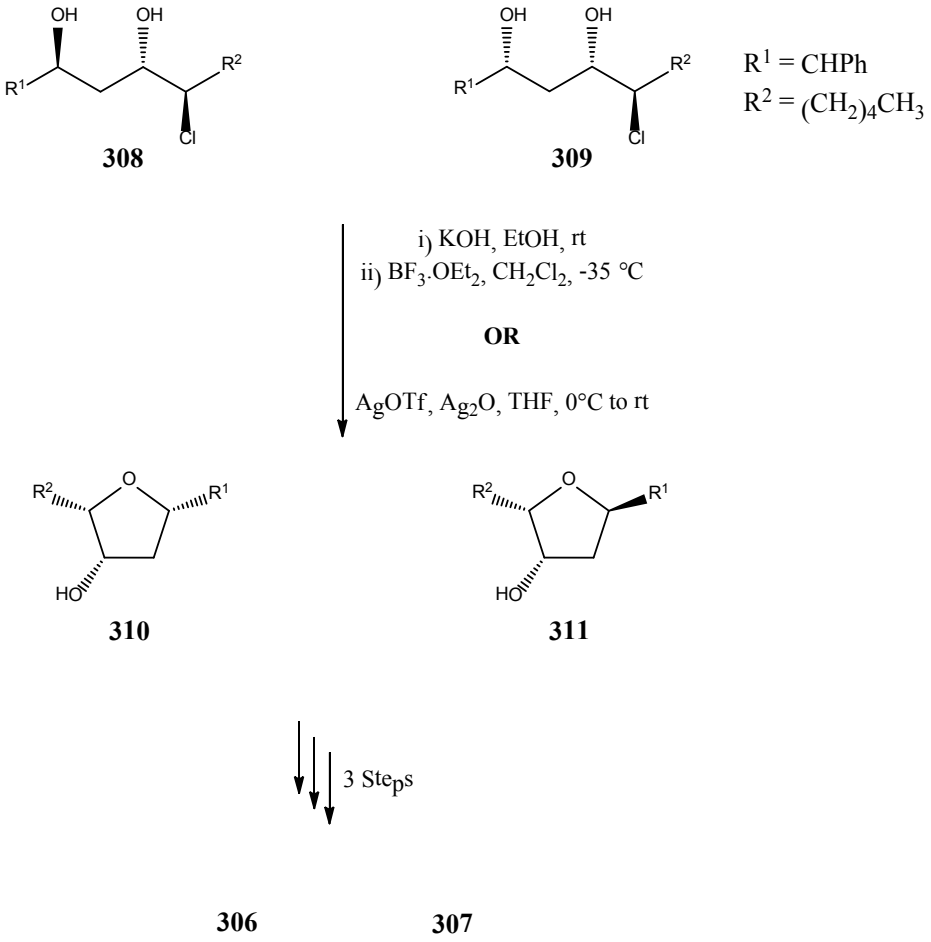
The diastereomeric brown algae metabolites **306** and **307** (Figure 1.7.3) possess as 3-hydroxytetrahydrofuran core and have demonstrated nematocidal activity comparable to that of commercially available nematocides.[161]



306 **307**

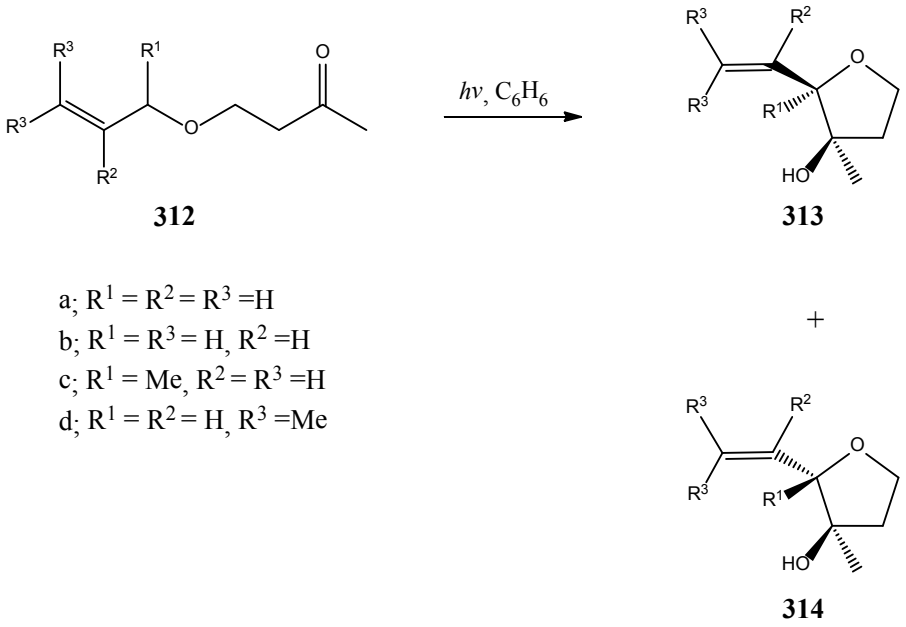
Figure 1.7.3 Structures of **306** and **307**

Britton *et. al.*[162] reported a publication providing access to **306** and **307** using a lithium aldol reaction of an α-chloroaldehyde as the starting point of the synthesis (Scheme 1.7.8). *Anti*-diol **308** was produced by reaction of *trans*-4-phenylbutene-2-one and (2*R*)-2-chloropentanal with LDA followed by Evans-Saksena reduction.[163] **309** was furnished *via* a similar method, however reduction of the aldol adduct β-hydroxyketone with catecholborane[164] resulted in the *syn*-diol. The 3-hydroxytetrahydrofuran was constructed either by silver catalysis or by reaction with $BF_3.OEt_2$ to produce **310** and **311** in good to excellent yield. The major limitation with the latter cyclisation method found epimerisation at room temperature on reaction with $BF_3.OEt_2$, carrying out this reaction at -35 °C minimised this issue. The natural products **306** and **307** were accessed using the same chemical synthesis *i.e.* oxidative cleavage of **310** and **311** followed by reductive workup with polymer-supported triphenylphosphine provided an aldehyde that was finally reacted with 8-nonenylmagnesium bromide in refluxing dichloroethane.



Scheme 1.7.8

Photochemical methods have also been utilised to produce 3-hydroxytetrahydrofurans. Carless and Haywood,[165] utilised the photochemical cyclisation of β-alloxycarbonyl compunds **312** to synthesise 2-alkenyl-3-hydroxytetrahydrofurans **313** and **314** (Scheme 1.7.9).



Scheme 1.7.9

The results of these photochemically-induced cyclisations are summarised in Table 1.7.3. The products **313** and **314** were easily separated by preparative GLC and their respective structures determined by ^{1}H and ^{13}C NMR.

Ketone	Product	Yield (%)
312a	**313a: 314a** 1.4:1	94
312b	**313b: 314b** 1.65:1	85
312c	**313c: 314c** 0.6:1	80
312d	**313d: 314d** 1.5:1	88

Table 1.7.3

1.8 Synthesis *via* Biotransformation

The field of biocatalysis has become a very widely studied and well regarded area for the synthesis of small molecules on a laboratory and, indeed, on an industrial scale. The fact that biocatalysts and the associated processes are much more environmentally favourable, not to mention that biocatalysts can often be recycled and reused, has led to a shift away from more traditional metal-based synthetic methods. Enzyme and whole cell catalysts have the advantage that they are much cheaper, much less toxic and easier to handle than their metallic counterparts. As a result they have become a much more attractive option to the pharmaceutical industry and in particular, many multinationals are employing their use in next generation process development.

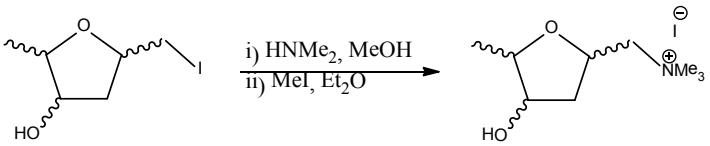
Two approaches to the use of biocatalytic reactions have been widely reported on; resolution of a racemate and biocatalysts that generate an asymmetric product. Enzymes are classified into six classes on the basis of the general type of reactions that they catalyse; hydrolases, ligases, lyases, oxidoreductases, transferases and isomerases.[178] A small number of examples are included herewithin to show the utility of biocatalysts, especially in the synthesis of 3-hydroxytetrahydrofurans, which is the scope of this review.

De Amici *et. al.*[166] accomplished efficient syntheses of the eight stereoisomers of muscarine (Figure 1.2.1) by dehydrogenase catalysed reduction of iodo ketones **315a** and **b**. Screening of various dehydrogenases revealed that hydroxysteroid dehydrogenases from *Streptomyces hydrogenans* (20*β*-HSDH) and *Pseudomonas testosteroni* (*β*-HSDH) were the most effective for reducing the respective *cis*- and *trans*-iodo furanones.

315a **315b**

Figure 1.8.1 Iodoketones **315a** and **b**

To furnish (-)-muscarine, (+)-epiallomuscarine and (-)-allomuscarine, inversion of stereochemistry at the hydroxyl position was effected using Mitsunobu[121] conditions of triphenylphosphine, DEAD and benzoic acid prior to hydrolysis to the respective alcohols. The eight stereoisomeric iodo alcohols **316** were individually reacted with dimethylamine and methyl iodide to produce all the possible stereoisomers of muscarine-iodide **317** (Scheme 1.8.1).

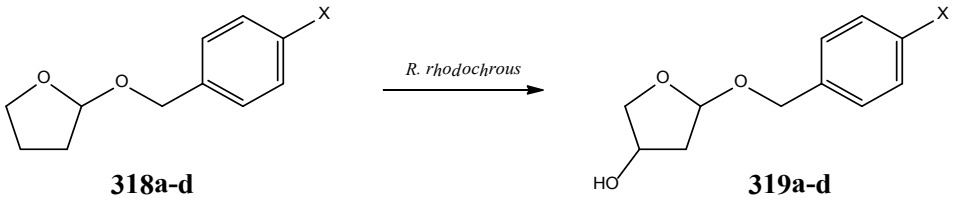


316 **317**

Scheme 1.8.1

In early 2012 Turner *et. al.*[167] released a publication outlining the biocatalytic regio- and stereo-selective oxidation of unactivated C-H bonds. This research group, in particular, have carried out extensive research of biocatalysts to carry out the desired hydroxylation reactions,[168-170] and this publication outlines the application of that research in the synthesis of a 3-hydroxytetrahydrofuran. The authors report that many hydroxylating enzymes have been identified within bacteria from the genus *Rhodococcus*, in particular *Rhodococcus rhodochrous*. This particular strain has been known to oxidise a range of aliphatic hydrocarbons, including *n*-alkanes and isoalkanes, and has been reported to catalyse the terminal hydroxylation of chloroalkanes and long-chain alkenes.[171] It has been suggested that this strain contains an alkane-inducable NADH-dependent hydroxylase that catalyses the oxidation of n-octane to 1-octanol.[171, 172] With this in mind, the ability of this strain to catalyse the desired oxidation reaction was investigated.

The compounds investigated were the racemic 2-alkoxytetrahydrofurans **318 a-d**, (prompted by the success of the ability of the organism to catalyse the corresponding tetrahydropyran series), and their conversion into the desired hydroxytetrahydrofurans **319 a-d**.



318a-d **319a-d**

318	X	% Yield
a	H	15
b	Me	18
c	Cl	*
d	NO_2	26

* Resulted in a mixture of products, see below for details

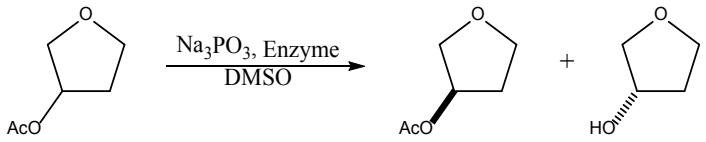
Figure 1.8.2 Scheme and yield data for selective hydroxylation of tetrahydrofurans **318 a-d**

Hydroxylated compounds **319 a,b** and **d** were isolated and identified as single products, with the *p*-nitrobenzyloxy derivative produced in 26% yield as opposed to the 15% and 18% yields of **319a** and **b** respectively. The chloro-substituted aryl derivative was found to consist of 14% of mixed hydroxylated furan derivatives along with 29% of *p*-chlorobenzoic acid. The isolation of benzoic acid suggests that benzylic hydroxylation takes place leading to cleavage of the unstable acetal.[173, 174]

With the advent of so many biocatalysts that carry out a variety of transformations, high-throughput screening has led to the identification of substrate-specific reactions providing high reaction efficiency and enantioselectivity to, in many cases, enantiopure products. This, of course, can lead to the use of biocatalysts in natural product and pharmaceutical synthesis to provide the desired products in high yield and excellent enantioselectivity in a clean and efficient manner.

One such example of this screening process was published by Bornscheuer.[175] The author utilises the two possible modes of lipase catalysed resolution; hydrolysis of a racemic ester and esterification of a racemic alcohol. While various substrates were screened, the result of most interest to our work is the resolution of 3-hydroxytetrahydrofuran **320** from its corresponding ester **321**. This acetate was chosen by

the authors as it had not been previously sufficiently resolved to allow the isolation of enantiomerically pure substrate and product.



321 **321a** **320b**

Enzyme	Temp (°C) / Time (h)	%ee Ester	%ee Alcohol	% Conversion	E
CAL B	37 / 0.5	90 (*R*)	37 (*S*)	69	6
PFE I	37 / 22	31 (*R*)	40 (*S*)	43	3
BD100	37 / 22	34 (*S*)	33 (*R*)	51	3

Figure 1.8.3 Table and reaction scheme for enantioselective hydrolysis screen of **321**

The results tabulated above, show that this substrate can, after all, be resolved by enzymatic means to give, at the very least, enantioenriched products. The E-value[176] (an equation for the efficiency of the transformation based on conversion and enantioselectivity of substrate/product) for these resolutions is very low. However, given that this compound was previously unresolved, the authors have shown that with a wide library of potential biocatalysts, one can eventually be found to resolve a stubborn substrate. What is very interesting from the above reactions is that hydrolase BD100 (Diversa Corporation, San Diego, USA) catalysed the formation of the opposite enantiomeric series. The authors did not comment on this result.

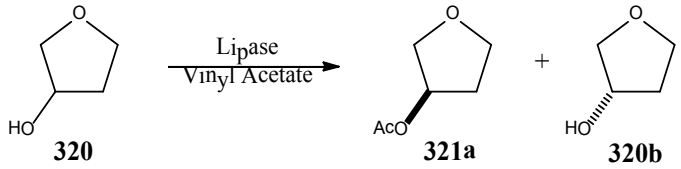
Preparative-scale resolutions were also carried out to investigate the reproducibility of the screened reactions on a larger scale (Table 1.8.1). As lipase B from *Candida antarctica* was the more successful, this formed the basis of the larger-scale resolutions. Unfortunately, the reactions did not show much improvement, however it did establish that the reactions could be performed on a larger scale in both hydrolysis of the racemic acetate and acetylation of the alcohol.

Substrate	Enzyme	Temp (°C) / Time (min)	% Conversion	%ee Ester	%ee Alcohol	E
321a	*CAL* B	37 / 63	75	83 (*R*)	28 (*S*)	4
321a	BD100	80 / 123	70	49 (*S*)	24 (*R*)	3
320a	*CAL* B immob	37 / 5	83	15 (*R*)	71 (*R*)	3

Table 1.8.1 Preparative-scale resolutions

Although the authors did not comment on the precise reason for the poor E-value, it could well be concluded that Kazlauskas' rule[177] has a major bearing on these results. This rule is used to predict that high E-values are achieved in secondary alcohols when there is a marked difference in the size of the substituents attached to the stereogenic centre. In the case of 3-hydroxytetrahydrofuran there is no substitution on the ring, therefore a lack of steric discrimination is available to the enzyme on the ring system. Hence, even with exhaustive screening processes by the authors, the E-value is very low.

A publication by Moody *et. al.*[179] also used **320** as a substrate in a lipase-screening process. This publication represented that a novel lipase enzyme panel exhibited superior activity and selectivity over *CAL* B for the kinetic resolution of secondary alcohols, but although they do show this, it also demonstrates the difficulty of an array of enzymes and reaction conditions in resolving **320** to any degree of synthetic utility.



320 **321a** **320b**

Enzyme	Time (h)	%ee Ester	%ee Alcohol	% Conversion	E
EL-13	0.08	40	2	5	2.5
EL-13	1	48	7	15	3.3
EL-15	1	47	12	21	3.1
CAL B	1	52	8	14	3.4

Figure 1.8.4 Table and reaction scheme for enantioselective esterification screen of **320**

Although, the E-value was not exceeded for the above screen, the authors carried out a screen where the solvents were altered and found a very small increase when EL-14 enzyme was used in conjunction with hexane.

Enzyme	Time (h)	Solvent	%ee Ester	%ee Alcohol	% Conversion	E
EL-14	16	Hexane	46	46	41	4.0
		MTBE	52	8	14	3.4
		Me-THF	16	1	4	1.4
		Toluene	45	6	12	2.8
CAL B	1	Hexane	23	9	29	1.7
	1	MTBE	31	7	19	2.0
	16	Me-THF	30	6	17	2.0
	1	Toluene	40	8	16	2.5

Table 1.8.2 Data for solvent screen of resolution of **320**

This review has shown there to be potential to access chiral 3-hydroxytetrahydrofurans through a variety of methods. The question as to whether these systems can be produced from their corresponding ketones has been previously studied within our laboratory with regard to the use of Baker's Yeast-mediated reduction in the synthesis of Muscarines.[180, 181] Also, enantioenriched 3-hydroxytetrahydrofurans have been synthesised within our laboratory by selective reduction of a 4,5-dihydro-3(*2H*)-furanone followed by lipase-mediated kinetic resolution (*via* acylation) of the resultant racemic alcohols.[177] The proceeding chapters of this thesis will detail further studies into the enzyme catalysed kinetic resolution of racemic 3-hydroxytetrahydrofurans and the search to obtain these compounds in enantioenriched/enantiopure form.

Results & Discussion

2.0 Results and Discussion

2.1 Introduction

This chapter describes the synthesis of a range of chiral 4,5-dihydro-3(*2H*)-furanones and their subsequent transformation into 3-hydroxytetrahydrofurans. These alcohols were then employed as substrates to provide access to enantiopure/enantioenriched 3-hydroxytetrahydrofurans *via* lipase-mediated kinetic resolutions in the presence of an acyl group donor. The work investigated the effect of varying the substitution pattern of the substrates and how this would impact on the yield and stereochemical outcomes of the reactions.

Earlier work by Hayes[178] in this area within our research group indicated that the 3-hydroxytetrahydrofuran moiety is suitable for these types of reactions. That work however surveyed a broad range of 3-hydroxytetrahydrofurans (twenty four compounds - largely aryl substituted) that involved kinetic resolutions with an acyl donor using a *Candida cylindracea* lipase but did not optimise any of the reactions - acyl donor, enzyme, solvent, temperature - for optimum enantiomeric composition (%e.e.) of the products on a synthetically useful scale.

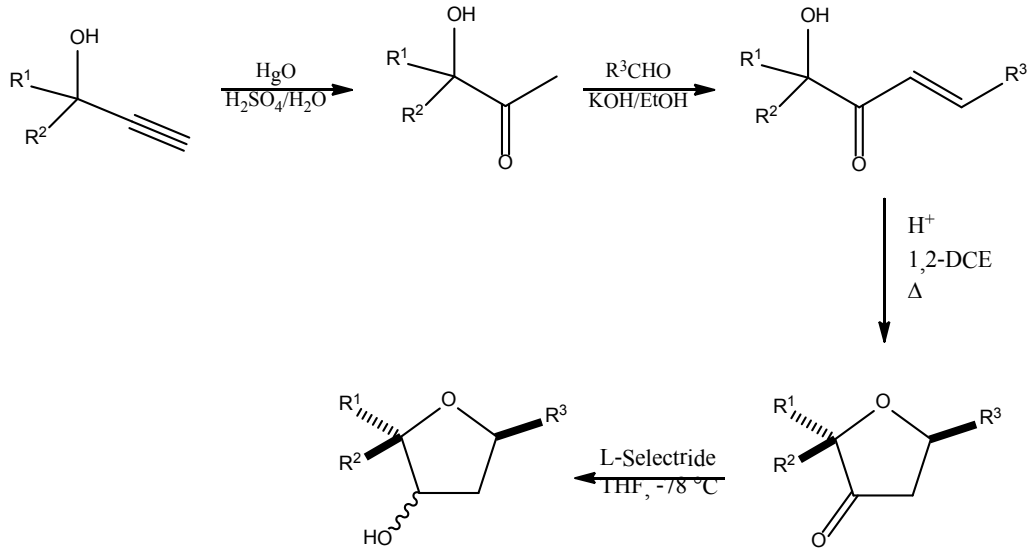
The objective of our work was to to take Hayes' preliminary results and optimise the lipase-mediated kinetic resolution to provide enantiomerically pure 3-hydroxytetrahydrofurans through variation of biocatalyst and conditions, to explore the reaction scope in terms of variation of substituent, to determine the enantiomeric series and establish that the process can be optimised for individual substrates as a result of the rigorous screening process that we employed.

Overall we studied twenty hydroxytetrahydrofurans in a substrate specific study, the majority of which are new compounds. Hayes' study had identified some of these compounds as substrates that were promising compounds as a starting point for our research to tune the reactions to access a range of enantiomerically pure 3-hydroxytetrahydrofurans. In addition we included in particular, several compounds containing polar substituents (amino, acetamido and nitro) in the aromatic ring of the hydroxytetrahydrofurans in order to investigate their reactivity towards these enzymes.

During the course of this work, we have also discovered a novel synthesis of 2,3,5-trisubstituted furans, a widely explored class of compounds. This chemistry also allowed synthesis of a number of novel diaryl-substituted cyclopentenones.

2.2 4,5-Dihydro-3(*2H*)-Furanones *via* α-Hydroxyenones

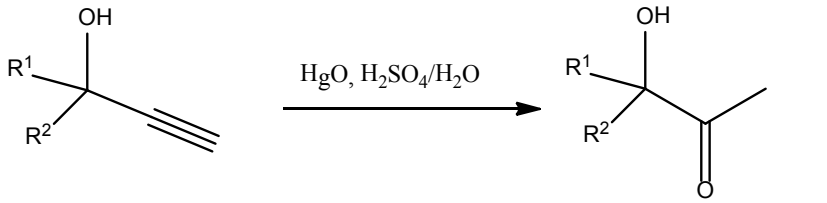
Scheme 2.2.1 shows the formation of 4,5-dihydro-3(*2H*)-furanones, the precursors of the 3-hydroxytetrahydrofurans that we required were synthesised from α-hydroxyenones. These were in turn prepared through a base-catalysed Claisen-Schmidt condensation of α-hydroxyketones mostly with arene carboxaldehydes. The hydroxyenones based on trimethylacetaldehyde, a non-enolisable aldehyde, were included in the range of compounds produced.



Scheme 2.2.1

2.2.1 Preparation of α-Hydroxyketones

α-Hydroxyketones were formed by hydration of commercially available terminal alkynes with aqueous sulphuric acid in the presence of mercuric oxide, utilising the procedure as described by Newman *et al.*[182]

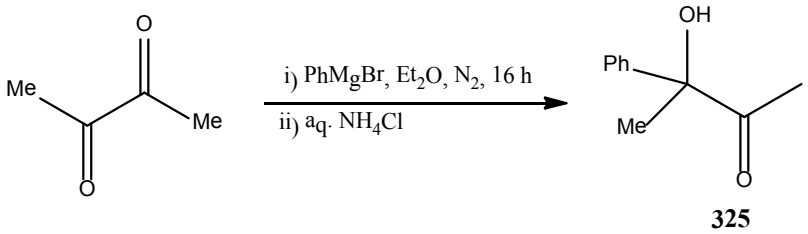


$R^1 = R^2 = Me$
$R^1 = R^2 = (CH_2)_5$
$R^1 = Me, R^2 = Et$

322 $R^1 = R^2 = Me$
323 $R^1 = R^2 = (CH_2)_5$
324 $R^1 = Me, R^2 = Et$

Scheme 2.2.1.1

The α-hydroxyketones **322** and **323** were isolated as clear oils in modest yields by distillation, with compound **324** being sufficiently pure by NMR analysis to carry forward as a brown liquid without any further purification. The low yield (Table 2.2.1.1) of **322** is attributed to its considerable solubility in water, resulting in loss of material during the aqueous work-up. The poor solubility of 1-ethynyl-1-cyclohexanol in water however, necessitated the use of 1,4-dioxane as a co-solvent in the alkyne hydration reaction to produce compound **323**.



325

Scheme 2.2.1.2

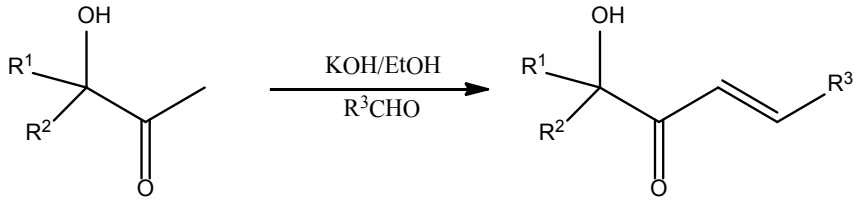
3-Hydroxy-3-phenylbutan-2-one **325**, was prepared by inverse addition of ethereal phenyl magnesium bromide to an ice-cooled solution of diacetyl in diethyl ether. Stirring for 16 h under an inert nitrogeneous atmosphere, addition of saturated aqueous ammonium chloride solution followed by extraction yielded the desired compound **325** that was used without further purification in subsequent reactions. The hydroxyketones were each characterised by a strong IR absorption *ca.* 1710 cm^{-1} attributed to the carbonyl group of the hydroxyketones structure and by ^1H NMR analysis by a three hydrogen singlet in each corresponding to the newly formed α-methyl groups.

Compound	Yield (%)	ν_{max} (cm^{-1})	δ_H C(1)$\underline{H}_3$
322	29	1715	2.26
323	46	1703	2.26
325	78	1713	2.08
324	46	1711	2.21

Table 2.2.1.1 Key IR absorptions, ^{1}H NMR assignments and Yields for compounds **322-325**

2.2.2 Preparation of α-Hydroxyenones *via* Aldol Condensation

The α-hydroxyketones were coupled *via* aldol condensation to a variety of aromatic aldehydes, generating a range of α,β-unsaturated ketones (Scheme 2.2.2.1).

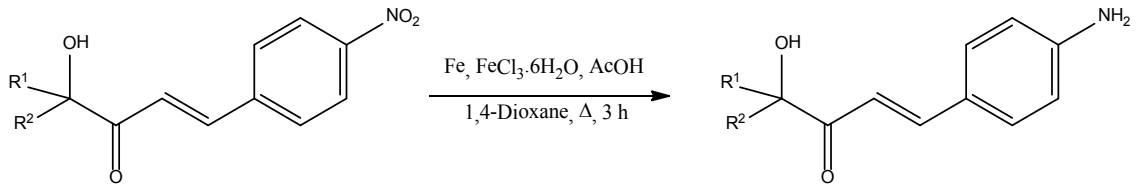


Scheme 2.2.2.1

These reactions were carried out, for the most part, by the addition of an ethanolic solution of potassium hydroxide to a solution of the hydroxyketone and appropriate aldehyde in the same solvent and stirring the mixture at room temperature for three to 5 hours. Acidic work-up, followed by either distillation or chromatography produced the enones as solids or viscous oils in good yield (Table 2.2.2.1). Upon addition of base, the formation of a highly coloured solution was observed and can be attributed to conjugation of the α,β-unsaturated carbonyl group with the aryl ring of the product enone. This procedure produced up to twenty substituted hydroxyenones throughout the course of this work.

In an attempt to synthesise an enone containing an amine functionalised aromatic amine, it was decided to approach this by reduction of a nitro arene derivative to yield the

4-aminophenyl derived α-hydroxyenones. This was carried out utilising a slightly modified procedure published by Gabriele *et al.*[183], whereby the respective nitro compounds were reacted with elemental iron, iron trichloride hexahydrate and acetic acid in 1,4-dioxane under reflux (Scheme 2.2.2.2). Subsequent work-up (including washes with aqueous sodium bicarbonate to remove residual acetic acid) resulted in formation of the desired amino compounds **326** and **327** in good yields following chromatographic purification. These compounds were readily identifiable by IR and NMR spectroscopy, with the amino functionality represented at *ca*. 3300 cm^{-1} and *ca.* 4.00 ppm as a broad, two hydrogen singlet, respectively. For compounds **326** and **327**, although these contain chemically incompatible functional groups (*i.e.* an amine and a ketone), no evidence of polymerisation was observed.



334 $R^1 = R^2 =$ Me
340 $R^1 = R^2 =$ $(CH_2)_5$

326 $R^1 = R^2 =$ Me
327 $R^1 = R^2 =$ $(CH_2)_5$

Scheme 2.2.2.2

The preparation of enones from alkanecarboxaldehydes is potentially problematic due to self-aldol condensation occurring at a greater rate than requisite crossed aldol condensations. It is limited to reactions involving aldehydes which do not contain enolisable α-hydrogens and ketones bearing only one enolisable proton. In order to avoid these complications while continuing to use the Claisen-Schmidt conditions, and because we required a alkyl group of some steric bulk, we synthesised *E*-2-hydroxy-2,6,6-trimethyl-hept-4-ene-3-one **328** and *E*-1-hydroxy-1-cyclohexyl-5,5-dimethyl-hex-3-en-2-one **329** using trimethylacetaldehyde which does not contain an enolisable α-hydrogen in its molecular structure.

Compound	R^1	R^2	R^3	$\nu_{C=O}$ (cm^{-1})	$\nu_{C=C}$ (cm^{-1})	Yield (%)
326	Me	Me	4-$NH_2C_6H_4$	1663	1630	87
327	$(CH_2)_5$		4-$NH_2C_6H_4$	1664	1593	80
328	Me	Me	t-Bu	1690	1619	57
329	$(CH_2)_5$		t-Bu	1683	1619	69
330	Me	Me	C_6H_5	1682	1608	70
331	Me	Me	4-FC_6H_4	1684	1614	82
332	Me	Me	3,4-$(MeO)_2C_6H_3$	1670	1599	70
333	Me	Me	3-$NO_2C_6H_4$	1690	1614	70
334	Me	Me	4-$NO_2C_6H_4$	1688	1614	88
335	Me	Me	4-MeC_6H_4	1683	1604	79
336	$(CH_2)_5$		C_6H_5	1674	1596	69
337	$(CH_2)_5$		4-FC_6H_4	1679	1599	88
338	$(CH_2)_5$		3,4-$(MeO)_2C_6H_3$	1685	1615	72
339	$(CH_2)_5$		3-$NO_2C_6H_4$	1683	1612	87
340	$(CH_2)_5$		4-$NO_2C_6H_4$	1683	1613	73
341	$(CH_2)_5$		4-MeC_6H_4	1674	1599	86
342	Ph	Me	C_6H_5	1684	1615	88
343	Ph	Me	4-FC_6H_4	1679	1597	78
344	Ph	Me	4-$NO_2C_6H_4$	1689	1615	78
345	Et	Me	C_6H_5	1682	1609	86

Table 2.2.2.1 IR Carbonyl Absorption Frequencies and Yield Data of Hydroxyenones **326-345**

The enones synthesised for this work were characterised by IR and ^{1}H NMR spectroscopy. Characteristic stretches at *ca*. 1680 and 1610 cm^{-1} were assigned to the carbonyl and alkene moieties respectively.

In their ^{1}H NMR spectra, these α-hydroxyenones exhibited characteristic resonances for alkene protons. The chemical shift of the enone β-proton was in the range of 7.13-7.87 ppm. This deshielding effect arises primarily from the resonance interaction of the alkene system with the carbonyl group with an additional contribution from the electronic effect of the aryl substituent. The more shielded α-proton also resonated as a

one hydrogen doublet in the range of 6.33-7.29 ppm. Coupling constants of approximately 15-16 Hz were observed allowing the enones to be clearly assigned the *trans*-stereochemistry. A summary of the ^{1}H NMR data for enones **326-345** is shown in Table 2.2.2.2. See Figure 2.2.2.1 for a typical ^{1}H NMR spectrum.

Compound	$\delta_{H\alpha}$ (ppm)*	$\delta_{H\beta}$ (ppm)*	*J* (Hz)	δ_{OH} (ppm)*
326	6.81	7.79	15.5	4.18
327	6.90	7.78	15.5	4.00
328	6.33	7.16	15.0	4.06
329	6.40	7.13	15.6	3.80
330	7.13	7.83	15.7	4.17
331	7.01	7.81	15.7	3.92
332	7.10	7.80	15.6	4.12
333	7.19	7.87	15.7	3.89
334	7.18	7.85	15.8	3.45
335	6.99	7.84	15.7	4.07
336	7.10	7.90	15.7	3.86
337	7.00	7.78	15.7	3.71
338	7.00	7.79	15.7	3.83
339	7.29	7.83	15.7	3.54
340	7.28	7.82	15.8	3.43
341	7.08	7.82	15.7	3.84
342	6.79	7.78	15.7	4.73
343	6.72	7.74	15.7	4.72
344	6.92	7.77	15.8	4.41
345	7.02	7.86	15.7	4.32

* ^{1}H NMR spectra in $CDCl_3$

Table 2.2.2.2 Selected ^{1}H NMR Assignments of α-Hydroxyenones **326-345**

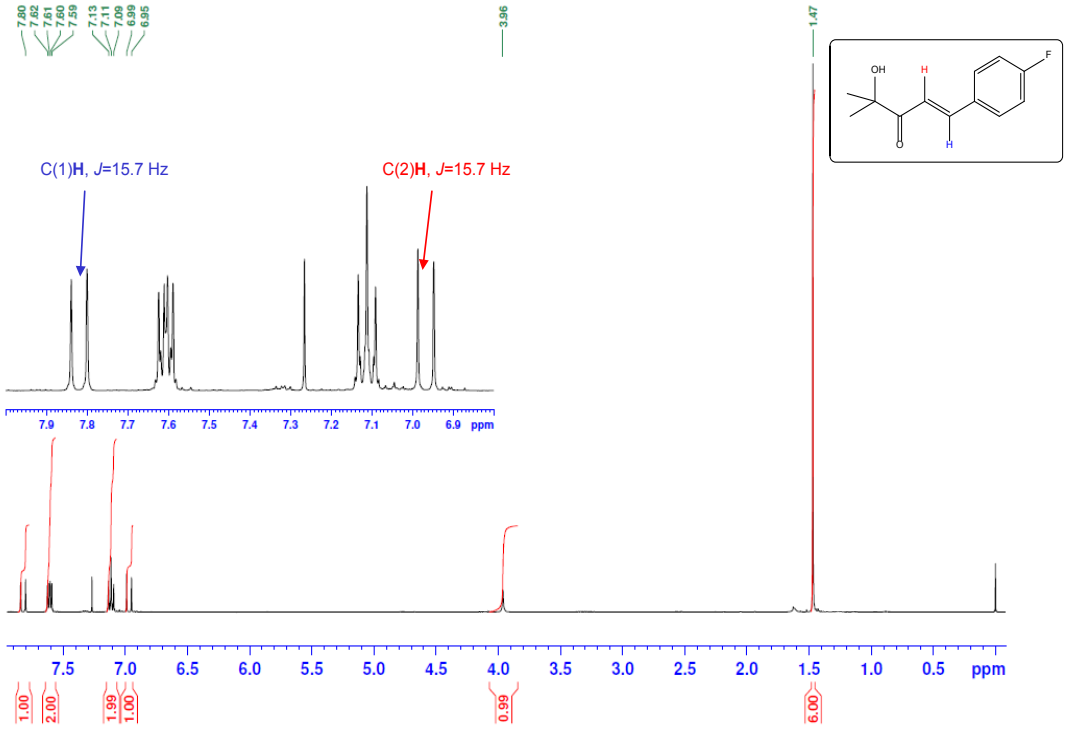
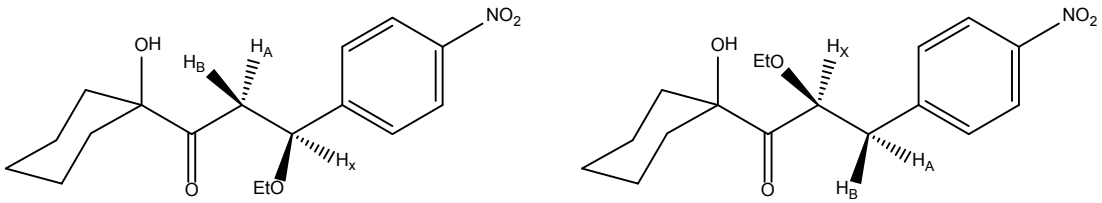


Figure 2.2.2.1 ^{1}H NMR Spectrum of Hydroxyenone **331** in $CDCl_3$

During the synthesis of hydroxyenone **340** an interesting side-product was encountered. This was initially observed by Kelly,[184] but the actual structure was not fully determined at the time. Initially it was thought the respective 4,5-dihydro-3(*2H*)-furanone had formed after the enone had undergone cyclisation mediated by the acidic work-up and heat generated by the water bath upon solvent evaporation. Our initial structure assignment was based on interpretation of an ABX spin system pattern seen in the ^{1}H NMR spectrum of the compound as that of the 4,5-dihydrofuranone (which will be discussed in greater detail in Section 2.2.3). When the data of the unknown compound was compared to a pure sample of **346** however, it was evident that the compounds were not the same material.

The 3H triplet at 1.15 ppm and a 2H quartet at 3.37 ppm was initially attributed to contamination of the compound with the ethanolic reaction solvent. However, this conclusion proved incorrect and further examination led us conclude that nucleophilic addition of ethanol to **340** had occurred resulting in the formation of the adduct **347a**.



347a **347b**

Figure 2.2.2.2

It was not possible to isolate this compound in a pure state as it chromatographically co-eluted with the precursor α-hydroxyenone in approximately a 25:75 mixture of compounds **347a**:**340**. Two-dimensional NMR spectroscopy made assignment of this compound possible. This was affected using HMBC, HSQC, COSY and TOCSY NMR experiments. The major resonances that allowed us to assign the signals for this compound came from the HMBC spectra. Firstly there are obvious interactions between Hx of **347a** and the carbon atoms from the aryl ring. Had the ethoxy- group added to the alternative carbon atom during the reaction (i.e. compound **347b**) then this interaction between the signals would not have been as evident. Further evidence was provided by the carbonyl carbon of **347a**; there is strong ^{2}J coupling to H_A and H_B respectively, with weak ^{3}J coupling to H_X. Formation of this adduct is attributed to the strong electron withdrawing ability of the nitro-substituent on the aromatic ring. This causes the alkene group of the enone to be more electrophilic towards the ethoxide anion generated from the reaction of potassium hydroxide with the ethanolic reaction solvent.

This discovery led us to re-examine the solvent in use for the synthesis α-hydroxyenones bearing nitrophenyl moieties. The use of 1,4-dioxane proved successful and produced the desired compounds **333, 334, 339, 340** and **344** in good to excellent yield without the presence of the ethoxy adduct analogous to compound **347**.

During purification of **340** on silica gel, another unanticipated compound was detected by the presence of a pair of doublets centred at 6.74 and 7.02 ppm respectively in its ^{1}H NMR spectrum. The coupling constants for both were calculated at 12.8 Hz which pointed to formation of the *cis*-isomer of the α-hydroxyenone *via* acid-catalysed isomerisation, bearing in mind the acidic nature of silica gel and the acidic work-up of the reaction mixture. To test this hypothesis a pure, small quantity of **340** was stirred in a

mixture of silica gel and 10% ethyl acetate/hexane (analogous to the solvent mixture used in the initial purification of **340**). This reaction was monitored by ^{1}H NMR analysis, and although the process did not complete the isomerisation from **340** to its *cis*-isomer, there was sufficient conversion to indicate the cause of the initial discovery and the *cis*-isomer **348** was isolated following chromatographic purification. Further evidence of the structure was made by mass spectrometry with the ESI^{+} high resolution mass spectrum determining the molecular mass at 276.1236 (calculated for $C_{15}H_{18}NO_4$, 276.1232).

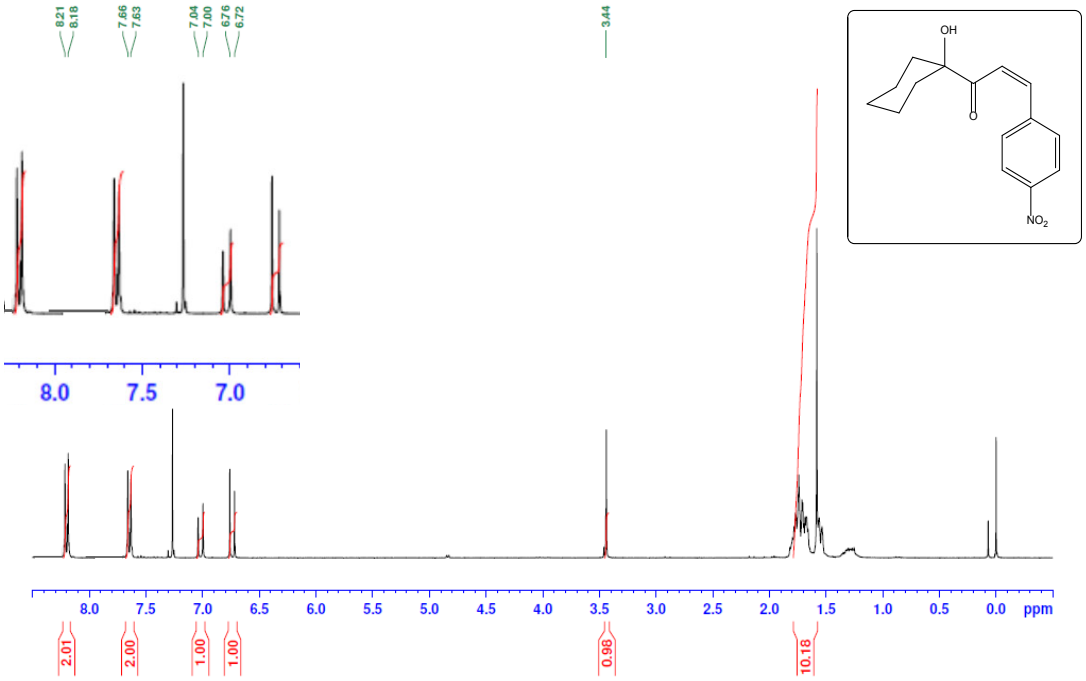


Figure 2.2.2.3 ^{1}H NMR Spectrum of **348** in $CDCl_3$

A ^{1}H NMR sample of the *cis*-enone was monitored to ascertain if it was stable or if it would revert to the *trans*-isomer. This sample (compound **348** in $CDCl_3$ and contained within an NMR tube) was left exposed to laboratory light for the duration of the study. Interestingly, conversion began to occur rapidly with a ^{1}H NMR spectrum taken within eight hours of chromatographic purification of **348** showing some evidence of isomerisation to **340**. Details of the extent of the conversion by ambient light over a longer time period are shown below in Figure 2.2.2.4. Integration of the respective alkene protons provided the conversion from *cis*- to *trans*- over time

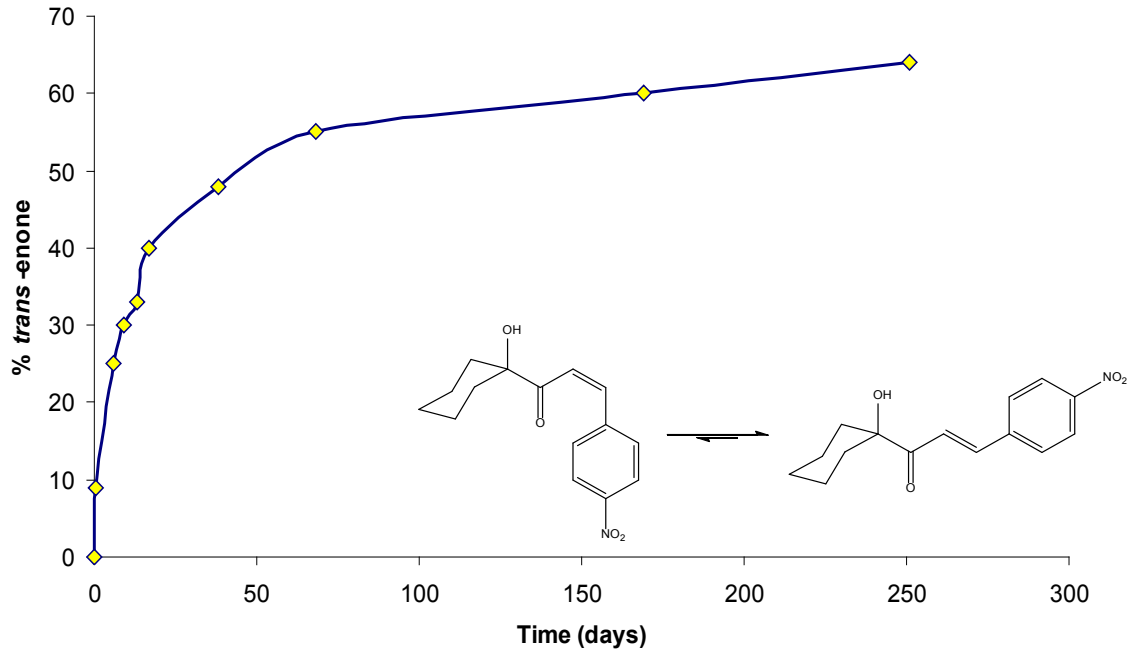
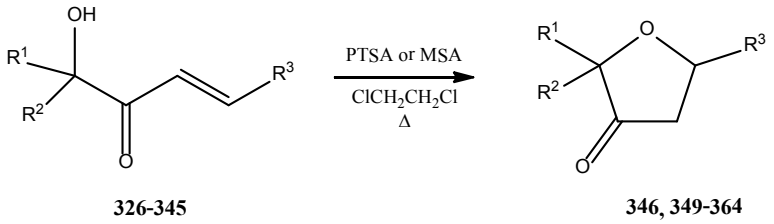


Figure 2.2.2.4 Equilibration of *Z*-**348** with its *E*-isomer, measured by ^{1}H NMR in $CDCl_3$

2.2.3 Synthesis of 4,5-Dihydro-3(*2H*)-Furanones

Acid-catalysed cyclisation of enones provided a convenient route to a variety of 2,2,5-trisubstituted 4,5-dihydrofuranones. Earlier investigations[178, 185, 186] revealed that the catalysts of choice for this cyclisation are *p*-toluenesulphonic acid (PTSA) or methanesulphonic acid (MSA) with 1,2-dichloroethane as the preferred solvent. Combinations of the above factors with varying reaction temperature and times lead to a range of conditions used for these cyclisations. The best observed conditions for each individual compound are given in Chapter 3 of this thesis but are not optimised, as the synthesis was progressed once sufficient quantities of target furanone had been generated.



326-345 **346, 349-364**

Scheme 2.2.3.1

Chromatography on silica gel afforded the target compounds in moderate to good yields (Table 2.2.3.1). All compounds displayed a characteristic IR carbonyl group absorption at *ca.* 1755cm^{-1}.

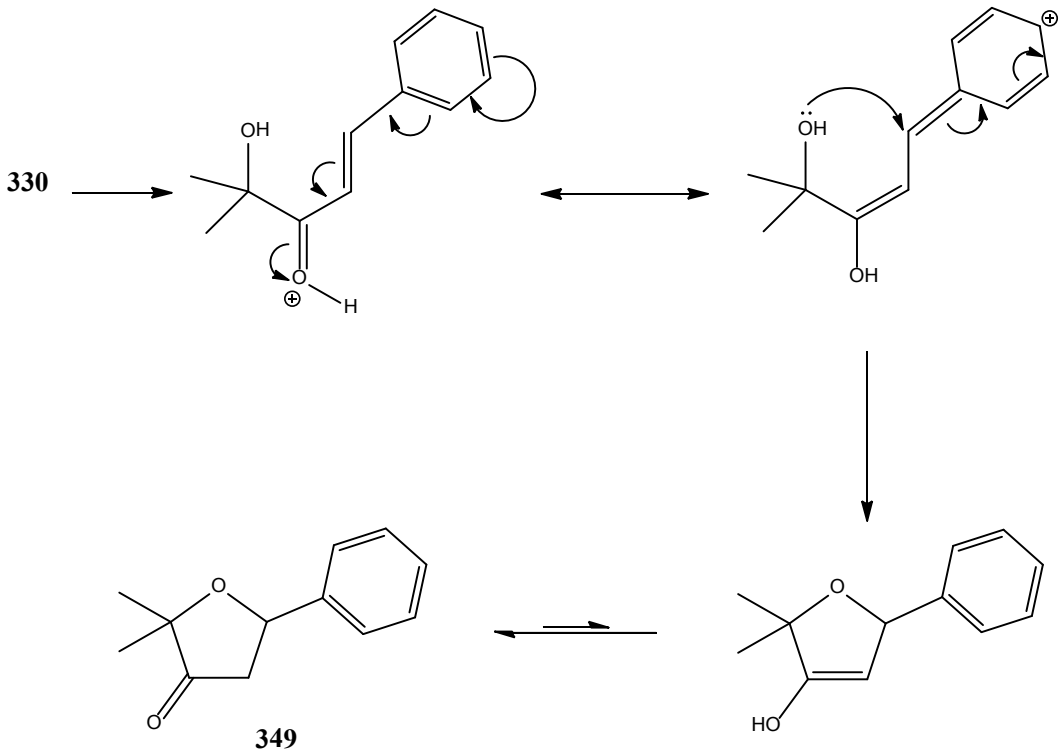
Compound	R^1	R^2	R^3	$\nu_{C=O}$ (cm^{-1})	Yield (%)
349	Me	Me	C_6H_5	1756	48
350	Me	Me	4-FC_6H_4	1755	67
351	Me	Me	3,4-$(MeO)_2C_6H_4$	1754	58
352	Me	Me	3-$NO_2C_6H_4$	1758	58
353	Me	Me	4-$NO_2C_6H_4$	1757	49
354*	Me	Me	4-MeC_6H_4	1756	66
355*	Me	Me	4-$NH_2C_6H_4$	1752	83
356	Me	Me	t-Bu	1757	51
357	$(CH_2)_5$		C_6H_5	1747	65
358*	$(CH_2)_5$		4-FC_6H_4	1751	68
359*	$(CH_2)_5$		3,4-$(MeO)_2C_6H_4$	1755	36
360*	$(CH_2)_5$		3-$NO_2C_6H_4$	1750	71
346*	$(CH_2)_5$		4-$NO_2C_6H_4$	1751	68
361*	$(CH_2)_5$		4-MeC_6H_4	1750	68
362*	$(CH_2)_5$		4-$NH_2C_6H_4$	1746	87
363*	$(CH_2)_5$		t-Bu	1751	82
364*	Et	Me	C_6H_5	1755	84

* Indicates novel compound

Table 2.2.3.1 IR Carbonyl Absorption Frequencies and Yields of 4,5-Dihydro-3(*2H*)-furanones **346** and **349-364**

These cyclisations conform directly with Baldwins[119] rules, *i.e.* that all of the exocyclic closures which generate five or six-membered rings are favoured reactions. Such reactions are referred to as 5-*exo*-trig cyclisations. For the furanone systems, Baldwin attributed the success of such cyclisations to the low rotational energy barrier of the enone (due to resonance effects), thereby allowing them to attain a conformation which is geometrically compatible with the rate-determining transition state for

dihydrofuranone formation. Attack of the tertiary alcohol group on the alkene, as shown for the conversion of **330** to **349**, followed by tautomerisation to the thermodynamically more stable keto form gives the required product



Scheme 2.2.3.2

^{1}H NMR analysis of the furanone products showed a collapsing of the alkene system that was a distinguishing feature of the enone precursors. The spectra of the dimethyl compounds contain two singlets which have been assigned to the diastereotopic methyl groups. This diastereotopicity arises from the stereogenic centre at the C(5) position of the heterocycle. Protons of the spiro-fused cyclohexyl groups appear as a ten hydrogen multiplet in their ^{1}H NMR spectra. Another consequence of the C(5) stereogenic centre on the ^{1}H NMR spectra, is that the C(4) and C(5) protons constitute an ABX spin system where the diastereotopic C(4) protons are the AB portion (an eight line multiplet) and the C(5) proton signal a deshielded doublet of doublets is the X constituent (Table 2.2.3.2). This deshielding effect is attributed to the combined electron withdrawing effect of the adjacent oxygen and aryl moieties. An analysis of the coupling constants is shown in Figure 2.2.3.1; geminal coupling of H_A and H_B gives rise to a coupling constant of approximately 18.0 Hz. The *trans*-coupling vicinal protons H_B and H_X have a *J*-value

of approximately 10.0 Hz with a value of approximately 6.0 Hz recorded for the *cis*-coupling of protons H_A and H_X.

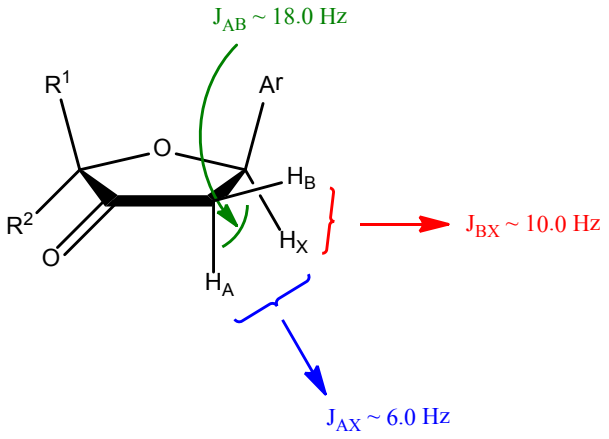


Figure 2.2.3.1 Illustration of the ABX Spin System and Associated Coupling Constants

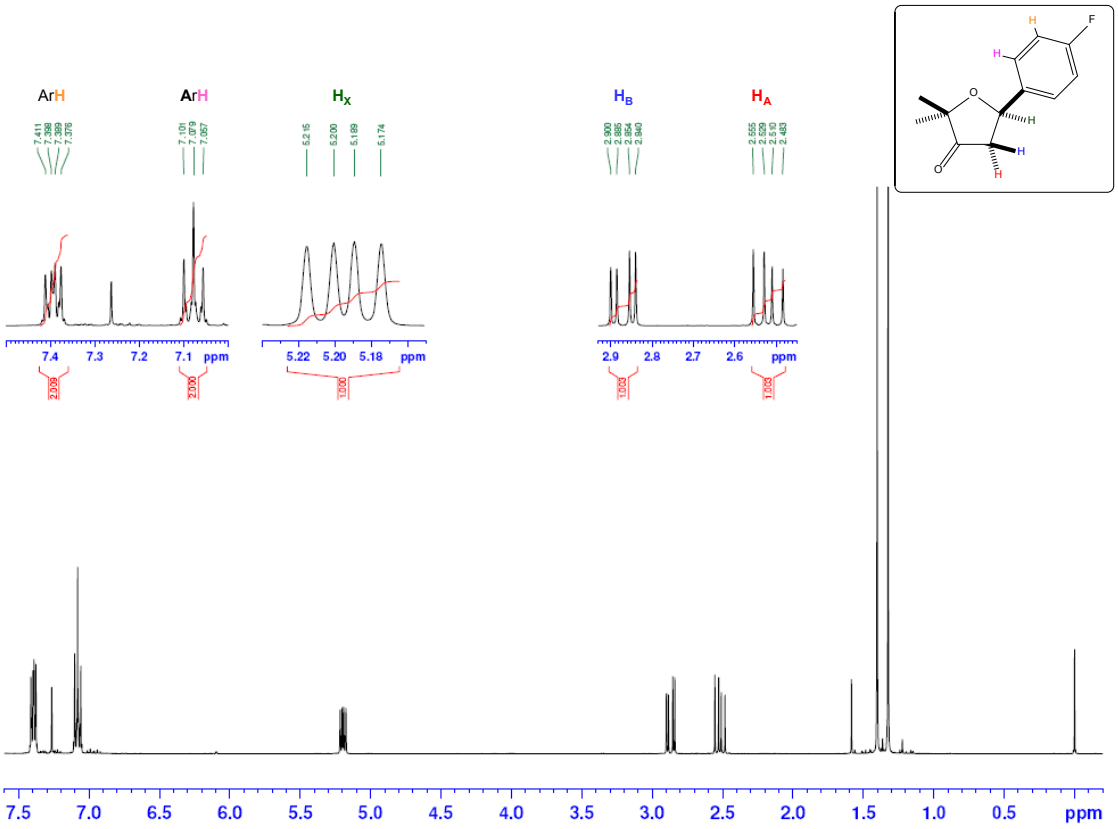


Figure 2.2.3.2 ^{1}H NMR Spectrum of 4,5-dihydrofuranone **350** in $CDCl_3$

Compound*	δ_{HA} -δ_{HB} (ppm)	δ_{HX} (ppm)	J_{AX} (Hz)	J_{BX} (Hz)	J_{AB} (Hz)
349	2.50 – 2.90	5.13	6.0	10.4	18.2
350	2.50 – 2.86	5.20	5.9	10.5	18.1
351	2.57 – 2.85	5.16	5.9	10.2	18.2
352	2.53 – 2.99	5.34	6.1	10.4	18.1
353	2.49 – 2.97	5.33	6.1	10.5	18.1
354	2.55 – 2.84	5.17	5.9	10.4	18.1
355	2.55 – 2.78	5.09	5.9	10.5	18.1
356	2.30 – 2.40	3.87	7.3	9.3	18.3
357	2.53 – 2.86	5.20	6.1	10.4	18.1
358	2.48 – 2.84	5.12	6.1	10.4	18.1
359	2.55 – 2.84	5.15	6.1	10.2	18.1
360	2.51 – 2.96	5.32	6.2	10.4	17.9
346	2.47 – 2.95	5.33	6.3	10.4	17.9
361	2.52 – 2.83	5.16	6.0	10.4	18.1
362	2.52 – 2.77	5.07	5.9	10.4	18.1
363	2.31#	3.87	-	-	-
364	2.35 – 2.90^	5.14 – 5.24	-	-	-

* See Table 2.2.3.1 for identity of substituents
# Appears as a doublet
^ Overlapping signals

Table 2.2.3.2 ^{1}H NMR Data of Compounds **349 - 364**

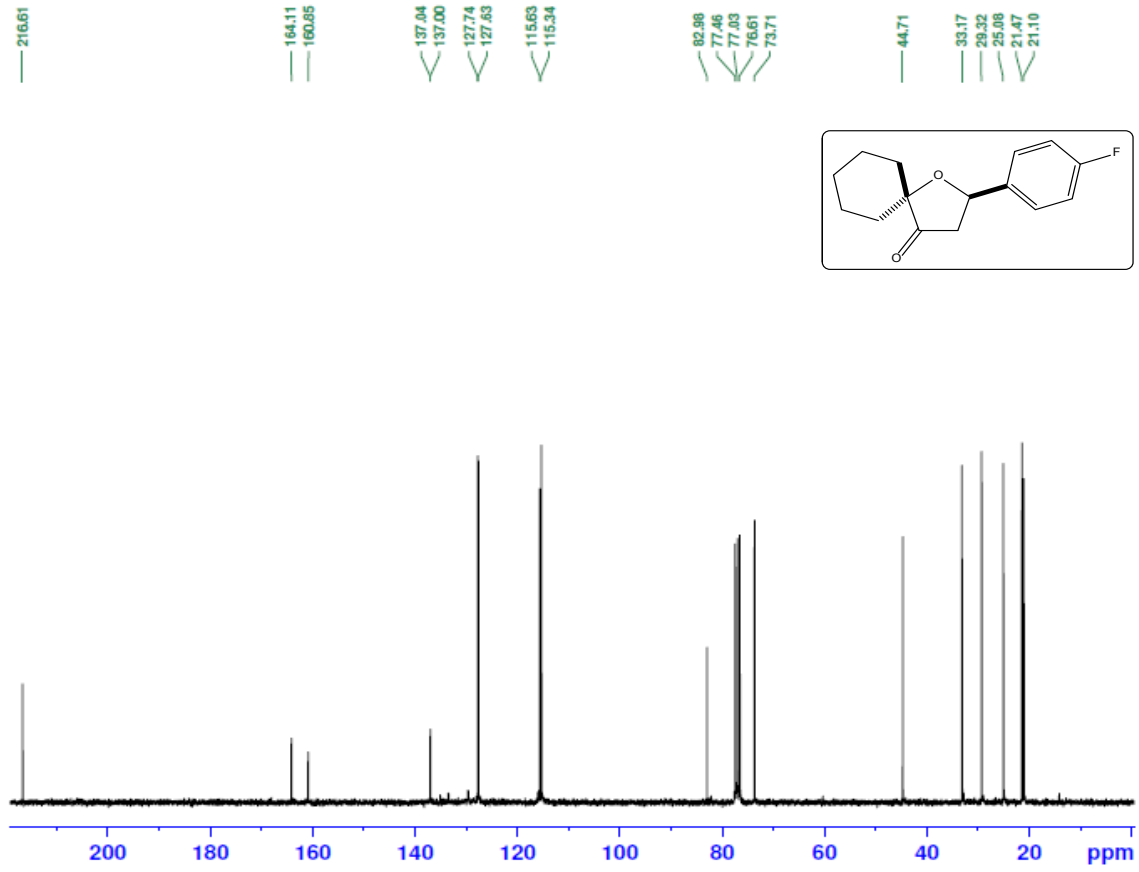
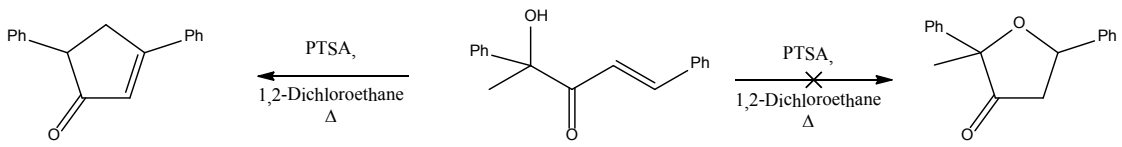


Figure 2.2.3.3 Proton Decoupled ^{13}C NMR Spectrum of Furanone **358** in $CDCl_3$

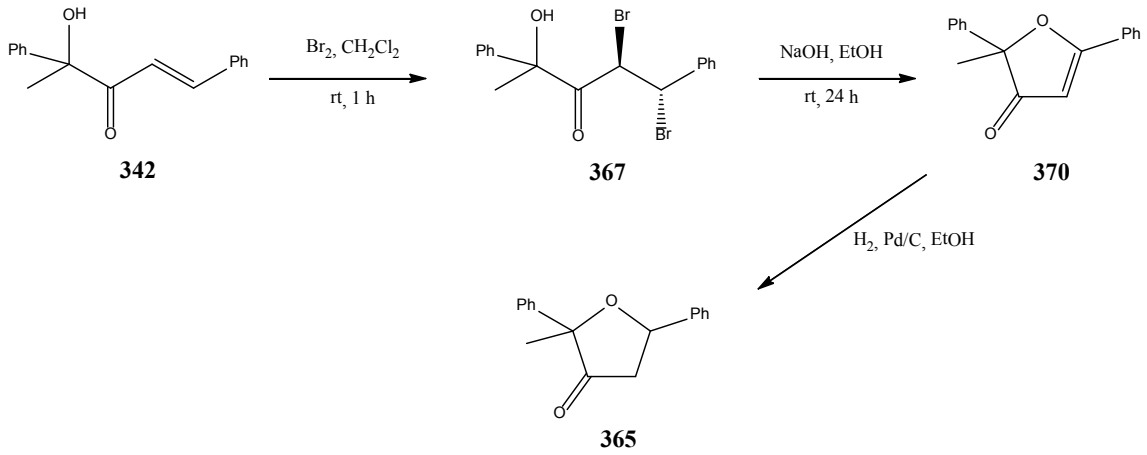
While attempting to synthesise an unsymmetrical 4,5-dihydrofuranone containing *geminal* phenyl and methyl groups at the two-position of the heterocyclic ring, we discovered that the 'traditional' method usually employed gave rise to the exclusive formation of a cyclopentenone type product (Scheme 2.2.3.3). This will be discussed in more detail in Section 2.7).



419 **342** **365**

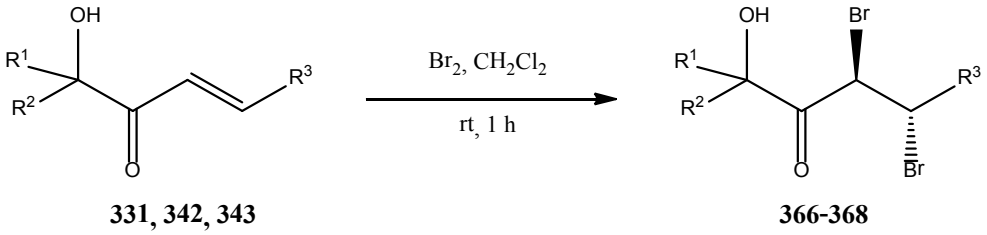
Scheme 2.2.3.3

This required reassessment of the synthetic route and we decided to follow the chemistry in Scheme 2.2.3.4 as a route to compound **365**.



Scheme 2.2.3.4

To achieve a target unsaturated 3(*2H*)-furanone, it was necessary to convert a number of the previously synthesised α-hydroxyenones into *anti*-dibromides using molecular bromine in dichloromethane (Scheme 2.2.3.5).



Scheme 2.2.3.5

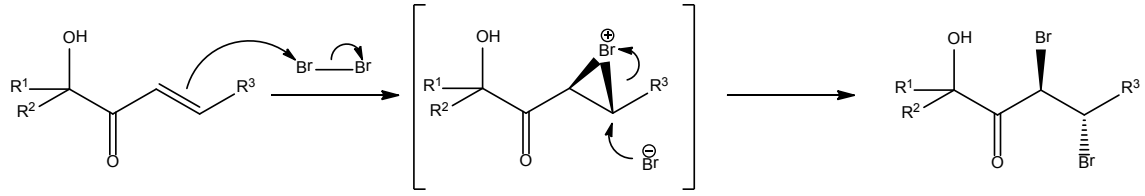
The reaction mixtures were stirred at room temperature for one hour before evaporation of the solvent yielded the desired dibromides in excellent yields (Table 2.2.3.3) and sufficiently pure to be directly cyclised to the 3(*2H*)-furanone without further purification. The dibromides were characterised by the presence of the carbonyl absorption at *ca.* 1720 cm^{-1}, an increase relative to that of the parent enone arising from loss of conjugation in the resulting dibromides.

Dibromide	R^1	R^2	R^3	$\nu_{C=O}$ (cm^{-1})	Yield (%)
366	Me	Me	4-FC_6H_4	1721	79
367	Ph	Me	C_6H_5	1723	82
368	Ph	Me	4-FC_6H_4	1723	93

Table 2.2.3.3 IR Carbonyl Absorption Frequencies and Yields for Dibromides for **366-368**

These dibromides were also readily identified from their ^{1}H NMR spectra. In the case of the geminal dimethyl derivative, **366**, the two methyl groups are no longer magnetically equivalent so resonate as a pair of three hydrogen singlets. Another characteristic trait of these compounds is a pair of doublets in the 5.30-5.70 ppm range, with coupling constants of approximately 12 Hz. This is consistent with the *anti*-relationship expected from the addition of bromine to an alkene species. As the dibromide containing the Ph/Me substituted quaternary carbon (also containing the hydroxyl group) is a chiral centre, the addition of bromine leads to the formation of diastereoisomers. Evidence of these can be clearly seen both in the ^{1}H and ^{13}C NMR spectra. There is another pair of the aforementioned doublets for the protons of the minor diastereomer, centred at *ca.* 5.30 and 5.50, with both doublets giving the expected coupling constant of ca. 12 Hz. The hydroxyl and methyl protons of **367** and **368** also exhibit different chemical shifts for the respective diastereomers. For bromination to compounds **367** and **368**, both reactions yield a 71:29 mixture of diastereomers.

The mechanism for addition of bromine to an alkene species most likely proceeds through a bromonium ion intermediate, thus giving rise to the *anti*-stereochemistry of the dibromides as shown in Scheme 2.2.3.6.



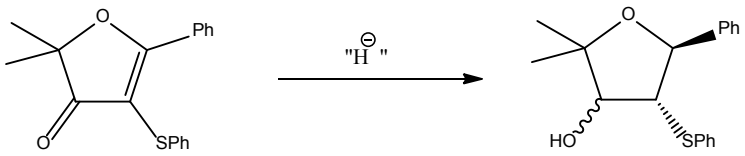
Scheme 2.2.3.6

To complete the synthesis of a number of 3(*2H*)-furanones, the next step in the synthetic pathway was base catalysed cyclisation of the *anti*-dibromides to the 3(*2H*)-furanone. Thus, compounds **366**, **367** and **368** were stirred in an ethanolic solution with two equivalents of sodium hydroxide for 24 h. Reaction completion was indicated by IR spectroscopy and the crude product purified on silica gel to yield the desired 3(*2H*)-furanone in good yield. These compounds are instantly recognisable from their IR and ^{1}H NMR spectra. The carbonyl stretch of the *anti*-dibromide at *ca*. 1720 cm^{-1} is replaced by the analogous stretch of the 3(*2H*)-furanone at approximately 1690 cm^{-1}, also observed upon cyclisation is obviously the complete disappearance of the hydroxyl group stretching frequency. ^{1}H NMR spectra show the appearance of a characteristic 1H singlet centred around 5.90 ppm for the proton attached to C(4) of the furanone ring. Also, for **369**, the resonance of the geminal methyl group protons that had been magnetically inequivalent in the dibromide, giving rise to two 3H singlets has been replaced by a 6H singlet at 1.49 ppm.

Compound	R^1	R^2	R^3	Yield (%)	$\nu_{C=O}$ (cm^{-1})	$\delta_{C(4)H}$ (ppm)
369	Me	Me	4-FC_6H_4	87	1694	5.92
370	Ph	Me	C_6H_5	74	1695	6.00
371	Ph	Me	4-FC_6H_4	69	1693	5.88

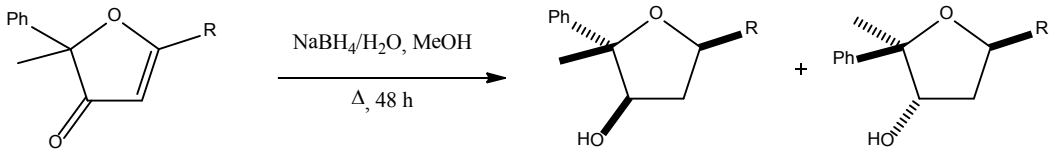
Table 2.2.3.4 Yield, IR Carbonyl Absorption Frequency and C(4) ^{1}H NMR Data for **369-371**

The concluding part of this section of work was completion of the synthesis of **365**. It was envisaged that hydrogenation of **370** with 10% Pd/C in ethanol under pressure would facilitate this transformation. However, this method proved unsuccessful and starting material was recovered. Collins[185] reduced 4-benzenethio-3(*2H*)-furanones (Scheme 2.2.3.7) with various hydride reducing agents to the corresponding 1,5-dihydro-3-hydroxytetrahydrofurans.



Scheme 2.2.3.7

This approach would clearly lend an extra step to the synthesis of **365**, however it is reasonably easy in our view to oxidise the resulting 3-hydroxytetrahydrofuran to the 4,5-dihydro-3(*2H*)-furanone in good yield. Attempted reduction of **370** and **371** was carried out by dropwise addition of a solution of sodium borohydride in water to a methanolic solution of **370** and **371** respectively at 0 °C. Regular TLC analysis of the reaction mixture showed absence of any desired product, the mixture was warmed to room temperature and analysed periodically in a similar fashion, with the same result. Synthesis of **372** and **373** was eventually attained after 48 h reflux (Scheme 2.2.3.8). Chromatographic purification gave the desired 3-hydroxytetrahydrofurans **372** and **373** as yellow oils which were isolated as a mixture of diastereomers.



R = C_6H_5 = **370**
R = 4-FC_6H_4 = **371**

R = C_6H_5 = **372a**
R = 4-FC_6H_4 = **373a**

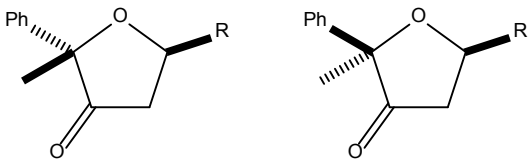
R = C_6H_5 = **372b**
R = 4-FC_6H_4 = **373b**

Scheme 2.2.3.8

Compound	R	Yield (%)	d.r.
372	C_6H_5	82	85:15
373	4-FC_6H_4	84	81:19

Table 2.2.3.5 Yield and Diastereomeric Ratio of **372** and **373**

To complete the syntheses of **365** and **374**, it was necessary to oxidise the alcohols **372** and **373** respectively, as a diastereomeric mixture, to the desired 4,5-dihydro-3(*2H*)-furanone. The reagent of choice was chromic acid which had been successful in oxidising similar compounds previously.[178] Solutions of **372** and **373** in ether were added to aqueous chromic acid at 0 °C and stirred for 30 min before warming to room temperature and continuing stirring for 90 min after which TLC analysis indicated reaction completion. Chromatographic purification on silica gel allowed for the isolation of each diastereomer of furanones **365** and **374** as light gold-coloured oils. The relative stereochemistry of the diastereomers was assigned with the aid of ^{1}H NOESY NMR analysis of **374a** and **374b.** In the case of **374a** there is a clear correlation of the methyl group protons to the protons attached to the *p*-fluorophenyl ring, with an absence of any correlation from the methyl to the C(5) proton resonance. Conversely, the NOESY spectrum of **374b**, showed a correlation between its methyl group and the C(5) proton with no correlation observed to the protons of the *p*-fluorophenyl system. These furanones were not forward processed to the alcohols for the lipase mediated kinetic resolution reactions, as the overall purpose of this synthetic pathway was to achieve a synthetic route to the furanone and to identify the relative stereochemical configuration of the compounds. However, in light of the work described in Section 2.5, the unsymmetrical nature of the substitution at the 2-position of the furanone ring would provide an interesting substrate for biocatalytic reactions of the associated 3-hydroxytetrahydrofurans.



a **b**

Compound	R	Yield (%)	δ_{HA} -δ_{HB} (ppm)*	δ_{HX} (ppm)*
365a	Ph	57	2.59 – 2.85	5.20
365b	Ph	16	2.67 – 2.89	5.38
374a	4-FC_6H_4	59	2.55 – 2.85	5.17
374b	4-FC_6H_4	19	2.62 – 2.88	5.35

* ^{1}H NMR spectra in $CDCl_3$. Refer to Figure 2.2.3.1 for designation of HA, HB and HX

Table 2.2.3.6 Yield and 1H NMR Data for **365a/b and 374a/b**

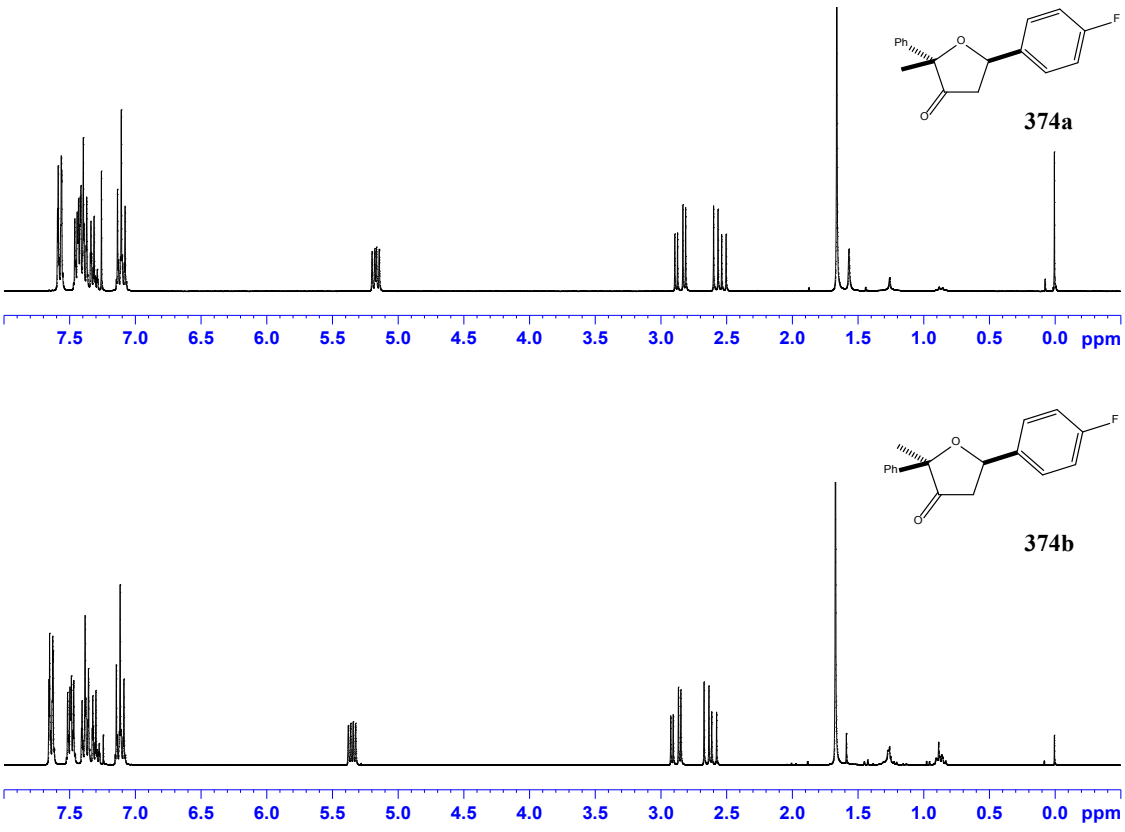


Figure 2.2.3.4 ^{1}H NMR Spectra of **374a** and **374b** in $CDCl_3$

2.3 Synthesis of Racemic 3-Hydroxytetrahydrofurans

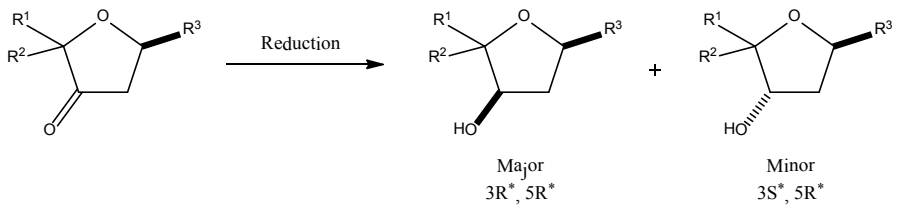
Determination of the enantiomeric composition of the chiral alcohols isolated from enzyme-mediated kinetic resolutions was carried out either by chiral HPLC analysis or chiral shift NMR studies. Both techniques required development of a set of analytical conditions for the racemate alcohols, which when applied to the enantioenriched/enantiopure material would allow for determination of their enantiomeric composition.

Stereoselective hydride reductions of unsymmetrically substituted ketones to their corresponding alcohols is an area of major interest.[187-190] This reaction, in theory, can give rise to a mixture of stereoisomers of the alcohol based on the face of the carbonyl group from which the hydride ion is delivered. Reagents such as L-Selectride® (lithium-tri-*sec*-butyl-borohydride),[191] containing bulky alkyl groups have been widely used for the diastereoselective reduction of ketones, and in our case cyclic ketones. For less bulky reagents, *e.g.* sodium borohydride, the observed diastereoselectivities are lower (Scheme 2.3.1 and Table 2.3.1). The stereoselectivity arises from interactions of the bulky groups on the central boron atom with substituent groups on the ketone substrate such that the hydride ion is delivered to the least hindered face of the carbonyl group giving rise to one diastereomer over the other.

Reductions of the *geminal* dimethyl and spiro-fused cyclohexyl derived 4,5-dihydrofuranones were carried out using the aforementioned reducing agents, L-Selectride® and sodium borohydride. The borohydride-mediated reductions were carried out in a methanolic solution of the substrate furanone with an aqueous solution of sodium borohydride, and the alcohols were isolated as a mixture of diastereomers following aqueous work-up of the reaction. In most cases where a mixture of diastereomers was obtained as a solid, it was possible to separate the major diastereomer from the mixture by recrystallisation from a hexane:ethyl acetate mixture. Those mixtures that were oils were found to be chromatographically inseparable.

The reductions involving L-Selectride® were carried out overnight under anhydrous conditions by dropwise addition of the reagent to a solution of the substrate furanone in dry THF at -78 °C. Upon completion, the reaction was quenched and extracted with ethyl acetate. Hayes[178] encountered purification issues with this protocol, however, due to the presence of residual boron reagent residues whose removal from the alcohol required repeated chromatography. This problem was solved by washing the

crude reaction mixture with 10% aqueous hydrogen peroxide solution, resulting in oxidation of the boron containing by-products to water soluble boronic acids. The isolation of the crude alcohols was completed by washing of their ethyl acetate extracts with 10% aqueous hydrogen peroxide solution. Flash chromatographic purification then yielded the alcohols in moderate to good yields.



Scheme 2.3.1

Compound	R^1	R^2	R^3	Reagent	Yield (%)	d.r.
375	Me	Me	C_6H_5	L-Selectride®	66	>98:2
375	Me	Me	C_6H_5	$NaBH_4$	87	86:14
376	Me	Me	4-FC_6H_4	L-Selectride®	71	>98:2
377	Me	Me	3,4-$(MeO)_2C_6H_4$	L-Selectride®	70	85:15*
377	Me	Me	3,4-$(MeO)_2C_6H_4$	$NaBH_4$	61	80:20
378	Me	Me	3-$NO_2C_6H_4$	$NaBH_4$	77	>98:2*
379	Me	Me	4-$NO_2C_6H_4$	$NaBH_4$	77	80:20
380	Me	Me	4-MeC_6H_4	L-Selectride®	63	>98:2
381	Me	Me	t-Bu	$NaBH_4$	71	>98:2
382	$(CH_2)_5$		C_6H_5	L-Selectride®	71	>98:2
383	$(CH_2)_5$		4-FC_6H_4	L-Selectride®	60	>98:2
384	$(CH_2)_5$		3,4-$(MeO)_2C_6H_4$	$NaBH_4$	64	90:10*
385	$(CH_2)_5$		3-$NO_2C_6H_4$	$NaBH_4$	77	>98:2*
386	$(CH_2)_5$		4-$NO_2C_6H_4$	$NaBH_4$	71	>98:2*
387	$(CH_2)_5$		4-MeC_6H_4	L-Selectride®	55	>98:2
388	$(CH_2)_5$		4-$NH_2C_6H_4$	$NaBH_4$	78	78:22
389	$(CH_2)_5$		$C_6H_4NHCOCH_3$^	-	60	33:67#
390	$(CH_2)_5$		C_6H_4NH*Cbz*~	-	76	30:70#
391	$(CH_2)_5$		t-Bu	$NaBH_4$	71	>98:2

See Scheme 2.3.1 for designation of substituents
* d.r. after recrystallisation (d.r. before recrystallisation was approx. 80:20)
# Major diastereomer in this case is 3S*,5R*
^ From hydrolysis of **392**
~ From N-protection of **388**

Table 2.3.1 Yield and Diastereomeric Ratios for Compounds **375 - 391**

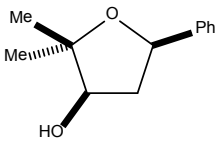
The issue of the stereochemical assignment of the two chiral centres has been addressed by our research group.[192] The relative stereochemistry of the alcohol product was assigned as (3R*, 5R*) for a stereoisomer of **375** based on a single crystal X-ray structure of its *p*-nitrobenzoate derivative (see Footnote) which facilitated a correlation with the proton and ^{13}C NMR spectra of the major and minor diastereomers. Further support of the stereochemical assignments of the major isomer is based on proton NMR NOE difference and GOESY experiments on the acetate ester of **375**[178] (see Section 2.4

of this thesis for NMR data of 3-acetoxytetrahydrofurans) For a reduction process, the stereochemical outcome observed for the furanones with L-Selectride® is not an overly surprising result as phenyl group directs hydride ion approach from the less sterically hindered face of the carbonyl group, resulting in preferential formation of the alcohol containing *cis*-3-hydroxyl and 5-aryl groups.

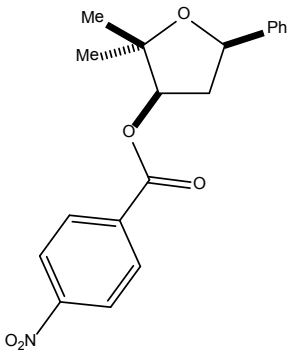
As can be seen from the results in Table 2.3.1, there were a number of reactions that proved problematic in terms of producing diastereomerically pure alcohols for use as substrates in the biocatalytic lipase reactions. In general, sodium borohydride gave a mixture of diastereomeric alcohols which could not be easily separated by chromatography or fractional crystallisation, whereas reductions with L-Selectride® were highly selective. A diastereomeric ratio of >98:2, while not intrinsically vital, makes the resolution process easier in terms predicting the outcome, not to mention that HPLC method development becomes much more facile when there are only two peaks to elute as opposed to the four expected when the substrate is a mixture of diastereomers.

Footnote:

For the alcohol (i) as its ester (ii):



(i)



(ii)

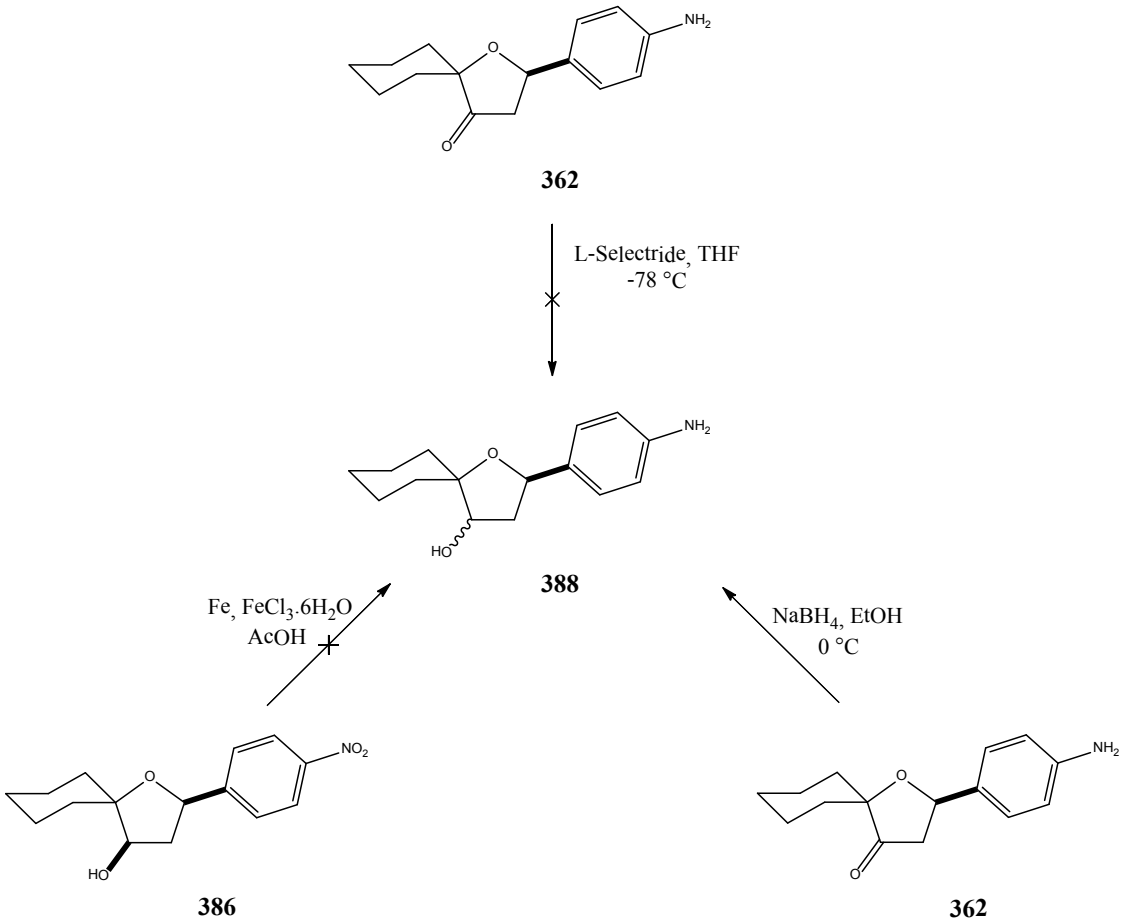
In most cases where L-Selectride® was employed as the reducing agent, the reaction yielded the desired (3R*, 5R*) alcohols in a diastereomeric ratio of >98:2. The only exceptions to this were **377** and **384** where the C(5) aryl substituent contained a 3,4-dimethoxyphenyl ring and could not be achieved in the desired diastereomeric ratio of >98:2. As the reductions of **377** and **384** using L-Selectride® did not provide the required selectivity, these were reduced with sodium borohydride. It was decided to attempt to recrystallise the product as there had been some success in isolating the desired diastereomer previously. The recrystallisation procedure succeeded in reducing the amount of the minor diastereomer; however there was too much product loss to make recrystallisation viable so we carried through the substrate as a diastereomeric mixture to ensure that there was sufficient substrate in order to perform the lipase-mediated kinetic resolution reactions. This would also give the opportunity to explore the reactivity of the minor diastereomer to the library of lipase enzymes at our disposal.

The alcohols bearing nitrophenyl substitution were all reduced with sodium borohydride. We envisaged potential issues in carrying out the reduction with L-Selectride® and an exploratory experiment verified these concerns as there were no recognisable products in the reaction mixture. Reduction of the ketone **352**, **353**, **360** and **361** was effected with sodium borohydride to give a mixture of diastereomers. The alcohols **378**, **385** and **386** were isolated as solids in a crude state, with recrystallisation enabling the isolation of each respective compound as a single diastereomer. Compound **379** was isolated as an oil and despite attempts to crystallise the compound, it was found necessary to use the compound as a mixture of diastereomers for the ensuing kinetic resolutions.

The ketones **356** and **363** were unique asm reduction with L-Selectride® and sodium borohydride yielded the respective diastereomerically pure alcohols. This should not be too much of a surprise given that the *t*-butyl substituent is extremely bulky and hydride ion approach would be directed exclusively to yield the major *cis*-isomer. Reduction with sodium borohydride is a much quicker reaction, with a greater yield, and in some cases the product did not require further purification from the crude compound, so this was employed as the method of choice for the synthesis of the alcohols **381** and **391**.

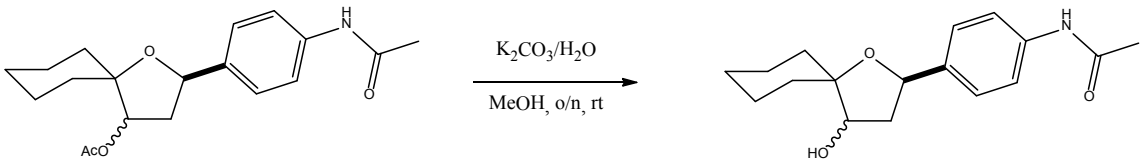
In the synthesis of an alcohol containing a *p*-aminophenyl group **388**, a number of issues were encountered. We attempted to reduce the parent furanone **362** with L-Selectride®, but found that only starting material was returned when the crude product

was isolated. We then attempted to access **388** by reduction of the *p*-nitrophenyl alcohol **386** using the iron/iron trichloride hexahydrate/acetic acid protocol employed previously but this method led to decomposition of the starting material. Sodium borohydride as the reducing agent gave **388** as a brown semi-solid with a 78:22 (major:minor) mixture of diastereomers after chromatographic purification of the product (Scheme 2.3.2).



Scheme 2.3.2

We found that alcohols **389** and **390** could not be accessed by reduction of the ketone precursors as circumstances dictated otherwise. In the case of **389**, esterification of **388** (to be discussed in further detail in Section 2.4) there was *N*-acetylation along with the desired esterification of the hydroxyl group. The acetamido alcohol was produced by addition of an aqueous solution of potassium carbonate to a stirring solution of **392** in methanol (Scheme 2.3.3). Overnight reaction and subsequent acidic work-up yielded **389** as a chromatographically inseparable mixture of diastereomers.

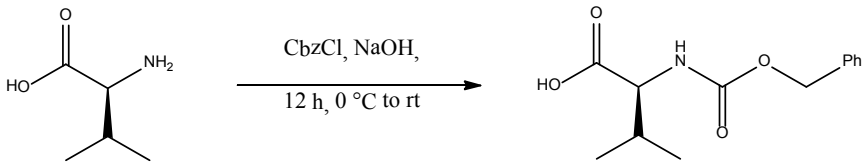


d.r. 38:62 d.r. 33:67

392 **389**

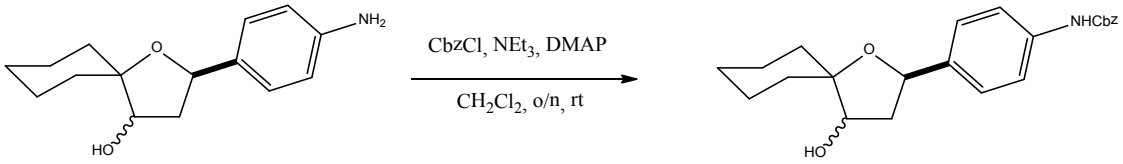
Scheme 2.3.3

As the synthesis of **390** could not be achieved by the customary method, it was necessary to employ protecting group chemistry. The procedure used by O'Callaghan[193] (Scheme 2.3.4) was modified slightly to afford the desired *N*-protected hydroxytetrahydrofuran.



Scheme 2.3.4

This was achieved by adding benzylchloroformate to a stirring solution of **388**, triethylamine and DMAP in dichloromethane. Stirring was continued overnight where TLC analysis indicated reaction completion. Subsequent work-up and purification yielded **390** as a chromatographically inseparable mixture of diastereomers (Scheme 2.3.5). It was possible to confirm the formation of **390** by NMR analysis. The ^{1}H NMR spectrum showed the disappearance of the broad two-hydrogen singlet at 3.63 ppm in **388**, and the appearance of a one-hydrogen broad singlet located much further downfield at 6.80 ppm in **390**. Also the additional signals of the methylene and aromatic protons of the carboxybenzyl group provided further evidence of the formation of **390**.



388 **390**

Scheme 2.3.5

The ^{1}H NMR spectra of the major diastereomers of the alcohols (*i.e.* 3*R**, 5*R**) exhibit splitting patterns characteristic of the range of alcohols synthesised in this work. The methylene protons attached to C(4) resonate as individual sets of doublet of doublet of doublets (ddd) centred *ca.* 1.90 and 2.70 ppm respectively for each proton H_A and H_B. The difference in chemical shift of the individual signals indicates that these protons exist in differing magnetic environments as H_B is in closer proximity to the hydroxyl group as well as the aryl ring system, resulting in a downfield shift for this proton resonance. The splitting pattern arises from geminal coupling and vicinal coupling with the protons attached to C(3) and C(5). No such effects were seen for the methylene protons of the minor diastereomer (*i.e.* 3S*, 5R*). These particular signals resonated as a multiplet in the 2.00-2.20 ppm range.

The C(3) and C(5) protons signals of the major diastereomer of the alcohols appeared, in most cases, as triplets at approximately 4.00 and 5.00 ppm respectively. These are more accurately assigned as overlapping doublet of doublets, in both cases, arising from splitting by the inequivalent C(4) protons. However in the minor diastereomer, the C(5) proton signal can clearly be seen as a doublet of doublets at *ca.* 5.10 ppm, with the C(3) proton having the same chemical shift as that of the major diastereomer. Although we did not isolate the minor diastereomer in a pure state, it was possible in certain cases to deduce the key NMR spectroscopic data from samples of the isomer mixtures produced in the sodium borohydride reductions of the ketones.

A typical ^{1}H NMR spectrum of a 3*R**, 5*R** (major) diastereomer is shown in Figure 2.3.1. The respective coupling patterns discussed above can be clearly seen, along with the corresponding patterns arising from the *m*-nitro substitution of the aromatic ring **393**.

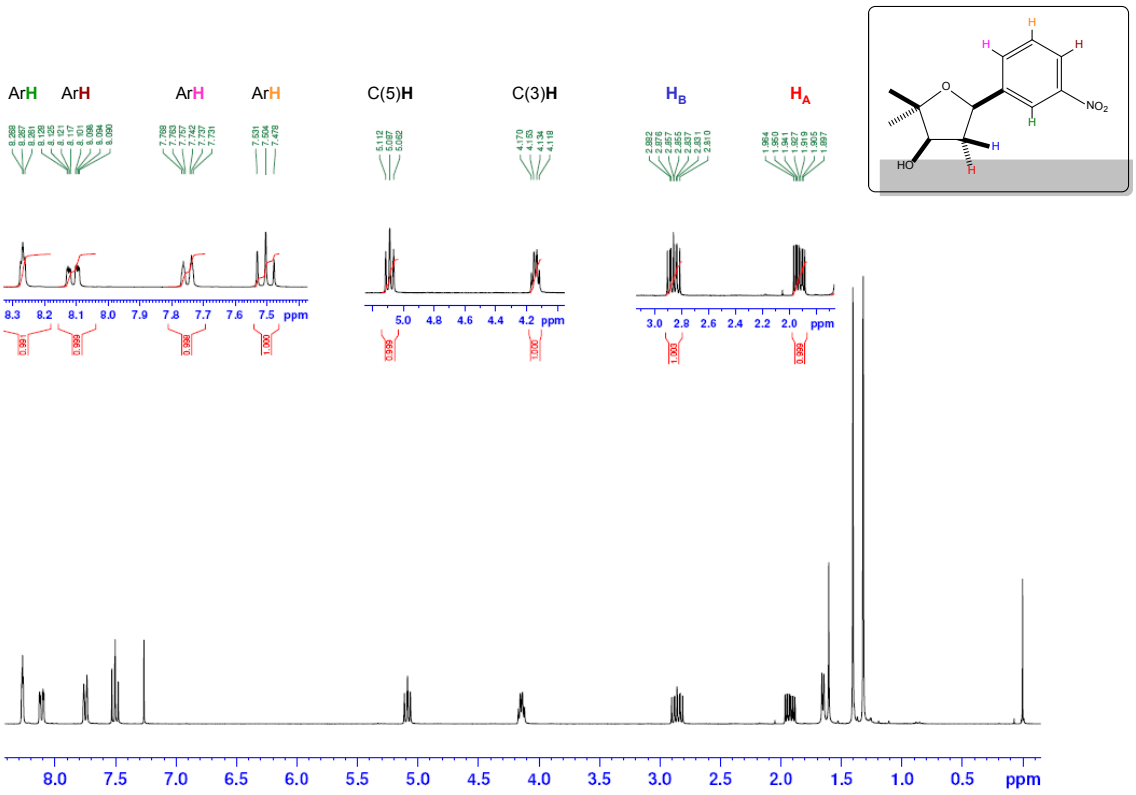


Figure 2.3.1 ^{1}H NMR spectrum of **378** in $CDCl_3$

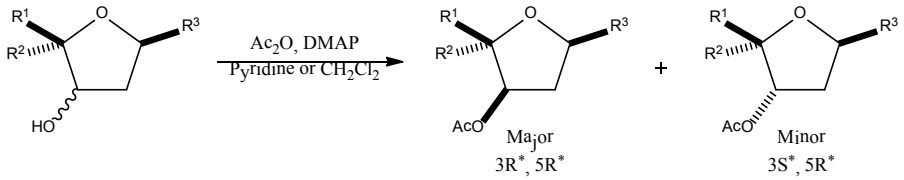
The ^{13}C NMR spectra of these compounds, in common with their ^{1}H counterparts, followed the same signal pattern. They were assigned with the aid of DEPT spectra that allowed the assignment of the various types of carbon signal present, especially those in the range of 70-80 ppm attributed to **C**(3) and **C**(5) of the tetrahydrofuran ring. Their definitive respective assignments were made possible by the use of HSQC spectra, whereby a 2-dimensional correlation was made between the proton and carbon spectra of **375**. This showed that the resonance attributed to **C**(3) occurred further downfield, with the resonances for **C**(2) and **C**(4) appearing *ca.* 80 and 40 ppm respectively. Table 2.3.2 shows an example of the assignment for compound **380**.

δ_C (ppm)	Assignment
21.13	Ar-**C**H_3
22.66	**C**H_3
25.84	**C**H_3
43.37	**C**(4)H_2
76.63	**C**(5)H
78.53	**C**(3)H
83.05	**C**(2)
125.83	Ar**C**(3)H
129.25	Ar**C**(2)H
136.97	Ar**C**-CH_3
140.17	Ar**C**

Table 2.3.2 ^{13}C NMR Assignment of Compound **380**

2.4 Synthesis of Racemic 3-Acetoxytetrahydrofurans

Esterification of the 3-hydroxytetrahydrofurans was carried out using acetic anhydride in pyridine originally, and later dichloromethane with catalytic amounts of DMAP. It was necessary to generate samples of the acyl esters in racemic form as reference materials for analysis of non-racemic esters generated later in this study (Scheme 2.4.1).



Scheme 2.4.1

For the most part, the racemic hydroxy compounds esterified were diastereomerically pure. The ester products were isolated as colourless oils or solids in good yields and were easily identifiable, having the characteristic carbonyl IR absorption at *ca.* 1740 cm^{-1} and an acetyl methyl singlet at *ca.* 2 ppm in the ^{1}H NMR spectrum. As would be expected, there is also a downfield shift in the **C**(3)H resonance in the ^{1}H NMR spectrum and the **C**(3) signal in the ^{13}C NMR spectra relative to the parent hydroxy compounds.

Compound	R^1	R^2	R^3	Yield (%)	d.r.	$\nu_{C=O}$ (cm^{-1})	δ_H CH_3CO (ppm*)
392	$(CH_2)_5$		$C_6H_4NHCOCH_3$ ^	80	38:62^	1737	2.05 minor^ 2.13 major
393	$(CH_2)_5$		C_6H_4NHCbz	80	30:70^	1736	1.95-2.20 #
394	Me	Me	C_6H_5	67	>98:2	1738	2.05
395	Me	Me	4-FC_6H_4	85	>98:2	1740	2.06
396	Me	Me	3,4-$(MeO)_2C_6H_3$	84	74:26	1736	2.08 major 2.14 minor
397	Me	Me	3-$NO_2C_6H_4$	77	>98:2	1738	2.08
398	Me	Me	4-$NO_2C_6H_4$	85	82:18	1740	2.03 major 2.15 minor
399	Me	Me	4-MeC_6H_4	87	>98:2	1736	2.06
400	Me	Me	t-Bu	63	>98:2	1739	2.06
401	$(CH_2)_5$		Ph	89	>98:2	1739	2.03
402	$(CH_2)_5$		4-FC_6H_4	83	>98:2	1734	2.04
403	$(CH_2)_5$		3,4-$(MeO)_2C_6H_4$	80	>98:2	1737	2.06
404	$(CH_2)_5$		3-$NO_2C_6H_4$	83	>98:2	1738	2.05
405	$(CH_2)_5$		4-$NO_2C_6H_4$	82	>98:2	1738	1.99
406	$(CH_2)_5$		4-MeC_6H_4	87	>98:2	1737	2.04
407	$(CH_2)_5$		4-$NH_2C_6H_4$	78	30:70^	1739	1.95-2.20 #
408	$(CH_2)_5$		t-Bu	80	>98:2	1739	2.04

* ^{1}H NMR Spectra in $CDCl_3$
# Appears as a multiplet with C(4)$\mathbf{H}_2$ of the major diasteroemer
^ Major diastereomer in this case is 3S*,5R*
Refer to Scheme 2.4.1 for location of substituents

Table 2.4.1 Yield, d.r., IR and ^{1}H NMR Data for Acetoxytetrahydrofurans **392 - 408**

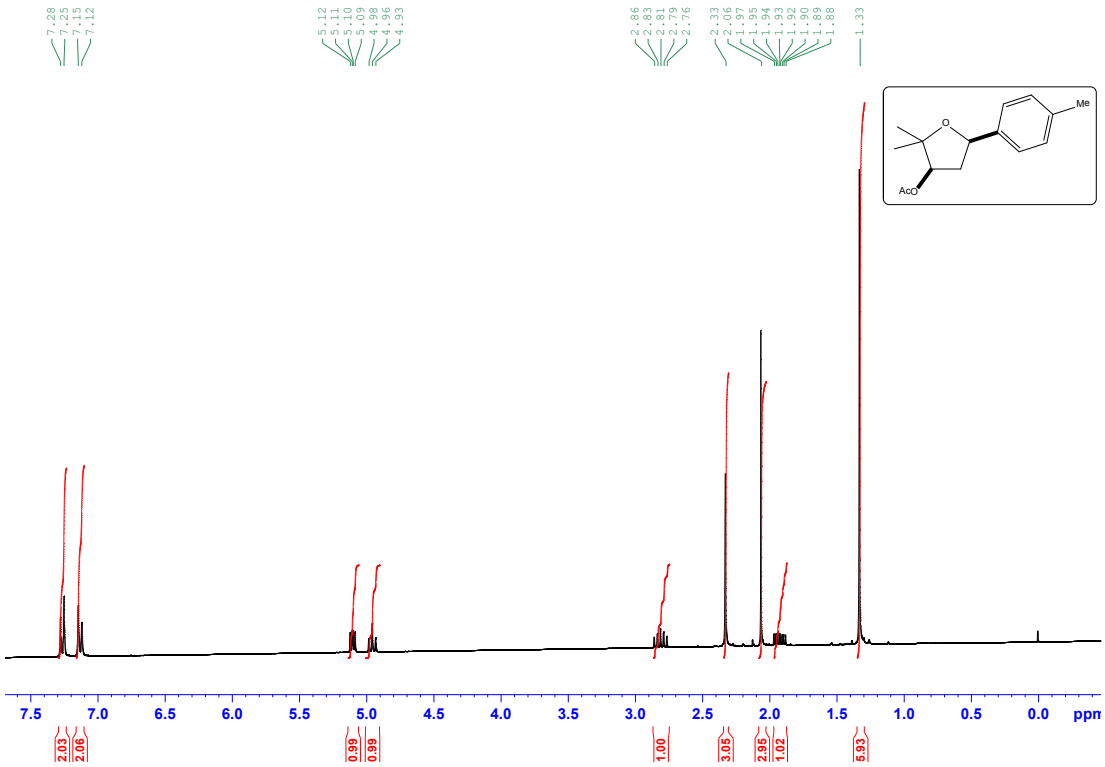


Figure 2.4.1 ^{1}H NMR Spectrum of Compound **399** in $CDCl_3$

Comparison of the proton NMR spectra of the 3-acetoxytetrahydrofurans with their parent 3-hydroxytetrahydrofurans shows a downfield shift of the **C**(3)H from 4.12 ppm to 5.12 ppm attributed to the deshielding effect of the ester carbonyl group. The relative upfield/downfield shift of the **C**(3)H and **C**(5)H signals varies for this series of compounds depending on the substituent at the 5-position, thus the assignments of these signals was made by correlation of the shift and coupling constants with these of the parent 3-hydroxy compound.

The introduction of the acyl moiety causes the ^{1}H NMR signals of the **C**(2) geminal methyl converge to the extent that in a lot of cases they almost overlap and for **399**, the two signals do overlap to show the two methyl groups resonating as a 6H singlet. This is due to the downfield shift of one of the methyl singlets relative to the alcohol precursors. From previous NOE and GOESY NMR analysis[178] we know that the protons of the methyl group *cis*- to the 3-hydroxy moiety resonates upfield relative to the *trans*- methyl group. The fact that we observe a downfield shift for one of the geminal methyl groups is evidence that the same relationship exists for the 4-unsubstituted tetrahydrofurans, as it is logical to suppose that the deshielded methyl group has a *cis* relationship to the acetoxy

group. The ester methyl signal resonates as a singlet at 2.08 ppm while the remainder of the signals are directly comparable for both compounds, *i.e.* the esters and alcohols.

Assignment	δ (ppm)	Signal	J (Hz)
C(2)C**H**$_3$	1.36	s	N/A
C(2)C**H**$_3$	1.39	s	N/A
C(4)**H**	1.92	ddd	13.9, 7.6, 4.4
COC**H**$_3$	2.06	s	N/A
C(4)**H**	2.84	ddd	13.9, 7.6, 6.9
C(5)**H**	4.96	t	7.6
C(3)**H**	5.10	dd	6.9, 4.4
ArC(3)**H**	7.13	d	8.0
ArC(2)**H**	7.27	d	8.0

Table 2.4.2 ^{1}H NMR Assignments for 2,2-Dimethyl-3-acetoxy-5-(4-tolyl)tetrahydrofuran **399**

The spectra of the related alcohols and acetates are extremely similar. Using acetate **399** and alcohol **380** as examples, the acyl methyl carbon of **399** resonates at 20.0 ppm while its carbonyl carbon resonates at 169.4 ppm. The C(3) signal of **399** is shifted downfield from 75.8, in **380**, to 78.3 ppm in **399** by the addition of the acyl moiety. The assignment of the C(3) and C(5) signals was made using C-H correlation spectra. Figure 2.4.2 shows a typical ^{13}C NMR spectrum of these compounds, in this case compound **399**. The signals were assigned based on the structural assignment carried out previuosly[178] and as such it was possible to assign all the carbon resonances within this compound.

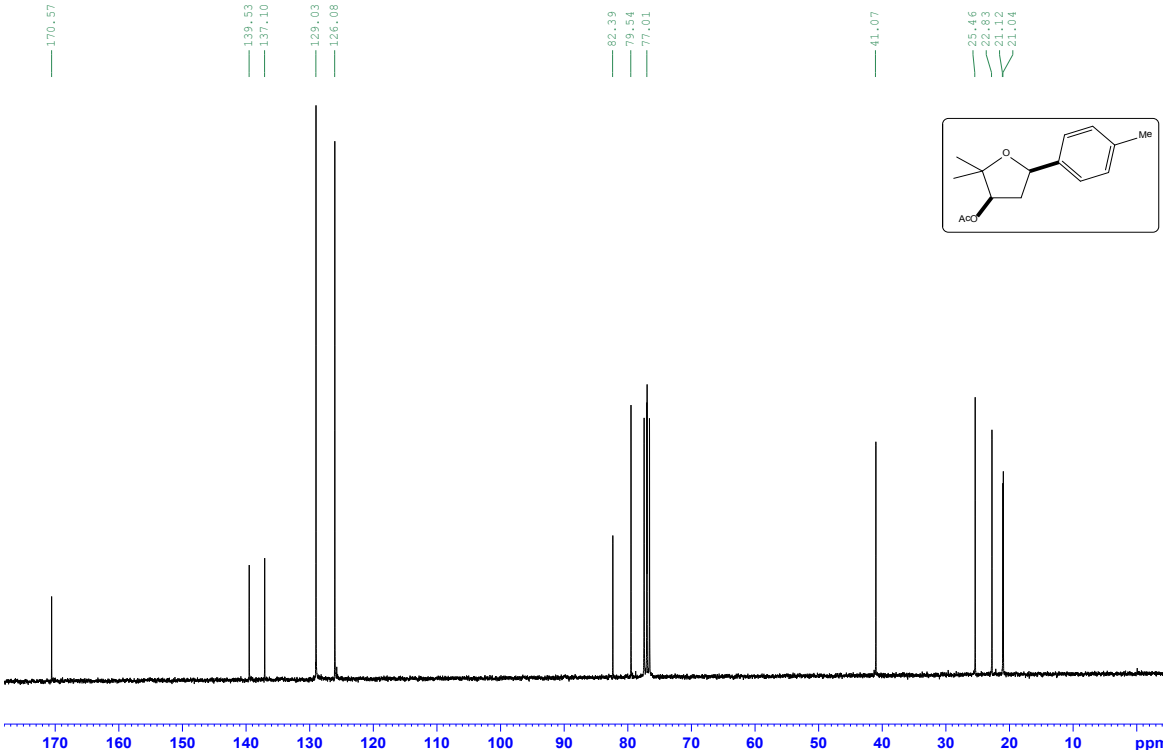


Figure 2.4.2 ^{13}C NMR spectrum of 2,2-Dimethyl-3-acetoxy-5-(4-tolyl)-tetrahydrofuran **399** in $CDCl_3$

Assignment	δ (ppm)	Assignment	δ (ppm)
$CO\mathbf{C}H_3$	21.05	Ar**C**(3)H	126.08
Ar-$\mathbf{C}H_3$	21.12	Ar**C**(2)H	129.25
C(2)$\mathbf{C}H_3$	22.83	Ar**C**-CH_3	137.10
C(2)$\mathbf{C}H_3$	25.47	Ar**C**	139.53
C(4)H_2	41.07	**C**OCH_3	170.58
C(5)H	77.01		
C(3)H	79.54		
C(2)	82.40		

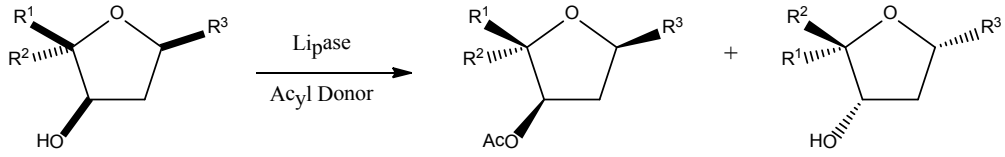
Table 2.4.3 ^{13}C NMR assignments for 2,2-dimethyl-3-acetoxy-5-(4-tolyl)tetrahydrofuran **399**

2.5 Lipase-Mediated Kinetic Resolution of 3-Hydroxytetrahydrofurans

The work described thus far in this thesis outlined the synthesis of racemic furanones from achiral materials and subsequent diastereomerically controlled reduction introducing an additional chiral centre to give racemic alcohols containing 2 or 3 chiral centres, whose relative stereochemistry has been controlled and assigned. This section describes our work in taking this synthesis to the next stereochemical level, that of enantiomeric selectivity in the production of chiral 3-hydroxytetrahydrofurans.

Chirality has always been an important feature of organic synthesis, and the importance of asymmetric synthesis can be understood in light of the very different biological activity of certain enantiomeric pairs, most notably those of Thalidomide.[194] The development of efficient methodology for the preparation of pharmaceutical candidates in enantiomerically pure form is essential in order to ascertain the biological activity of the individual enantiomers and has driven the need for widening of understanding in all areas of asymmetric induction and resolution to the forefront of research in chemistry during this period.

Here we demonstrate the use of biotransformations as a strategy in the asymmetric synthesis of 3-hydroxytetrahydrofurans through the use of hydrolytic enzymes *i.e.* lipase-mediated biotransformations (Scheme 2.5.1). These lipase enzymes catalyse the formation of esters from alcohols and carboxylic acids (including the derivatives of carboxylic acids), and also the reverse reaction (*i.e.* ester hydrolysis)



Racemic Enantiopure (enriched)

Scheme 2.5.1

All lipases consist of between 200-600 amino acid residues, and thus are very large molecules (M_r ~ 20,000-60,000) where the presence of a water/lipid interface dramatically changes the hydrolytic activity of lipases; the activation phenomenon is associated with a conformational change in the enzyme.[195] Reported lipase structures have the Ser-His-Asp/Glu catalytic triads of the active site blocked by a polypeptide flap,

and hence are not exposed to the solvent. However, Grochulski[196] in 1993 reported the first example of an "open" form of lipase with an accessible active site, where the flap was almost perpendicular to the protein surface exposing a large depression that surrounds the active site of the enzyme. The catalytic triad is formed by Ser-209, His-449 and Glu-341 with Ser-209 lying at the bottom of the depression (Figure 2.5.1).

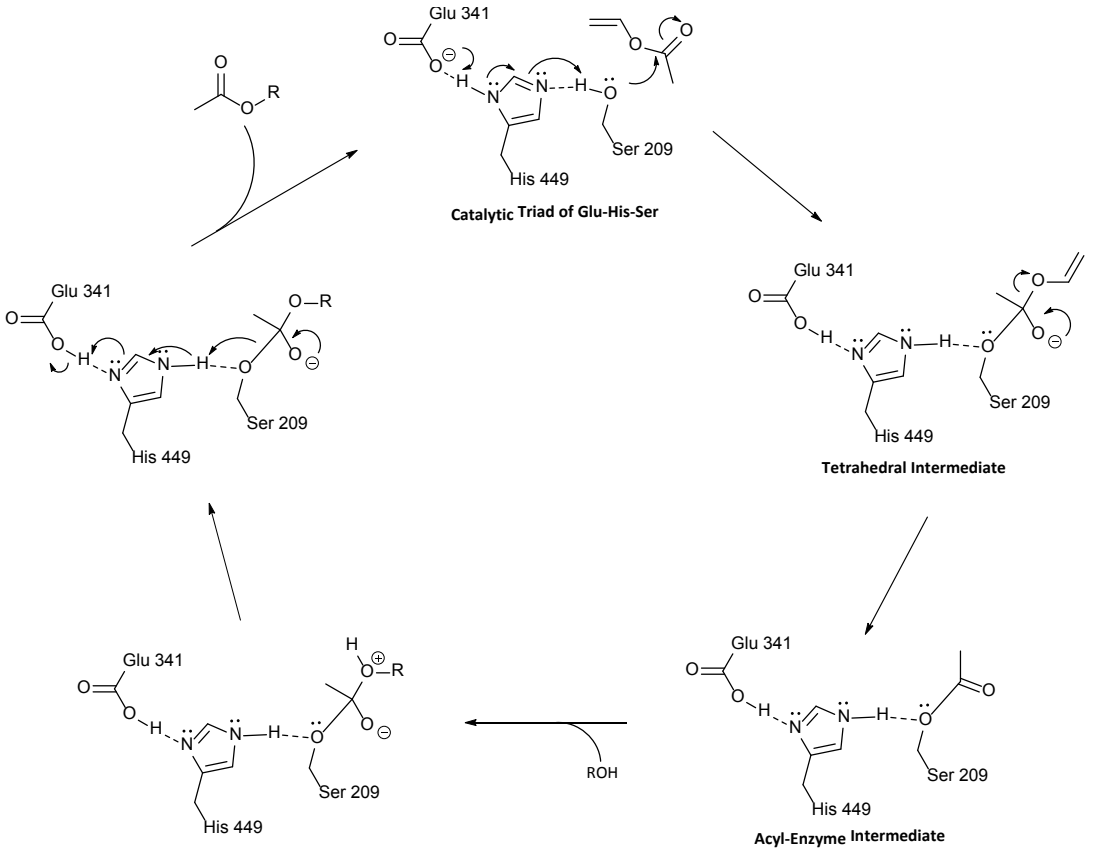


Figure 2.5.1 Mechanism of Lipase-Mediated Kinetic Resolution

Here, we discuss the selective esterification of substituted 3-hydroxytetrahydrofurans to yield enantioenriched 3-acetoxytetrahydrofurans and recovery of the enantioenriched unreacted alcohols under conditions of kinetic resolution.

Kinetic resolution is the process whereby one of the enantiomers of a racemic mixture is more readily transformed into a product than its mirror image. Thus, in order to achieve good selectivity the enantiomers must have sufficiently different rates of conversion to product, the ideal case being that the "faster" reacting enantiomer is transformed quickly and the other is not converted at all (k_R/k_S=infinity). In practice however, most cases of enzymatic resolution does not show this ideal situation, generally

the rate of conversion is markedly different but measurable, therefore the reaction does not come to a complete cessation at 50% conversion but shows a considerable decrease in reaction rate at this point (Figure 2.5.2).[195] In such cases two crucial dependencies are encountered: (i) the velocity of the transformation of each enantiomer varies with the degree of conversion and (ii) the optical purity of both substrates ($e.e._s$) and product ($e.e._p$) becomes a function of the extent of conversion.

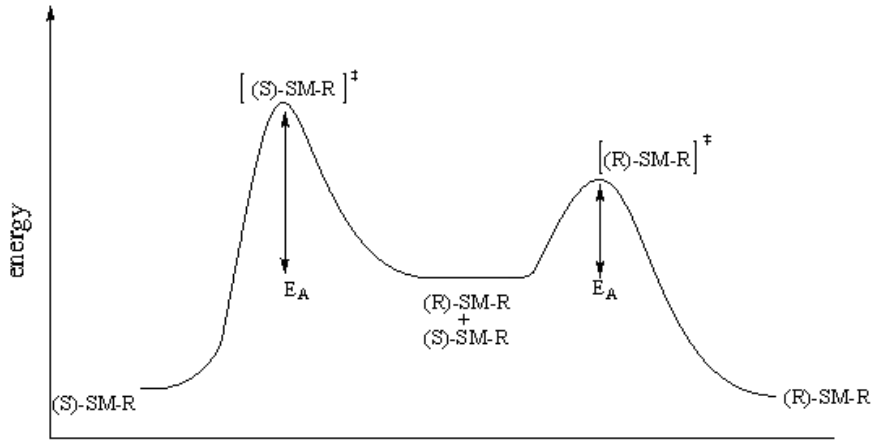


Figure 2.5.2 Energy diagram for Lipase-Mediated Kinetic Resolution

Kazlauskas'[177] rule formulated to predict which enantiomer of a chiral secondary alcohol reacts faster under conditions of kinetic resolution with an acyl transfer agent is based upon the relative size of the substituents at the stereocenter. This rule generalises the observed enantioselectivity of lipases in both hydrolysis reactions and esterifications. The importance of substituent size was confirmed by studies which show that lipases resolve secondary alcohols with two similarly sized substituents poorly, but they resolve the secondary alcohols effectively when the relative size of one of the substituents is increased.[197]

Using this rule, Hayes[178] concluded that 3-hydroxytetrahydrofurans were very useful substrates for lipase-catalysed kinetic resolutions. They possess the correct geometry, having a medium size substituent (*i.e. gem*-dimethyl or spiro-fused cyclohexyl groups of 3-hydroxytetrahydrofurans) and a larger substituent (*i.e.* aryl or *t*-butyl groups of 3-hydroxytetrahydrofurans) tied into a rigid system by the furan ring. The challenge now was to extend the studies previously carried out and to screen a range of lipases against a broader range of substrates. Once the screening process had identified a suitable

biocatalyst, tuning and optimisation of the conditions would provide a synthetically useful route to enantiomerically enriched hydroxytetrahydrofurans while minimising yield losses.

2.5.1 Effect of Enzyme Species

Examples of biocatalytic reactions have become much more prevalent since the initial studies were carried out within our laboratory. As a consequence, the library of available biocatalysts has increased exponentially, a fact that we envisaged taking advantage of in the search for an enzyme that would provide us with a route to compounds with high enantiomeric purity. Collaboration with Almac Sciences provided us with quantities of some enzymes that we could utilise in the screening process to identify biocatalysts that would then prove useful on a large scale. The enzymes used were of natural origin and the products of a genetically engineered process. The initial screening process was quite straight forward; taking *ca.* 20 mg of substrate, 1 equivalent of acyl donor (vinyl acetate), a spatula tip of enzyme in diisopropylether and stirring the mixture at room temperature for 24 h. The enzyme was removed by filtration and the filtrate concentrated under reduced pressure before ^{1}H NMR analysis determined the extent of conversion, if any to the acetate esters. Determination of enantiomeric composition was carried out at a later stage when the more successful enzymes in terms of conversion efficiency had been identified. To begin with, we took a number of aryl substituted substrates; containing an electron withdrawing substituent (**376** and **383**), an electron donating substituent (**380** and **387**), and an unsubstituted aryl system (**375** and **382**). The results of the initial conversion screen are shown below, the species of enzyme is depicted on the x-axis, with the extent of conversion on the y-axis. Table 2.5.1 details the library of enzymes screened in this process.

Lipase Abbreviation	Microbial Source
CCL	*Candida cylindracea*
Alcaligenes spp.	*Alcaligenes species*
Pseudomonas cep.	*Pseudomonas cepacia*
	Peudomonas stutzeri
	Rhizopus niveus
	Mucor javinicus
Penicillum cam.	*Penicillum camemberti*
CAL	*Candida Antarctica*
Pseudomonas fluor.	*Pseudomonas fluorescens*

Table 2.5.1.1 Abbreviations and Full Names of Microbial Sources of Lipase Species Employed in Biocatalyst Screening

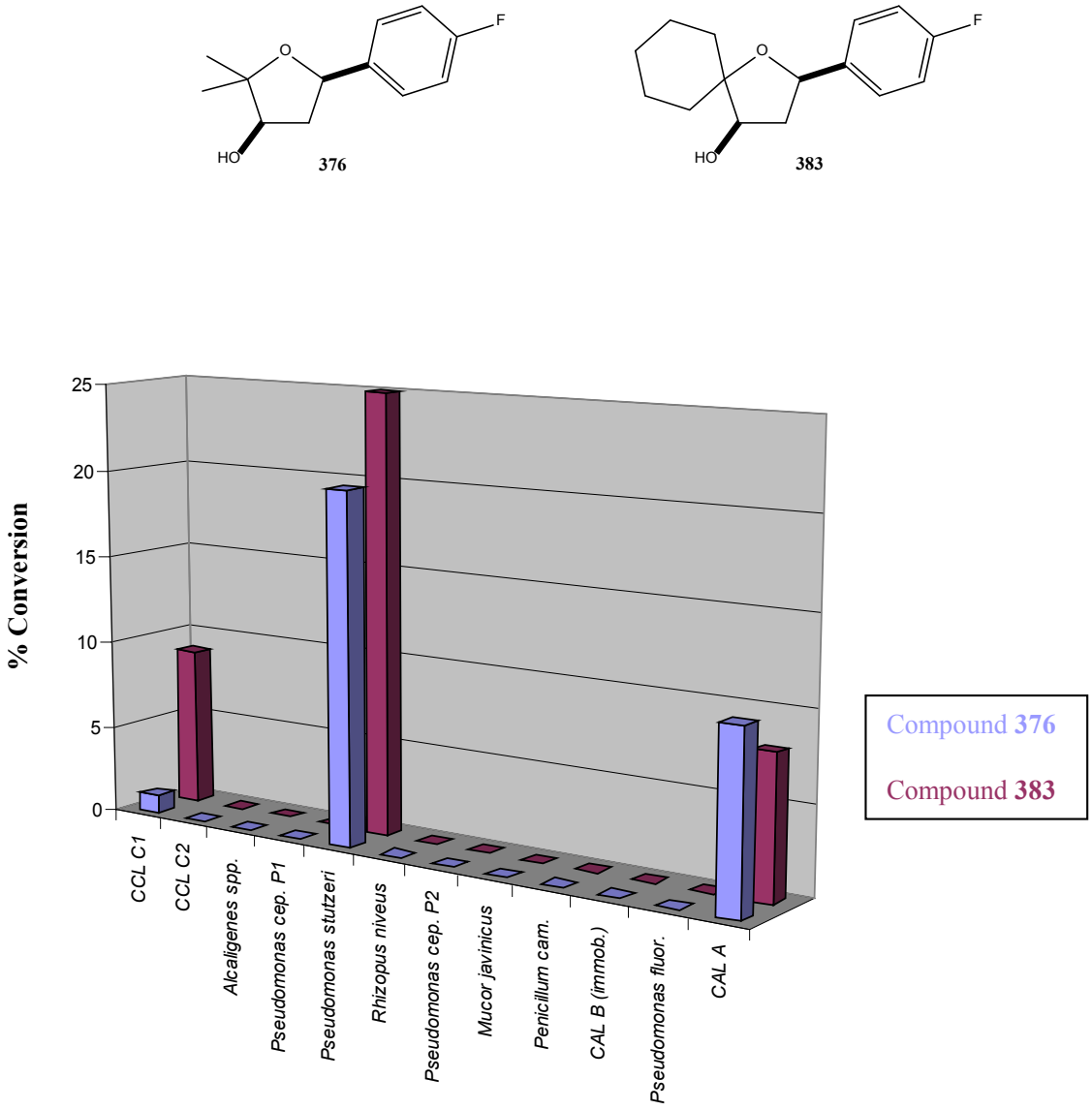


Figure 2.5.1.1 Extent of Conversion of Hydroxytetrahydrofurans **376** and **383** Using a Range of Lipases

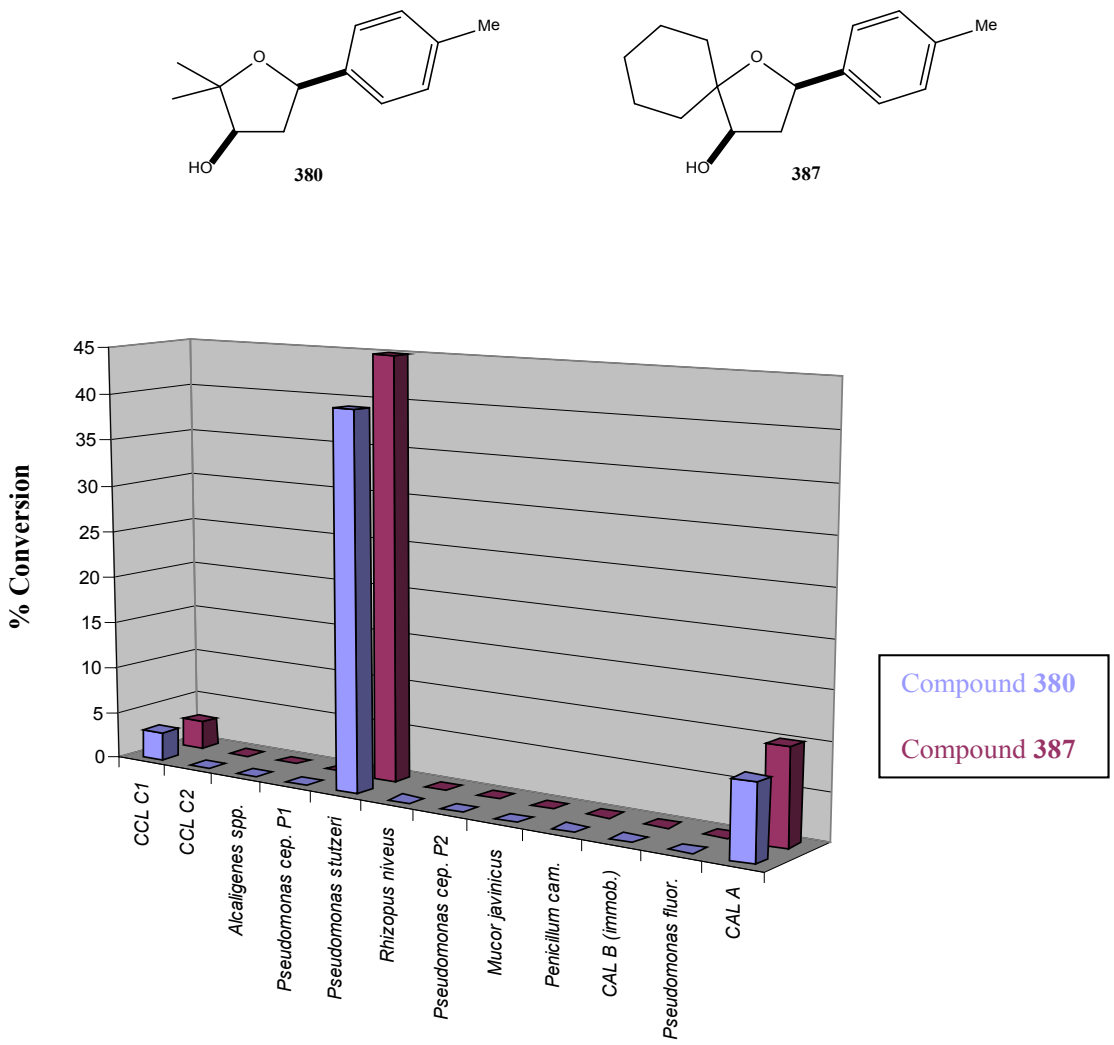


Figure 2.5.1.2 Extent of Conversion of Hydroxytetrahydrofurans **380** and **387** Using a Range of Lipases

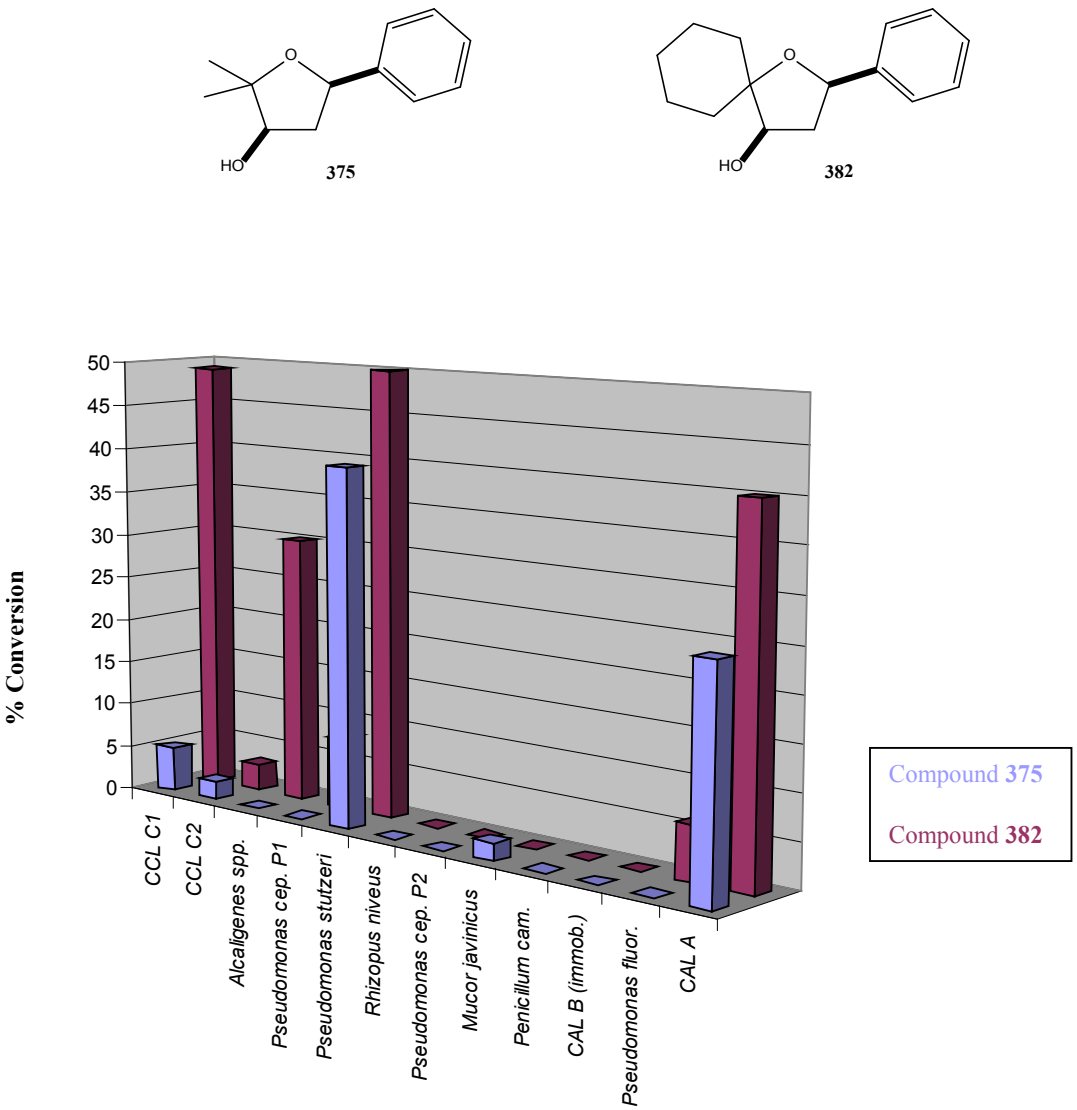


Figure 2.5.1.3 Extent of Conversion of Hydroxytetrahydrofurans **375** and **382** Using a Range of Lipases

The results shown above are interesting from the point of view that in general, the substrate with the spiro-fused cyclohexane group at the 2-position of the tetrahydrofuran ring gave a better degree of conversion than their *gem*-dimethyl analogues. This is in agreement with Kazlauskas' rule where more efficient kinetic resolution of the racemate takes place when there is marked difference in the steric bulk of the substituents at either side of the stereogenic centre.

The next step in the identification of a suitable enzyme for the preparative scale kinetic resolutions was to determine the enantiomeric compositions of the reaction products. It was at this stage that we also began to focus our attention and narrow the range of biocatalysts under investigation. Taking the results of the conversion screens into account it can clearly be seen that the most successful lipases were those isolated from *Pseudomonas stutzeri* and *Candida antarctica* A. Although the lipase from *Candida cylindracea* was highly effective for the conversion of substrates **375** and **382** into their respective acetates, it was much less efficient against the substrate pairs **376** and **383**; **380** and **387**, where there was either and electron withdrawing or donating substituent within the molecular structure of the compound. With this in mind we excluded *Candida cylindracea* from further studies and concentrated on *Pseudomonas stutzeri* and *Candida antarctica* A lipases. The results of the enantiomeric composition of the compounds resolved using these enzymes are outlined in Table 2.5.1.1.

Compound	Lipase	% Conversion	%e.e. Acetate	%e.e. Alcohol
376	*Pseudomonas Stutzeri*	20	>99	40
376	*CAL* A	9	96	11
383	*Pseudomonas Stutzeri*	25	97	43
383	*CAL* A	8	95	10
380	*Pseudomonas Stutzeri*	40	99	89
380	*CAL* A	8	96	6
387	*Pseudomonas Stutzeri*	45	>99	90
387	*CAL* A	10	>99	9
375	*Pseudomonas Stutzeri*	40	99	91
375	*CAL* A	19	92	12
382	*Pseudomonas Stutzeri*	50	99	99
382	*CAL* A	48	91	13

Table 2.5.1.1 Conversion and e.e. Data for Kinetic Resolution Screens of Compounds **376**, **383**, **380**, **387**, **375** and **382**

These results clearly indicate that *Pseudomonas stutzeri* lipase is the leading candidate of the entire library of enzymes screened to be brought forward to resolve our library of substrates on a preparative scale. Resolution with this enzyme has shown good conversion, with high enantiomeric composition. Further tuning of these reactions on the larger scale would be required to ensure the optimal performance level of this enzyme for production of the acetate and alcohol products in high % e.e. compositions.

2.5.2 Effect of Enzyme Concentration

A routine experiment was carried out to determine the optimal amount of *Pseudomonas stutzeri* lipase to be used in the preparative scale reactions. The screens were carried out in a similar manner to the experiments described earlier, with **375** (20.00 mg, 0.10 mmol) in diisopropyl ether (3 mL) and vinyl acetate (8.60 mg, 0.10 mmol) stirred (750 rpm) with the respective amount of *Pseudomonas stutzeri* lipase at room temperature for 24 h. The respective crude products were isolated as per the procedure previously described and extent of conversion determined by ^{1}H NMR spectroscopy.

Enzyme (% w/w)	% Conversion
10	7
25	18
50	40
75	41

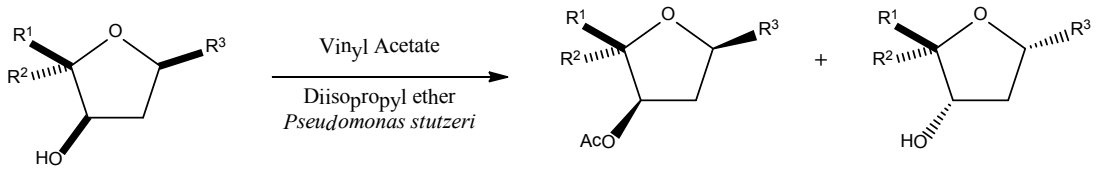
Table 2.5.2.1 Quantity of Enzyme Used and the Corresponding Conversion of Compound **375**

Based on the results in Table 2.5.2.1, the optimal amount of enzyme is 50% w/w. There is a marked difference between 25% and 50% w/w that would affect the efficiency of the transformation. However, with only a 1% difference in conversion when going from 50% to 75% there is no advantage to the increased loading of biocatalyst to this level.

It was not deemed necessary to investigate other potential variables on these reactions *i.e.* reaction temperature, solvent and acyl donor. In all cases the screens carried with the variable from the conditions developed by Hayes[178] being the enzyme employed. This proved to be sufficiently successful to negate the need for further development of these conditions and armed with the knowledge that a 50% w/w loading of *Pseudomonas stutzeri* lipase is the ideal starting point to bring the resolution of 3-hydroxytetrahydrofurans from screen-scale to preparative scale synthesis.

2.5.3 Preparative Scale Biotransformations

A range of 3-hydroxytetrahydrofurans were synthesised and their reactivity and selectivity tested under the conditions established in the screening process outlined above. For the most part, the compounds tested consisted of 5-aryl 3-hydroxytetrahydrofurans, with a large number being phenyl moieties with varying substitution patterns. The reactions were carried out using *Pseudomonas stutzeri* lipase, with vinyl acetate as the acyl donor and diisopropylether as solvent (Scheme 2.5.3.1). The reaction mixtures were stirred gently in a water bath at room temperature until ^{1}H NMR indicated 50% conversion (or that reaction has ceased) when the enzyme was removed by filtration. The enzyme was washed with ethyl acetate, with the combined reaction mixture/washings concentrated and purified by flash chromatography using ethyl acetate/hexane as eluant.



Scheme 2.5.3.1

Conversion of the alcohols into the esters was calculated from the ^{1}H NMR spectra of the crude reaction products by integration of the C(4)**H** signals. These figures are quoted in Table 2.5.3.1 along with the isolated post-chromatography yields.

The lipase enantioselectivity (E) values were determined from the following equation:[176]

$$E = \frac{\ln[1-c(1+ee_{product})]}{\ln[1-c(1-ee_{product})]}$$

where c is the extent of conversion and $ee_{product}$ is the enantiomeric excess of the product. The significance of the E value is that it is a measure of the efficiency and selectivity of the biotransformation that is being studied. Reactions that have E values >200 are deemed to be highly desirable. These high E values indicate that not only are the conversion rates of the reactions highly efficient, but that the enantiomeric composition of the biotransformation products also proceeds with a very high degree of selectivity.

Enantiomeric composition was determined by chiral HPLC for all compounds (see Figure 2.5.3.1 and 2.5.5.1 for examples) except 2,2-dimethyl-5-*tert*-Bu-3-hydroxyfuran **381**, which was analysed by chiral shift ^{1}H NMR techniques using tris-[3-heptafluoropropyl-hydroxymethylene-(+)-camphorato]-europium (III) derivative, [(+)-Eu(hfc)$_3$] as the chiral shift reagent.

Alcohol*	Time (h)	Conversion (%)	Yield Acetate# (%)	e.e. Acetate (%)	Yield Alcohol # (%)	e.e. Alcohol (%)	E
375	24	48	30	>99	40	91	>200
376	40	47	27	>99	37	92	>200
377	24	50	31	>99	24	>99	>200
378	48	50	37	>99	38	>99	>200
379	28	50	27	>99	25	>99	>200
380	24	50	34	>99	39	>99	>200
381	480	5	Not Isolated	-	36	-	-
382	24	48	31	>99	40	93	>200
383	24	50	35	>99	34	>99	>200
384	24	50	25	>99	39	>99	>200
385	48	50	38	>99	35	>99	>200
386	20	49	28	>99	37	95	>200
387	24	50	29	>99	31	>99	>200
388	700	0	-	-	-	-	-
391	504	0	-	-	-	-	-

* Refer to Table 2.3.1 for the identity of the substituents

\# For assignment of absolute configurations, see Section 2.5.4

Table 2.5.3.1 Yield and Enantiomeric Composition Data for Compounds **375-388** and **391**

Table 2.5.3.1 shows the yield and enantiomeric composition data for the resolution of our library of compounds. What is clear is that the reactions have, for the most part, been extremely successful and we have produced enantiopure products from

the kinetic resolution of racemic 3-hydroxytetrahydrofurans **375-387**. Where the reactions reached 50% completion, all products were enantiopure. Those reactions that did not reach 50% completion produced enantiopure acetates and highly enantioenriched alcohols. With some further tuning it is envisaged that these could achieve full conversion and deliver both products in an enantiopure form.

The data contained within Table 2.5.3.1 also requires discussion with regard to the rate at which reaction completion (*i.e.* 50% conversion) is achieved. In the *gem*-dimethyl series, for the most part full reaction completion was achieved within 24 h. *para*-fluoro substituted compound **376** did not go to full completion at 47% and this took place over 40 h. The precise reason for this is unknown but it could be postulated that as fluorine is the most electronegative element, it could have a bearing on the interaction at the active site of the enzyme. *meta*-nitro substituted **378** (and also its corresponding fused cyclohexyl derivative **385**) exhibited a greater reaction time than the others within the series, however similar was observed by Hayes within his work[178] that the position of the substituent on the aryl ring can have a bearing on reaction rate. His study was performed using mono-methyl and mono-bromo substituted aryl compounds and found that the extent of conversion increased going from *ortho* - *meta* - *para*. It is interesting from our point of view that we also observed this while employing a different enzyme species for our work. With regard to the fused cyclohexyl series only the aforementioned **385** was outside of the 24 h range, but there were no major differences between the other compounds within this series or indeed when comparing the the difference of the rates of the gem-dimethyl and fused cyclohexyl groups containing the same aryl substituent. The *para*-fluoro (40 and 24 h) and *para*-nitro (28 and 20 h) substituted derivatives of each series were the only to show any appreciable difference in achieving reaction completion within this study. This could be attributed to Kazlauskas' Rule *i.e.* when one side of the chiral centre is larger than the other, the reaction proceeds faster. By increasing in the size of the substituent at the 2-position of the furan ring from *gem*-dimethyl to fused cyclohexyl for each derivative, this could have provided the relevant substrates with the structural facility to increase the rate of reaction. As to why there is no rate increase for the other substrates it is reasonable to deduce that the the substitution pattern on the aromatic ring allied with the active site of the enzyme has allowed the reaction to proceed at a rate independent of the size of the alkyl substitution at C(2). The polarity of the fluoro and nitro groups on the aromatic ring has clearly had an effect on the rate of

reaction and only by changing the substitution at C(2) has the rate increased as outlined by Kazlauskas.

For substrates **388** and **391** an exhaustive search for conditions to effect the desired, or any, biotransformation proved fruitless (the conditions attempted are described in Chapter 3). Compound **388** was highly insoluble under the standard conditions employed. A screen of solvents was used to identify a solvent or mixture of solvents that would allow us to proceed with this resolution. A mixture of diisopropylether/DMSO was the only successful result and this was then screened against a variety of biocatalyst, at different temperatures and various acyl donors. All attempts employed proved unsuccessful. It is envisaged that the 5-(4-aminophenyl) substituent in someway inhibits the biotransformation. One potential reason for the unsuccessful attempt at biotransformation is that there may be competitive acylation of the amine of the aryl ring that gives rise to a product(s) that block the enzyme active site. It had previously been observed[178] that compounds that do not contain an aromatic substituent are more sluggish towards biocatalysts, and that property was observed in our study of fifteen compounds, thirteen of which were 5-aryl substituted 3-hydroxytetrahydrofurans. The alcohol **391** was found to be unreactive under the conditions developed during this study, and also towards other biocatalysts screened at varying temperatures in an attempt to promote reaction (refer to Table 3.2.4.8). Its *gem*-dimethyl derivative **381** proved to be slightly more reactive, however after three weeks of reaction there was only 5% conversion to the acetate ester. Owing to the small scale of these reactions we were unable to isolate the acetate for chiral analysis and the reaction was not repeated. The inability to successfully resolve the *5-tert*-butyl hydroxytetrahydrofurans **381** and **391** to the extent of the 5-aryl derivatives could be attributed to a number of factors; the aforementioned lack of an aryl substituent within the molecule, that the *tert*-butyl simply may not fit within the active site of the enzyme or that the tetrahedral geometry of the *tert*-butyl group is not compatible with the enzyme when compared with the planar nature of aryl substituted compounds.

We also found a very interesting result when carrying out the resolution of the alcohols **377** and **379**. These substrates were reacted as a mixture of diastereomers because earlier attempts to isolate a single diastereomer proved fruitless. What was observed was a 50% completion for both substrates, which would not be unexpected, but also that the minor diastereomer was resolved to produce both enantiopure acetates and alcohols respectively. This is surprising as Hayes[178] had screened a diastereomeric

mixture of **375** in his initial studies to find that the minor diastereomer (*i.e*. 3*R*, 5*S*/3*S*, 5*R*) was not processed by the lipase from *Candida cylindracea*. It is highly probable that the change in biocatalyst from that employed by Hayes was the cause of the different behaviour of the compound. It was not possible to isolate a diastereomerically pure form of these products **377** and **379** for crystallographic analysis that would enable confirmation of the absolute stereochemistry of the resolved minor diastereomer. However, it could be envisaged that (3*R*, 5*S*) would be the configuration of the resolved diastereomer. This conclusion is reasonable given that the (3*R*, 5*R*) diastereomer is the preferred diastereomer in our other substrates. This, however, is a hypothesis and would need to be investigated further to prove. It was possible to determine the enantiomeric composition of **377** and **379** by chiral HPLC analysis as all four peaks for the respective diastereomers were separable in the one run. An example of this behaviour is shown in Figure 2.5.3.1 and Figure 2.5.3.2.

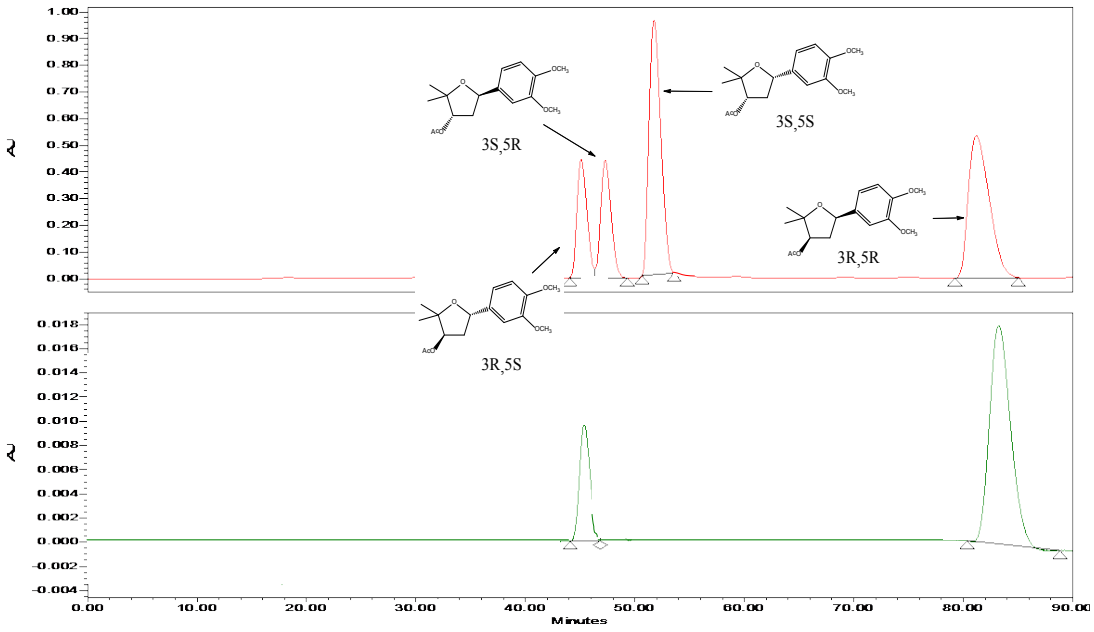


Figure 2.5.3.1 HPLC Traces of **396** (mixtures of diastereomers, red and products of bioresolution, green; see Appendix A for HPLC conditions)

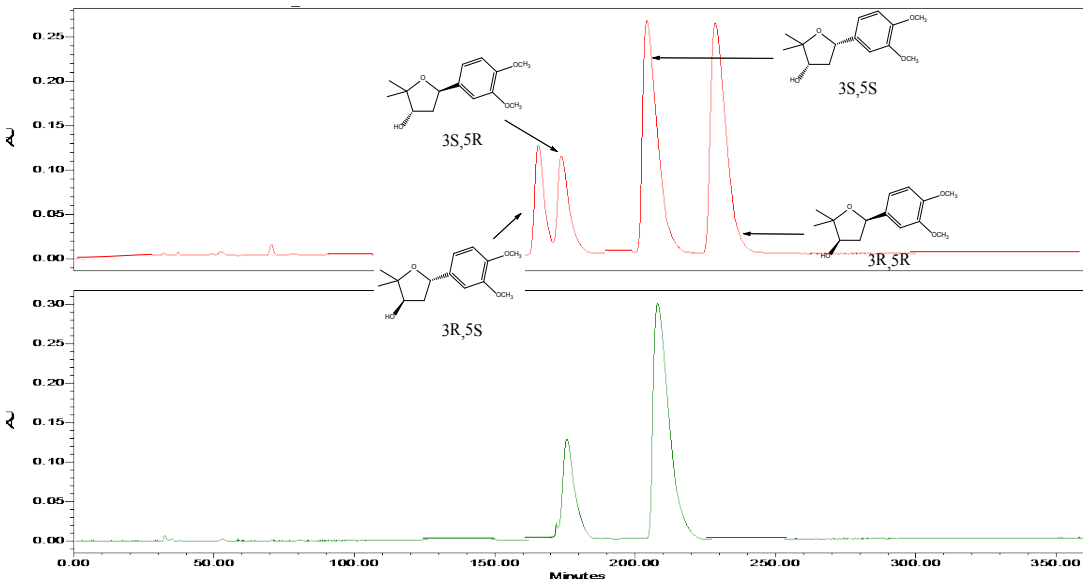


Figure 2.5.3.2 HPLC Traces of **377** (mixtures of diastereomers, red and products of bioresolution, green; see Appendix A for HPLC conditions)

The study carried out by Hayes[178] employed a wide range of substrates (approximately twenty-three compounds), some of which we repeated as a means of comparing the results of our work with the initial studies that he had carried out. Table 2.5.3.2 summarises the extent of conversion and enantiomeric composition of the products achieved in both studies.

Compound	Time (h)	Conversion (%)	e.e. Acetate (%)	e.e. Alcohol (%)	E
375	24	48	>99	91	>200
375	50	25	95	33	53
376	24	50	>99	>99	>200
376	96	46	98	86	>200
377	28	50	>99	>99	>200
377	162	45	98	84	>200
382	24	48	>99	93	>200
382	115	48	97	86	>200

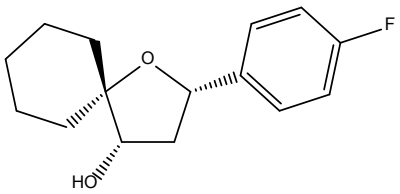
Table 2.5.3.2 Comparison of Biotransformations from Current Work (using P*seudomonas stutzeri*) with that of Hayes[178] (using *Candida cylindracea*, highlighted in yellow)

What is clear from the results above is that the biocatalyst employed in our study was much more efficient than that used by Hayes. This would be expected given the rapid advances made in the field of biocatalysis in the intervening years. We found much quicker reaction of the substrate, higher conversion to the acetate and higher enantiomeric composition of both the acetate and alcohol products. What is also noteworthy is that for Hayes' study, it was necessary to heat the reaction mixtures to temperatures of 29–45 °C to effect the extent of reaction achieved whereas in our work, all reactions were carried out at ambient temperature.

2.5.4 Determination of Absolute Configuration

In order to ascertain the absolute stereochemistry of the products from the lipase mediated esterifications, we employed X-ray crystallography*. A suitable crystal was grown from the highly crystalline product **383** (e.e >99%). To ensure that the crystal submitted for crystallographic analysis was enantiopure, it was confirmed by chiral HPLC analysis to possess an e.e. >99%. There was no need to attempt to synthesise a crystalline derivative of **383**, as had been previously required.[178] This verified that the

compound had (3*S*, 5*S*) absolute configuration and allowed the absolute stereochemistry of the precursor materials to be deduced. By extension, this result and the application of Kazlauskas' rule has allowed us to extend the (3*S*, 5*S*) configuration of the absolute stereochemistry to the remaining 3-hydroxytetrahydrofurans produced in this work. The importance of the X-ray structure determination is that it permits a correlation between the key NMR signals of **383** and the relative absolute configuration of the stereogenic centres at the C-3 and C-5 positions of the tetrahydrofuran ring. The NMR/X-ray correlation is supported by determination of the absolute configuration work previously carried out.[178]



383

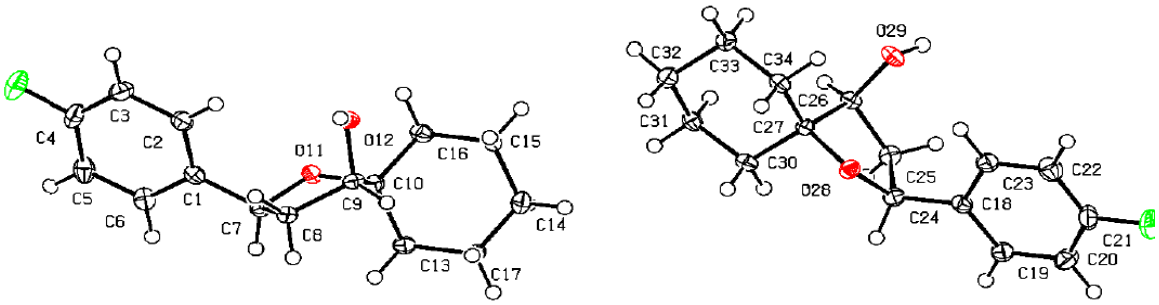


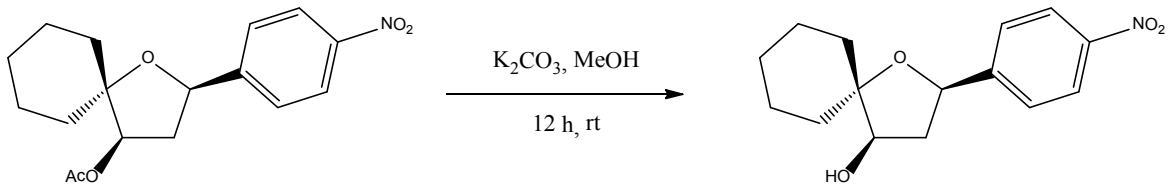
Figure 2.5.4.1 Crystal Structure of (3*S*, 5*S*)-2-(4-fluorophenyl)-1-oxaspiro[4.5]decan-4-ol **383**. Oxygen atoms are shown in red and fluorine atoms in green.

*Structure Determination Carried Out by Dr. Simon Lawrence and Dr. Kevin Eccles, National University of Ireland, Cork.

2.5.5 Hydrolysis of an Enantiomerically Pure 3-Acetoxytetrahydrofuran

Incorporated within this study is the attempt to isolate a pair of enantiomerically pure 3-hydroxytetrahydrofurans. Failing this, an enantiomerically enriched pair would suffice to illustrate that the products of the biocatalytic resolutions could be reacted further to furnish compounds that would retain their optical purity. This would be of major benefit in the area of total synthesis should kinetic resolution be required to access a variety of synthetic targets.

It was decided, owing to its enantiopurity, to hydrolyse **405** to the corresponding alcohol. The transformation was effected by reaction of the ester with potassium carbonate in methanol at room temperature over 12 h (Scheme 2.5.5.1). TLC analysis indicated reaction completion before acidic work-up and chromatographic purification yielded **386** in enantiomerically pure form and in 92% yield.



405 **386**

Scheme 2.5.5.1

On isolation of the desired product, its enantiomeric composition was determined by chiral HPLC analysis. The results of the analysis can be observed in Figure 2.5.5.1.

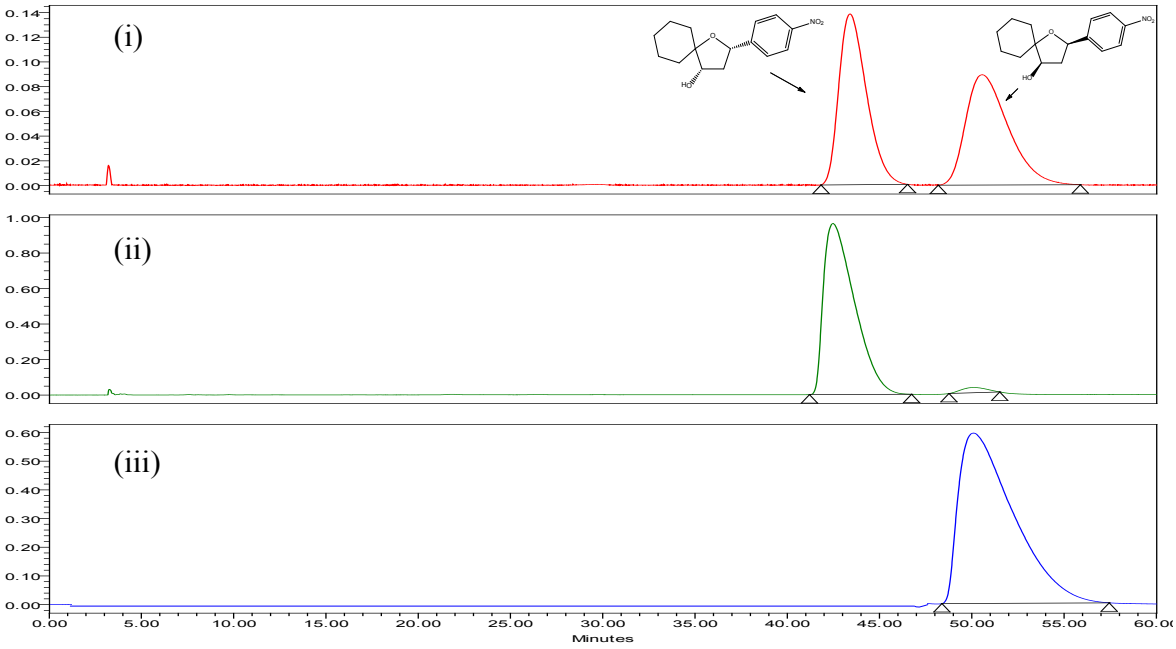
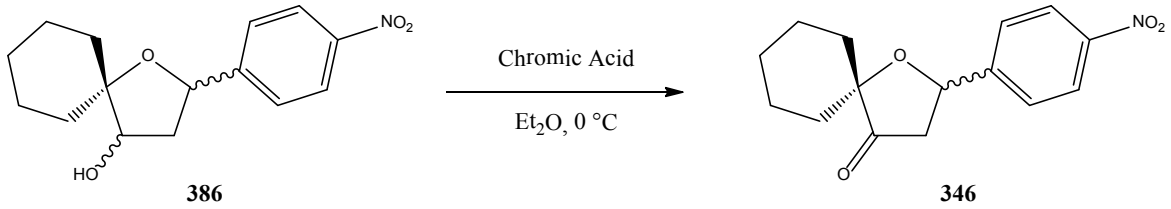


Figure 2.5.5.1 Stack HPLC Plots of (i) Racemic-**386**, (ii) (*S*, *S*)-**386** and (iii) (*R*, *R*)-**386** (see Appendix A for HPLC conditions)

Trace (i) shows the plot of racemic-**386**, with the (*S*, *S*) and (*R*, *R*)-diastereomers eluting at *ca*. 43 and 50 minutes respectively. As can be seen from trace (ii), and as reported earlier, (*S*, *S*)-**386** is present in 95% e.e. Finally, trace (iii) is the product from the acetate hydrolysis and is enantiomerically pure in the (*R*, *R*) configuration with >99% e.e.

2.5.6 Oxidation of Enantioenriched 3-Hydroxytetrahydrofurans

Incorporated within this study is the attempt to isolate a pair of enantiopure 4,5-dihydro-3(*2H*)-furanones. Failing this, an enantiomerically enriched pair would suffice to illustrate that the products of the biocatalytic resolutions could be reacted further to furnish compounds that would retain their optical purity. Thus, (*S*, *S*)-**386** and (*R*, *R*)-**386**, respectively, were treated with chromic acid in ether at 0 °C until TLC analysis indicated consumption of the starting alcohol.



Scheme 2.5.6.1

Chromatographic purification afforded the desired 4,5-dihydro-3(*2H*)-furanones in good yield, that were then assayed by chiral HPLC analysis for enantiomeric composition. The results of which can be seen in Figure 2.5.6.1.

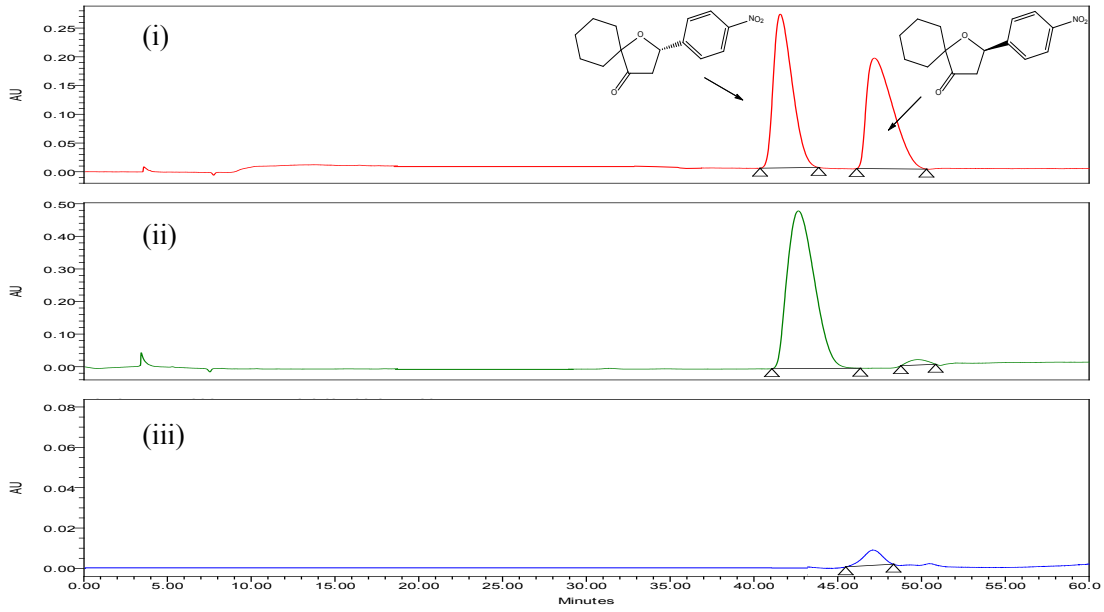


Figure 2.5.6.1 Stack HPLC Plots of (i) Racemic-**346**, (ii) (*S*)-**346** and (iii) (*R*)-**346** (see Appendix A for HPLC conditions)

Trace (i) shows the plot for racemic-**346**, with the (*S*, *S*) and (*R*, *R*)-diastereomers eluting at *ca*. 42 and 47 minutes respectively. As can be seen from trace (ii), (*S*)-**346** is the predominant form (95% e.e.). Finally, trace (iii) relates to the product from the acetate ester hydrolysis after oxidation and is enantiomerically pure in the (*R*) configuration with >99% e.e.

Conclusions

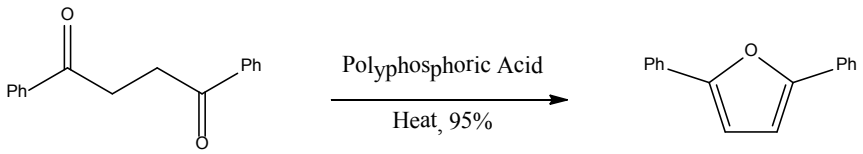
We conclude that the aldol condensation of arenecarboxaldehydes with acetyl substituted tertiary carbinols such as 2-hydroxy-2-methylbutan-2-one and 1-acetylcyclohexanol, under Claisen-Schmidt conditions is a reliable route to conjugated α-hydroxyenones on synthetically useful scales. The process occasionally generates interesting secondary products derived from conjugate additions of solvent molecules to the enone system and enone alkene *Z*-isomers which readily equilibrate with the corresponding *E*-isomers. Acid-catalysed cyclisation of the hydroxyenones to the corresponding 4,5-dihydro-3(2H)-furanones gives access to a wide range of the heterocyclic ketones provided that the correct combination of catalyst and reaction temperature (solvent boiling point) is employed: heating the reaction mixture in either toluene or 1,2-dichloroethane under reflux to disappearance of the starting material is a suitable set of conditions. Prolonged heating of the reaction mixtures under these conditions induces a secondary process - the production of 1,3,5-trisubstituted furans. That outcome can be optimised through use of higher boiling solvents (see later). α-Hydroxyenones bearing aryl groups as substituents at the carbinol carbon are not suitable substrates for the production of 4,5-dihydro-3(2H)-furanones however, and produce cyclopentenones as the major products when treated with acids. An alternative approach involving reduction of 3(2H)-furanones is available for the targeted 4,5-dihydro-3(2H)-furanones. Reductions of the 4,5-dihydro-3(2H)-furanones with L-Selectride® is a reliable route to a range of 3-hydroxytetrahydrofurans with high stereochemical control in a predictable manner. While it is likely that another hindered reducing agent, lithium tri-*t*-butoxyaluminium hydride would also be effective, the practical advantages of the L-Selectride® are superior in our view. For certain substrates, sodium borohydride in aqueous methanol gives equally good results and while it is limited in substrate scope, it has the advantage of being successful with nitro aromatic systems which are problematic with the more hindered boron reagent as competing reactions at the carbonyl and nitro groups are an issue.

Transformations of racemic 3-hydroxytetrahydrofurans into a mixture of the corresponding, highly enantioenriched alcohols and acetates is a highly successful process using lipase enzymes, under the conditions of kinetic resolution in an organic solvent (typically di-isopropyl ether containing a trace of water). The process is applicable to a wide range of substrates and enzymes including catalysts with partially

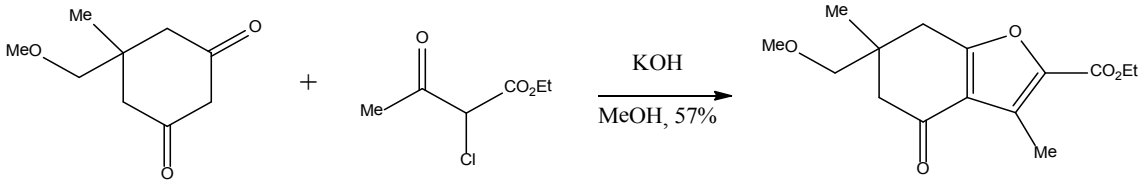
engineered structures. A clear pattern of behaviour involving the same sense of enantioselectivity (hydroxytetrahydrofuran production), accompanied by high efficiency (E) factors is evident for the alcohols studied and the process is in conformity with Kazlauskas' rule for lipases. The superior behaviour of lipases derived from *Candida cylindracea* and *Pseudomonas stutzeri* species for the conversion of certain hydroxytetrahydrofurans into their acetates is clearly evident and provides a basis for use of these enzymes in the preparation of synthetically useful quantities of enantioenriched acetates and alcohols: in effect both enantiomers of the chiral alcohols. Oxidation of the latter compounds yields the individual enantiomers of the corresponding 4,5-dihydro-3(2H)-furanones. The lipases from the two organisms in question can tolerate spiro-cyclohexyl substitution at the two-position of the heterocyclic ring: compound pairs **375** and **382**, **376** and **383**, **380** and **387**. A lipase from the species *Candida antartica A* together with that from *Pseudomonas stutzeri* emerged as the best possibe biocatalysts for these compounds, however, and particularly if the acetates are required in high %ee. In contrast, the corresponding alcohols were isolated in a range of enantiomeric compositions (%ee 10-90) from the same reactions. Appropriate optimisation of the reaction conditions and in particular the enzyme:substrate ratio can address this issue in an effective manner for the *Pseudomonas stutzeri* lipase in combination with the alcohols **375-380** and **382-387**. Here, it is interesting to note that the highly polar nitro group in substrate **386** did not inhibit the success of the transformation for that substrate. Overall however, it is unlikely that one lipase will be effective for the synthesis of a wide range of enantiopure hydroxytetrahydrofurans in general, and that the type of specificity of individual enzymes that we have encountered for (small) groups of hydroxytetrahydrofuran substrates (see above) will prevail.

2.6 Synthesis of 2,3,5-Trisubstituted Furans

Many strategies have been developed for the preparation of furans. The most widely used approach to furan synthesis is the Paal–Knorr reaction in which 1,4-dicarbonyl compounds are converted to furan derivatives in a cyclodehydration process induced by acid (Scheme 2.6.1),[198] such as HCl, H_2SO_4, P_2O_5 and PTSA[199-203] and the Feist-Benary[204, 205] synthesis between an α-haloketone and β-dicarbonyl compound[206] (Scheme 2.6.2).



Scheme 2.6.1 Paal-Knorr Furan Synthesis from a 1,4-Diketone



Scheme 2.6.2 Feist-Benary Furan Synthesis from α-Haloketone and β-Dicarbonyl Compounds

Recently there has been widespread literature reporting of furan syntheses, most probably as an indication of the need to synthesise pharmaceutically active compounds such as Ranitidine (trade name Zantac®), which is mainly used in the treatment of ulcers of the stomach and intestine (Figure 2.6.1). Examples reported include syntheses from α-substituted β,γ-unsaturated ketones,[207] propargyl alcohols and terminal alkynes,[208] oxidation of α-diazo-β-ketoacetates,[209] gold(III) porphyrin-catalyzed cycloisomerization of allenones,[210] palladium-catalyzed reaction of 2-propynyl-1,3-dicarbonyls,[211] microwave-mediated Paal–Knorr cyclisation reaction[212] and other methodologies to give 2,3,5-trisubstituted furans were reported.[213-222]

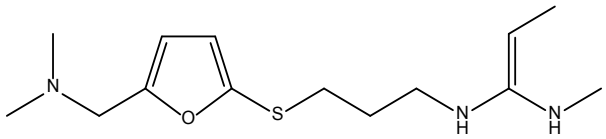


Figure 2.6.1 Structure of Ranitidine

2.6.1 Discovery of a Synthesis of 2,3,5-Trisubstituted Furans

During the course of our studies, and along the pathway towards synthesis of racemic 3-hydroxytetrahydrofurans, we envisaged that the standard method of acid-catalysed conversion of the nitro-enone **334** into the corresponding 4,5-dihydrofuranone **353**, with PTSA in refluxing 1,2-dichloroethane would be applicable. An additional (less polar than the furanone) compound was observed on TLC analysis of the crude reaction mixture and the components (i.e. the furanone **353** and an as yet unidentified compound, Scheme 2.6.6.1) were isolated by flash chromatography. The unknown compound was subjected to the full array of spectroscopic analysis including 2-dimensional NMR experiments to determine the actual structure. This analysis indicated that the new compound could be a substituted furan. Further evidence for this species included the absence of IR carbonyl group absorptions and the presence of a cluster of ^{1}H and ^{13}C NMR signals in the chemical shift ranges 6.5-8.5 and 115-150 ppm respectively. ^{1}H-^{13}C HSQC experiments (Figure 2.6.1.1) were the most useful in this regard as the presence of certain ^{1}H-^{13}C correlations enabled us to assign the correct structure. The proton resonating at 6.67 ppm interacts with the carbon resonance at 117.40 ppm indicating that this is the proton and carbon signals for the C(4) section of the molecule. Also in the HSQC spectrum, the methyl groups at 2.01 and 2.31 ppm interact with the carbon signals centred at 9.88 and 11.68 respectively.

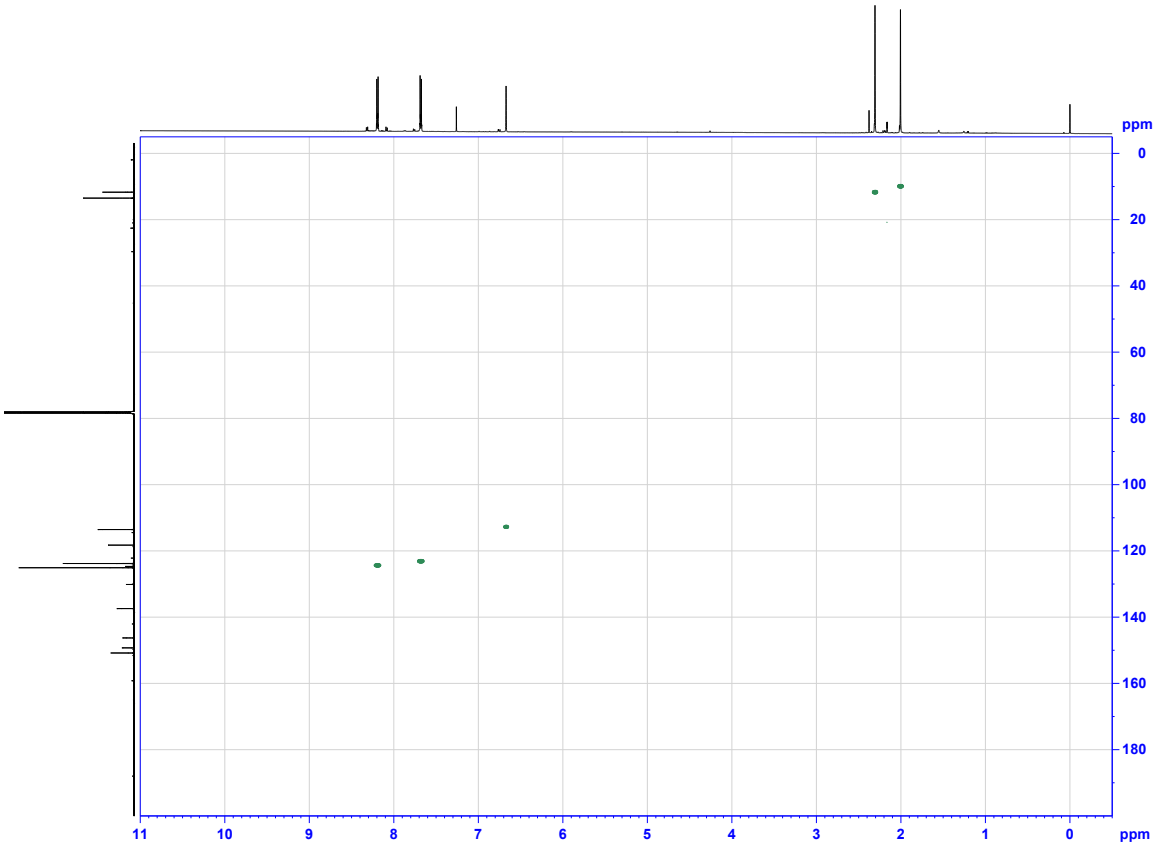
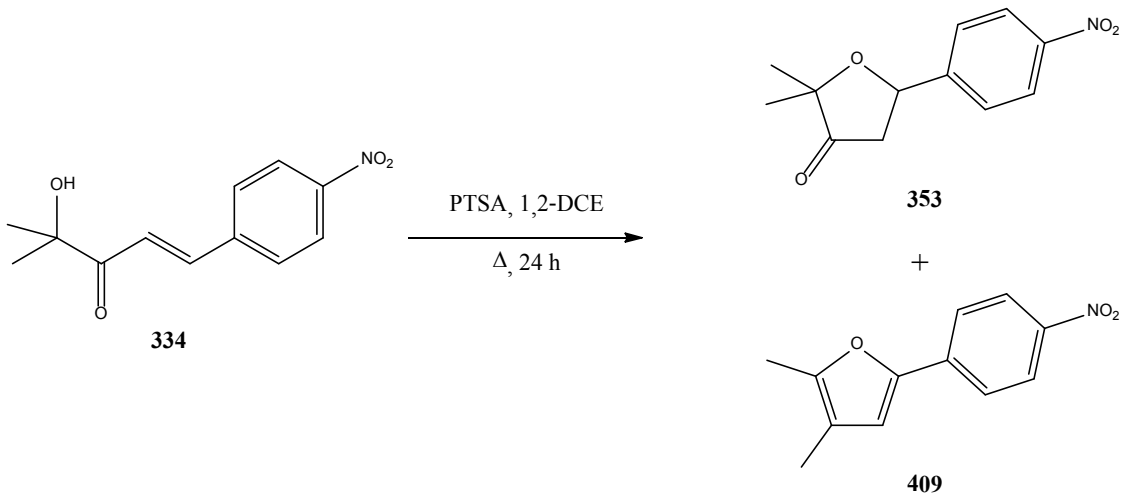


Figure 2.6.1.1 HSQC Spectrum of **409** in $CDCl_3$

The use of HMBC spectra enabled ultimate identification of the location of the methyl signals outlined previously as there was an interaction between the carbon resonance at 117.40 ppm and the methyl signal at 2.01 ppm, with the absence of any interactions observed with the methyl signal at 2.31 ppm. This enabled assignment of the signals belonging to each methyl group i.e. C(2)C**H**$_3$ at 2.31 ppm and C(3)C**H**$_3$ at 2.01 ppm. The methyl group signal on C(3) of the furan ring would be expected to be located further downfield than that on C(2) owing to the deshielding nature of the neighbouring oxygen atom of the furan ring. Fortunately, the material was highly crystalline and a suitable crystal was grown to allow for X-ray Crystallographic determination of its structure[*]. What was discovered was 2,3,5-trisubstuted furan **409** (Figure 2.6.1.2) *via* dehydration of enone **334**. Tables 2.6.1.1 and 2.6.1.2 depict the microanalytical data and NMR assignments for **409**.



Scheme 2.6.1.1 Initial Formation of 2,3,5-Trisubstituted Furan **409**

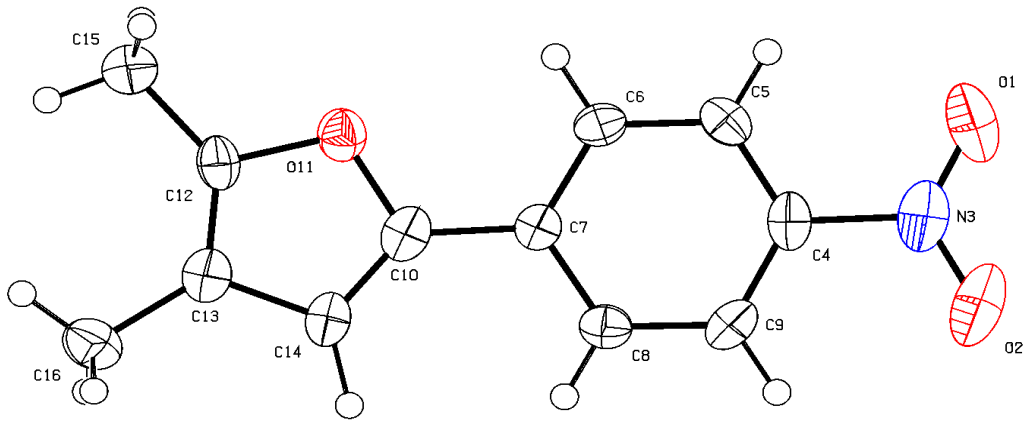


Figure 2.6.1.2 Crystal Structure of 2,3-Dimethyl-5-(4-nitrophenyl)-furan **409**

*Structure Determination Carried Out by Dr. Simon Lawrence and Dr. Kevin Eccles, National University of Ireland, Cork.

Element	Theoretical*	Found
C	66.35	66.14
H	5.10	5.30
N	6.45	6.27

* For $C_{12}H_{12}NO_4$

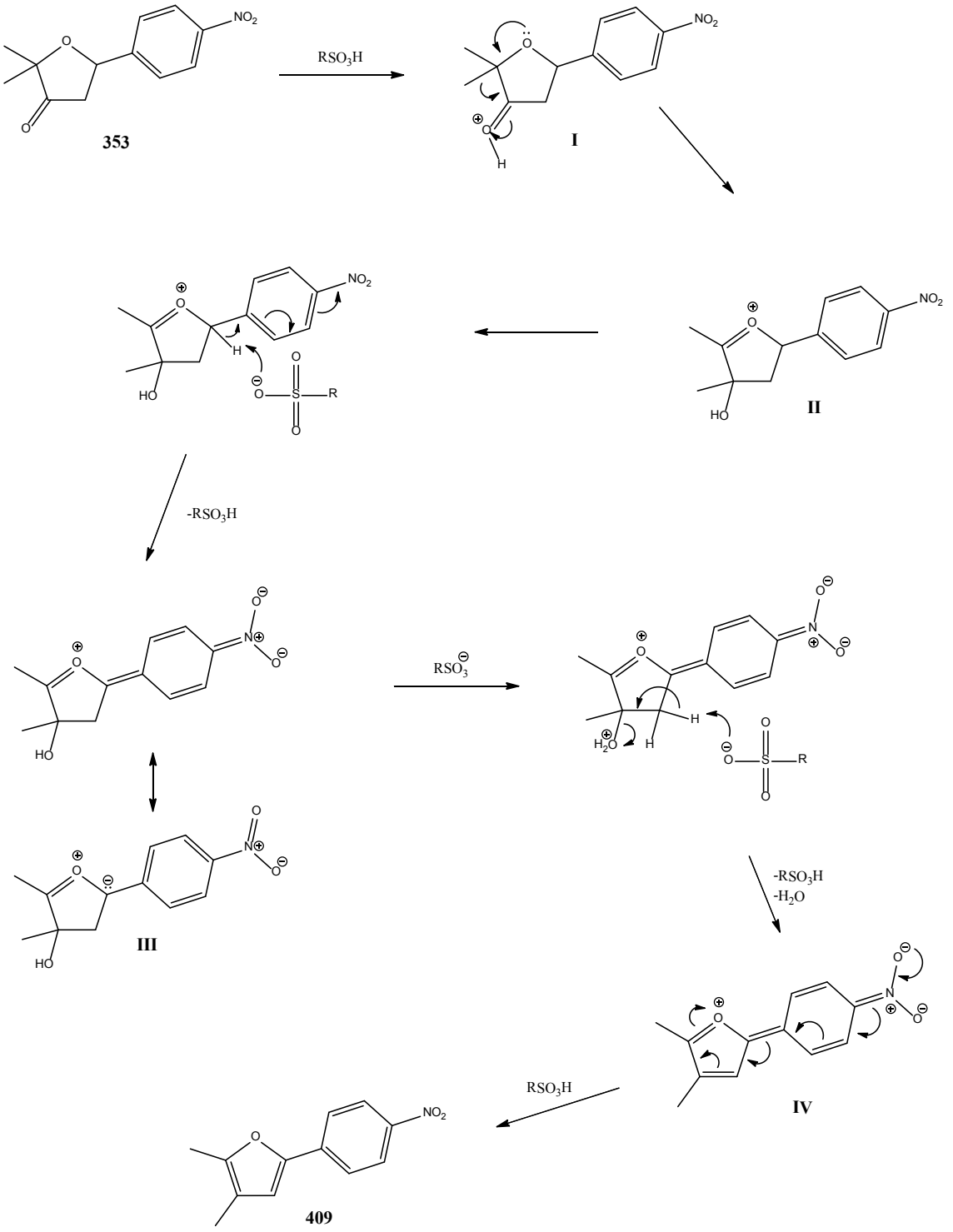
Table 2.6.1.1 Elemental analysis of **409**

δ_H (ppm)	Assignment	δ_C (ppm)	Assignment
2.01	C(3)C**H**$_3$	9.88	C(3)**C**H$_3$
2.31	C(2)C**H**$_3$	11.68	C(2)**C**H$_3$
6.67	C(4)**H**	117.40	**C**(4)H
7.76	ArC(2)**H**	117.45	**C**(3)
8.30	ArC(3)**H**	123.06	Ar**C**(2)H
		124.34	Ar**C**(3)H
		136.79	Ar**C**-NO$_2$
		145.79	Ar**C**
		148.77	**C**(5)
		150.33	**C**(2)

Table 2.6.1.2 ^{1}H and ^{13}C NMR Data of Furan **409**

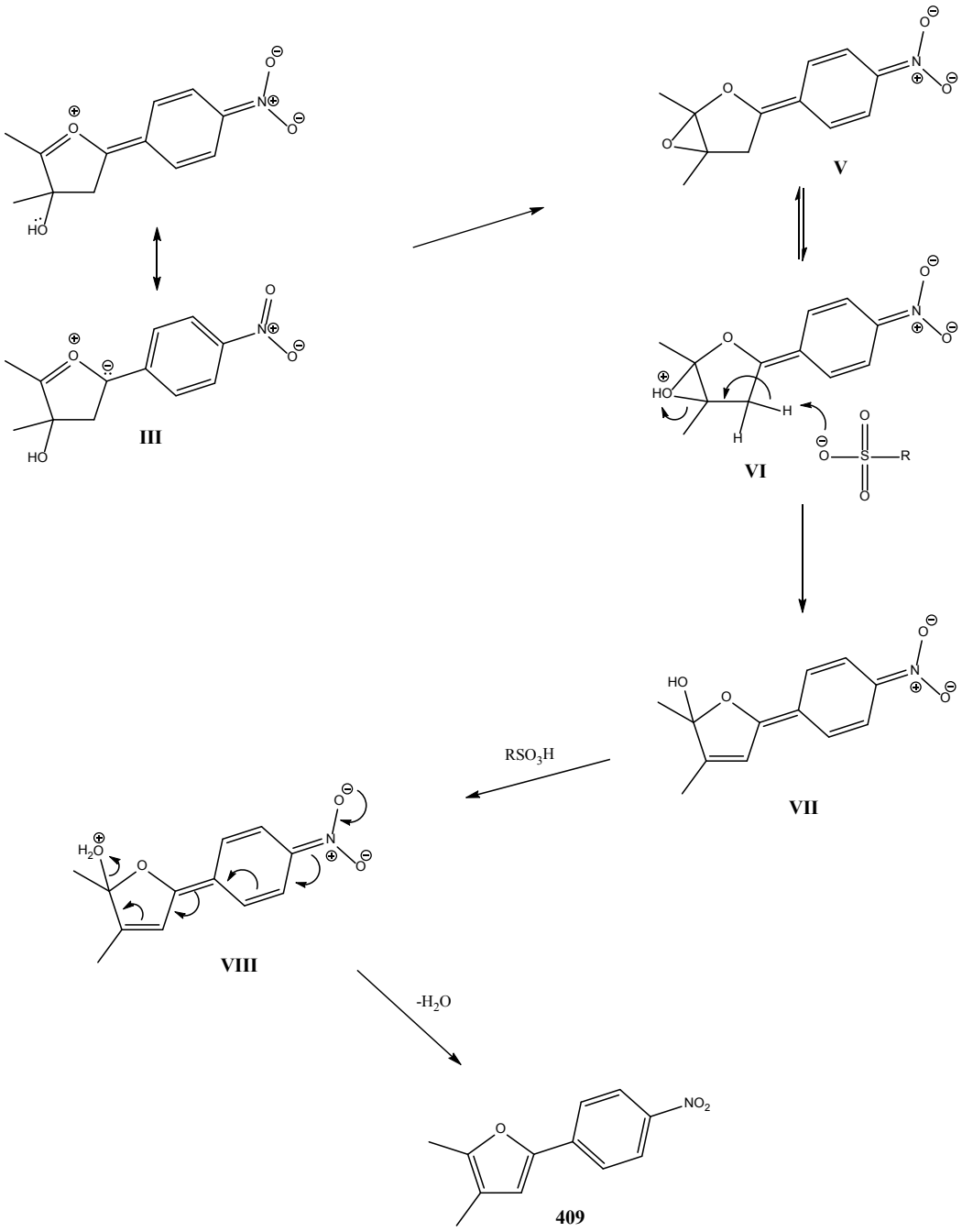
This is the first known synthesis of a 2,3,5-trisubstituted furan from an α-hydroxyenone. As the product was now identified, it was important to develop an understanding of the route from **334** to **409** at a molecular level. To test our theory that the reaction proceeds *via* the 4,5-dihydro-3(*2H*)-furanone, a sample of **353** was reacted with methanesulphonic acid in refluxing 1-2-dichloroethane to furnish furan **409** in moderate yield. With this knowledge we could formulate a plausible mechanism, which is essentially a dehydration of an α-hydroxyenone to form a furan. Starting from the enone, it would proceed to the 3(2H)-furanone *via* the route already discussed in Section 2.2.3. The mechanism we have postulated for this unique transformation is outlined in Scheme

2.6.1.2. After protonation of the carbonyl oxygen, a lone pair of electrons on the furanyl oxygen forms an oxonium species on this furanyl oxygen and this drives the 1,2-methyl shift on **I**, resulting in one of the *gem*-methyl groups moving to the 3-position of the heterocyclic ring to give **II**. The rest of the mechanism to form the furan is a series of deprotonation *via* carbonyl ylide **III** and delocalisation of electron density on to the 4-nitrophenyl group. As the carbonyl ylide intermediate is a 1,3-dipole, it in principle could be trapped using a 1,3-dipolar cycloaddition reaction, however we did not carry out any trapping experiments as part of this work. The final step in the mechanism to **409** is a cascade to restore the aromaticity of the aryl moiety on **IV** to complete the structural arrangement of **409**.



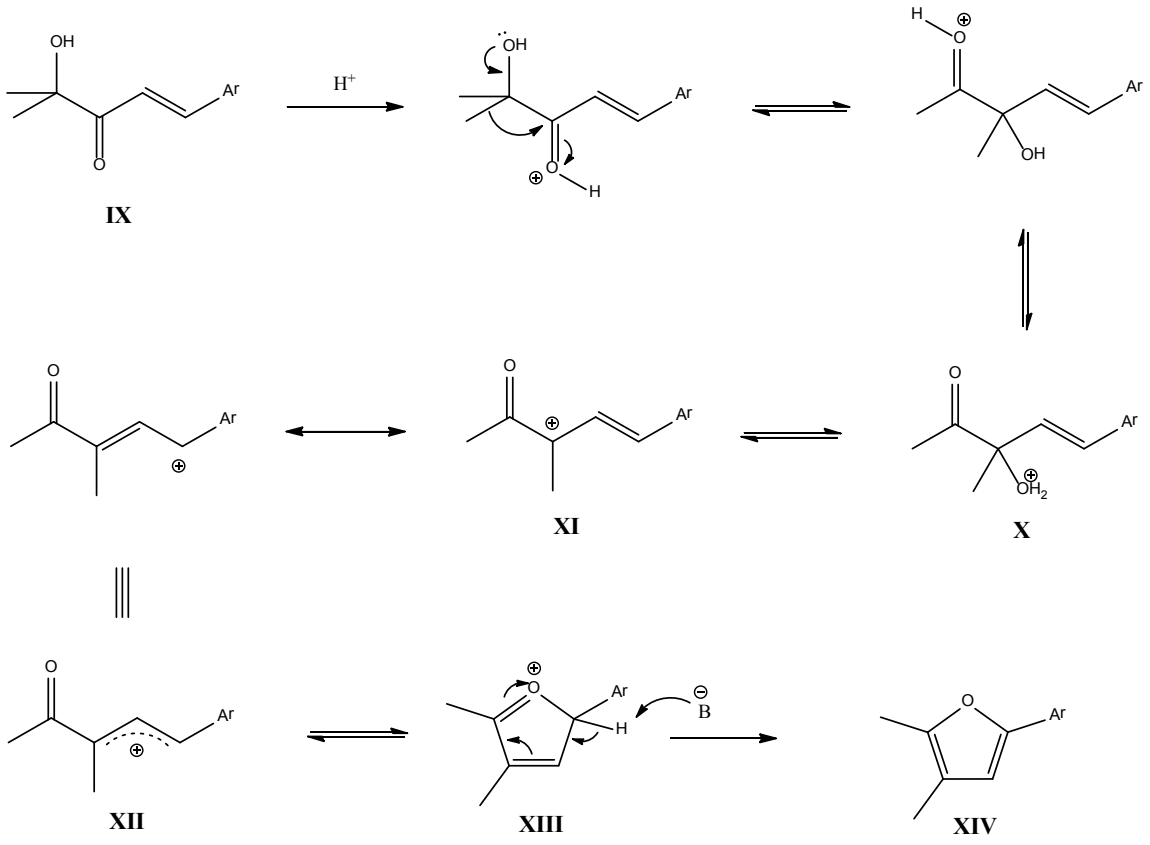
Scheme 2.6.1.2

The reaction mechanism could also progress *via* formation of epoxide **V** from ylide **III** (Scheme 2.6.1.3). The three-membered epoxide ring then opens as a result of deprotonation and resonance delocalisation of **VI** to form alcohol **VII**. This alcohol then becomes protonated, resonance delocalisation of the nitroaryl moiety restores aromaticity, before dehydration of **VIII** to result in the desired furan **409**.



Scheme 2.6.1.3

An alternative, entirely different mechanism that proceeds directly from the α-hydroxyenone to the furan, without the intermediacy of the dihydrofuranone (Scheme 2.6.1.4) is possible. This initially involves the acid-catalysed 1,2-alkyl group migration (i.e. α-ketol rearrangement) of **IX** to **X**.[223] This α-ketol rearrangement is well known and can be acid- or base-catalysed, with heat also facilitating the formation of an α-hydroxyenone to the isomeric ketonic product. Dehydration of **X** to the cationic intermediate **XI**, provides the basis for the intramolecular cyclisation of **XII** to form the furan framework of **XIII**. Deprotonation followed by resonance delocalisation results in the formation of the desired 2,3,5-trisubstituted furan.



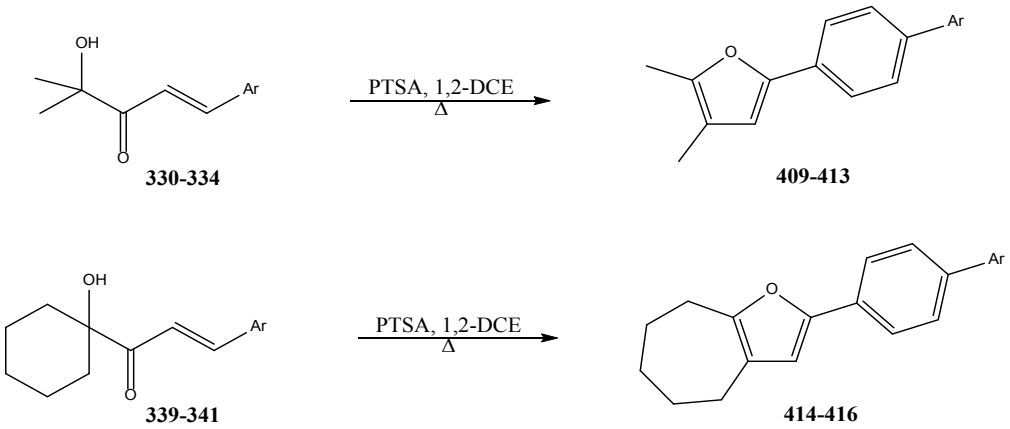
Scheme 2.6.1.4

2.6.2 Thermal Synthesis of 2,3,5-Trisubstituted Furans

Given the transformation that we unearthed, it was decided to extend the scope of the reaction to other enones and furanones that we had produced to date. It is interesting to note that when subjected to similar conditions as outlined above, the nitrophenyl substituted compounds proceeded as per the observed formation of **409**, albeit as a minor product in a mixture with the furanone and unreacted enone. When enones **330**, **331**, **335** and **341**, and furanones **349**, **350**, **354** and **361** respectively were subjected to similar treatment *i.e.* PTSA or MSA in refluxing 1,2-dichloroethane, there was no conversion into the respective furans, and therefore the possibility of using a higher boiling point solvent could facilitate driving the reaction to allow for formation of the furan. Use of 1,2-dichlorobenzene made isolation of the crude reaction mixture much more difficult. After basic work-up, removal of the reaction solvent by kugelröhr distillation was required, as opposed to the more standard rotary evaporator for the lower boiling point solvent. As 1,2-dichlorobenzene is a benzene derivative it is more hazardous. Also, given the very high temperatures of these reactions (b.p. 1,2-dichlorobenzene = 180 °C), the ^{1}H NMR spectra of the crude product was often not very clean. The purified furans were separated, isolated and characterised as isolated compounds. The other chromatographic fractions did not yield any identifiable compounds.

These reactions were optimised as far as was possible. The reactions were monitored by TLC analysis of aliquots of the crude reaction mixture for the disappearance of the hydroxyenone. In some cases, there was also evidence of furanone present in the ^{1}H NMR spectra of the isolated crude reaction mixture. The most successful, optimised results of the thermal transformation (Scheme 2.6.2.1) to the furan are summarised in Table 2.6.2.1. Note that our earlier attempts to synthesise the parent enone and furanone of **410** were unsuccessful using the standard conditions employed within this study to furnish enones and furanones. As a result, the aminofuran **410** was accessed *via* the iron/acetic acid mediated reduction of the nitro group of **409** to the corresponding amine using the procedure outlined previously. As this transformation is formally a dehydration process, an experiment was conducted using **334** to investigate if the reaction could be driven to completion using a Dean-Stark water separator. This was unsuccessful in terms of effecting entire reaction completion as there was a ratio of 62:38 **353**:**409** (furanone:furan) observed. It is a route and method that could be further

optimised to explore if it is possible to ensure that reaction completion entirely to the furan occurs.



Scheme 2.6.2.1

Enone	Furan	Ar	Time (h)	Yield (%)[#]	Acid
334	**409**~	4-$NO_2C_6H_4$	18	51	PTSA
N/A*	**410**~	4-$NH_2C_6H_4$	N/A*	71	N/A
330	**411**~	C_6H_5	18	50	PTSA
331	**412**~	4-FC_6H_4	24	60	PTSA
333	**413**~	3-$NO_2C_6H_4$	26	71	PTSA
339	**414**^	3-$NO_2C_6H_4$	18	78	PTSA
340	**415**^	4-$NO_2C_6H_4$	24	67	PTSA
341	**416**^	4-MeC_6H_4	18	52	PTSA

* Fe/AcOH reduction of **409**
# Isolated Yields of Furans
~ 2,3-Dimethyl derivatives
^ Fused Cycloheptyl Derivatives

Table 2.6.2.1 Reaction Time, Yield Data and Acid Employed for Thermal Synthesis of 2,3,5 Trisubstituted Furans **409-416** From Their Parent α-Hydroxyenones

Figure 2.6.2.1 shows the ^{1}H NMR spectrum of furan **410**. It is of a similar nature to the data reported for **409** in Section 2.6.1. The proton resonances for the methyl groups are centred at 1.95 and 2.25 ppm respectively. The broad signal located at *ca*. 3.65 ppm is attributed to the two protons of the amine group. The proton attached to C(4) of the furan ring is centred at 6.23 ppm, and finally the other aromatic protons each resonate as a doublet with the proton attached to ArC(3) located further upfield due to the shielding effect of the amino group.

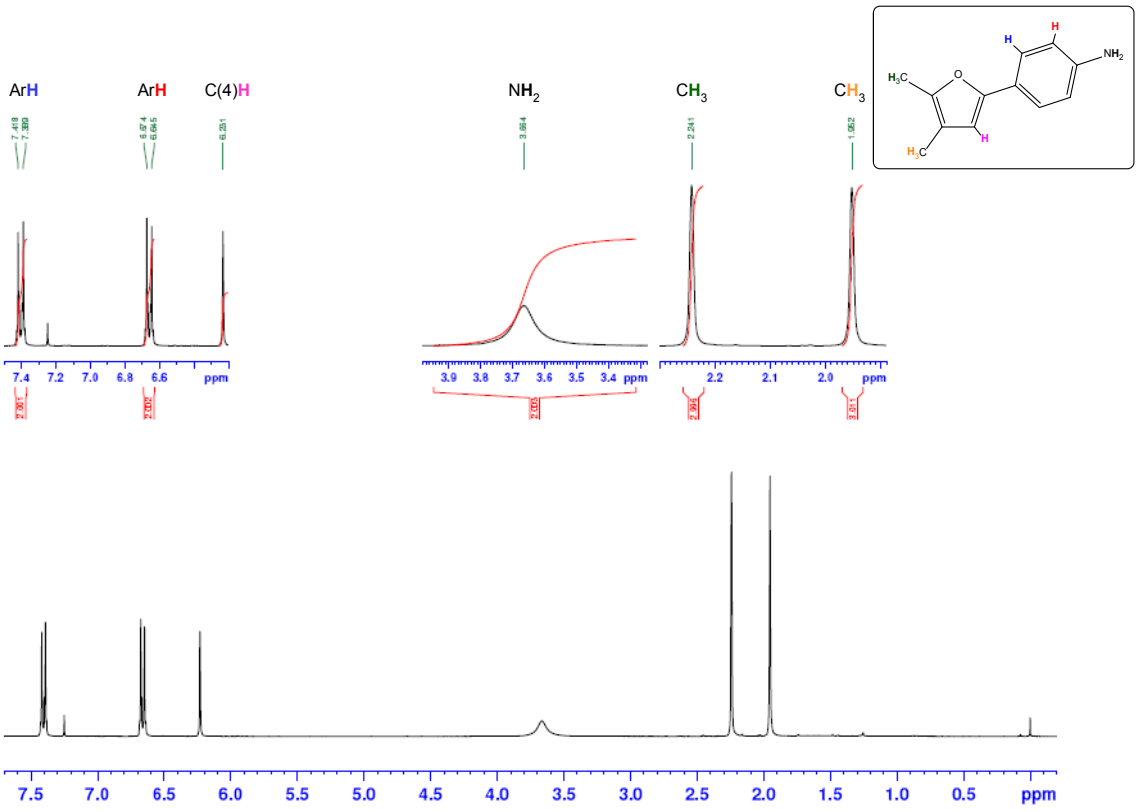
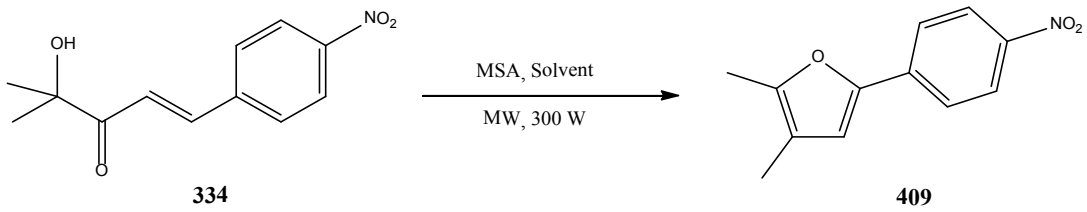


Figure 2.6.2.1 ^{1}H NMR Spectrum of Furan **410** in $CDCl_3$

2.6.3 Microwave Synthesis of 2,3,5-Trisubstituted Furans

Experience within our research group of microwave-mediated organic synthesis led us to attempt to carry out our furan transformation reaction *via* microwave heating in an effort to establish conditions that could be more efficient and possibly cleaner than the thermal methods employed in Section 2.6.2. The starting point for this particular

synthesis was to try and use a solvent other than 1,2-dichlorobenzene to effect a more user friendly and cleaner method to the desired furans. Initial screens were carried out using 1,2-dichlorobenzene and 1,2-dichloroethane to enable a comparison between the two. Thus, compound **334** was treated as per Scheme 2.6.3.1



334 **409**

Scheme 2.6.3.1

The results of the initial screen of reaction conditions are shown in Table 2.6.3.1., and were obtained by integration of the proton at C(2), C(5) and C(4) of the enone, furanone and furan respectively. Those highlighted in yellow are the best results achieved for that particular solvent. As with the thermal method, there was no advantage to using either PTSA or MSA in these reactions (Note that for the results reported below PTSA was the acid used in all cases). Those reactions highlighted in red resulted in decomposition and no products were readily identifiable from the ^{1}H NMR spectra of the crude reaction product material.

Solvent	Temp (°C)	Time (min)	% Enone	% Furanone	% Furan
1,2-DCE	125	10	83	17	-
1,2-DCE	125	20	83	17	-
1,2-DCE	125	30	76	20	4
1,2-DCE	125	60	2	63	35
1,2-DCE	150	60	24	64	12
1,2-DCE	125	90	13	72	15
1,2-DCE	125	120	-	70	30
1,2-DCE	175	120	-	65	35
1,2-DCB	225	60			
1,2-DCB	225	10			
1,2-DCB	225	20			
1,2-DCB	150	10	-	91	9
1,2-DCB	175	10	-	70	30
1,2-DCB	175	30	-	71	29

Table 2.6.3.1 Screen Results for Microwave Conversion of Hydroxyenone **334** into the Furan **409** and Furanone **353**

Given that both the dihydrofuranone and the furan are formed from **334** under the conditions specified in Table 2.6.3.1 and that in some cases, conversion of the hydroxyenone into these products is incomplete, the question arises as to whether or not the matter of kinetic *versus* thermodynamic control is operative in determining the product outcome from treatment of **334** with an acid catalyst in a solvent under reflux. Since the dihydrofuranone **353** is the major product in the lower boiling solvent (1,2-dichloroethane), it is arguably the kinetic product, i.e. the product that is formed fastest when **334** is exposed to an acid. This hypothesis is supported by our observation that when heated independently, furanone **353** produced the furan **409** and in addition furanone intermediates were detected when hydroxyenones were heated at reflux in 1,2-dichlorobenzene (refer to Table 2.6.2.1). Clearly, the furan is thermodynamically more stable than the furanone and it is possible that in the higher boiling solvent that the latter compound reverts to the hydroxyenone which then undergoes conversion into the furan by another pathway (Scheme 2.6.1.4). We have not however, carried out any experiments to establish reversal of the dihydrofuranone to the hydroxyenone under acidic catalysis. A

related interesting point is the difference in thermodynamic stability between the hydroxyenone and the furan.

What is obvious from the results above is that both solvents had successful outcomes. However, the reaction time was much shorter in 1,2-dichlorobenzene. This is obviously much more advantageous, however as noted in the Section 2.6.2, the crude reaction mixture was not as clean as in its 1,2-dichloroethane counterpart and the need to remove the solvent by kugelröhr distillation actually negated the time saved on the reaction itself. With this in mind, it was decided to pursue the microwave-mediated synthesis of these compounds using 1,2-dichloroethane as the solvent of choice. We took advantage of the shorter reaction times of the microwave-assisted reactions versus thermal reactions, and were able to screen a broader range of hydroxyenone substrates in a much shorter space of time to produce the optimal conditions that the scope of this work allowed. Table 2.6.3.2 summarises the results of these reactions which were carried out in a closed-vessel microwave reactor and all reactions were performed at 300 W heating power.

Enone	Furan	Ar	Time (h)	Temp (°C)	Furan (%)[#]	Furanone (%)[#]	Acid
334	**409**~	4-$NO_2C_6H_4$	1	175	56	10	PTSA
330	**411**~	C_6H_5	1	190	58	-	MSA
331	**412**~	4-FC_6H_4	0.16	175	48	17	MSA
333	**413**~	3-$NO_2C_6H_4$	1	175	53	9	PTSA
339	**414**^	3-$NO_2C_6H_4$	1	150	64	-	MSA
340	**415**^	4-$NO_2C_6H_4$	1	150	24	-	PTSA
341	**416**^	4-MeC_6H_4	1	150	48	-	PTSA
335	**417**~	4-MeC_6H_4	0.16	175	43	15	MSA

[#] Isolated Yields
~ 2,3-Dimethyl derivatives
^ Fused Cycloheptyl Derivatives

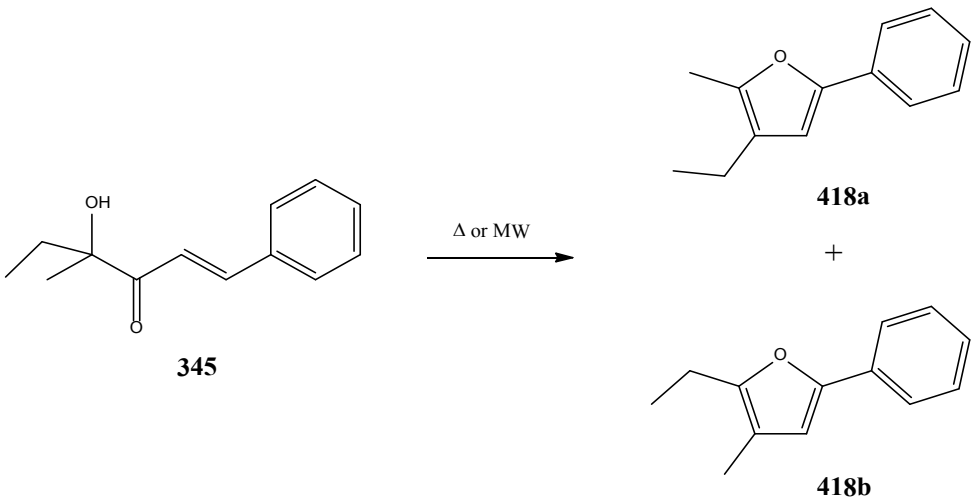
Table 2.6.3.2 Reaction Time and Yield Data for Microwave Induced Synthesis of 2,3,5-Trisubstituted Furans **409-416** From Their Parent α-Hydroxyenones using 1,2-dichloroethane as solvent.

The results in Table 2.6.3.2 show that our study into the feasibility of the microwave synthesis was successful. The interesting point from the results above is that

the compounds that originate from a *gem*-dimethyl enone show more resistance in going to full completion to the furan than those enones that have a cyclohexane group within the molecule; albeit the isolated yields are similar for both classes of compounds. This could be attributed to an enhanced Thorpe-Ingold effect. When the size of the substituent(s) is increased on a tetrahedral centre, the reaction with other parts of the molecule is enhanced *i.e.* the rate acceleration produced in an intramolecular reaction by substitution of hydrogen atoms in the chain linking the two reacting functional groups with alkyl groups.[224-229] In this case increasing from a *gem*-dimethyl group to a spiro-fused cyclohexyl group enhances the reaction and enables it to proceed more efficiently. As the cyclohexyl group is sterically larger, it has the effect of decreasing the angle of the C-OH bond. This, in effect, is 'pushing' the nucleophilic hydroxyl group closer to the electrophilic site, allowing for the ring closing reaction to proceed at an increased rate. The *gem*-dimethyl compounds would of course be expected to react faster than the unsubstituted compound; however the latter substrates have not been investigated. As these reactions were all carried out on a small scale i.e. ≤200 mg, there is potential for yield loss on work-up and purification. A more accurate reflection of the yield of these compounds would be if these reactions could be carried out in the future in a vessel that could accommodate larger amounts.

2.6.4 Investigation of Alkyl Group Migratory Ability

To complete our study into this transformation, we carried out a series of reactions that intended to investigate the migration of different alkyl groups. The substrate of choice was the enone **345** to furnish furans as a mixture of **418a/b**. Compound **345** was subjected to the same conditions that we had developed earlier for the thermal and microwave syntheses (Scheme 2.6.4.1).



Scheme 2.6.4.1

Table 2.6.4.1 summarises the results of the respective reactions carried out in 1,2-dichloroethane and PTSA as the acid catalyst. Both methods yielded a mixture of isomers in exactly the same ratio. The thermally induced furan reaction was not optimised and was only carried out to enable us to have a sample that could be analysed to determine the composition of the isomeric mixture.

Time (h)	Temp (°C)	% Yield	418a:418b
18	Reflux	10	91:9
1	150	39	91:9
0.6	150	67	91:9

Table 2.6.4.1 Results for Cyclisation of Hydroxyenone **345**
Thermal reaction highlighted in yellow, microwave reactions highlighted in pink

As this mixture of furan isomers was inseparable, identification of the respective isomers was much more difficult. It was possible to work out the basic ^{1}H NMR signals using the previously produced furans as a reference and from there to work out the ratio in which each respective isomer was present. To determine the exact structure of each isomer it was necessary to employ 2-dimensional NMR techniques to differentiate between the two isomers. The use of HMBC, HSQC and COSY experiments made it

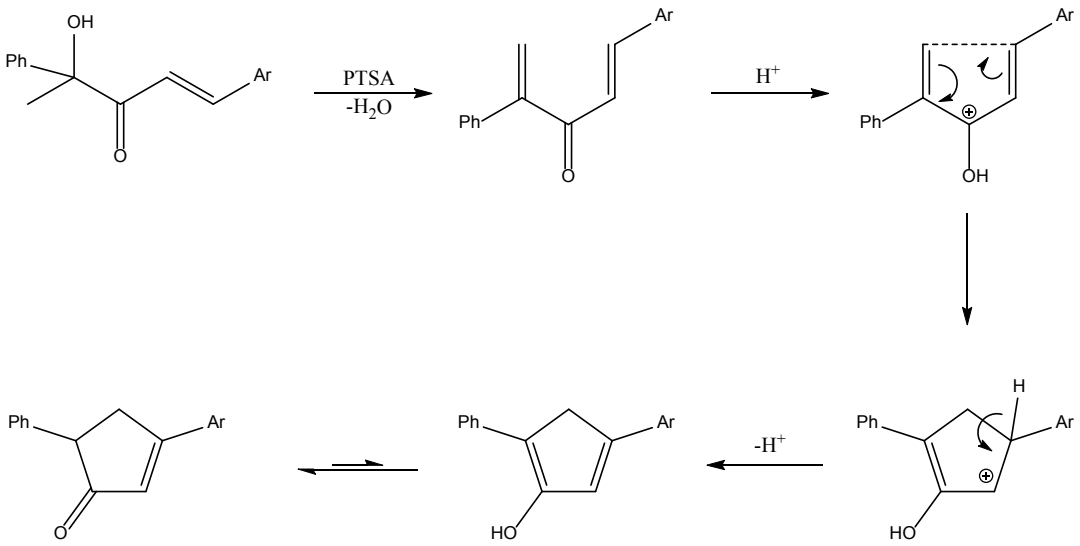
possible to establish that the major product was **418a** with **418b** present as the minor isomer. The HMBC experiments were the most useful in this regard as the presence, and indeed absence, of certain ^{1}H-^{13}C correlations enabled us to assign the correct structure. The proton attached to C(4) of the furan ring of **418a** at 6.49 ppm interacts with the carbon resonances at 18.17 (C(3)**C**H_2CH_3), 122.94 (**C**(3)) and 151.08 (**C**(5)). As this is strong evidence that this proton resides between an ethyl group and C(5), the structure of **418a** could be confirmed. Evidence for **418b** arises from the correlation between the C(4) carbon signal at 108 ppm and the proton resonance of C(3)H_3 at 1.98 ppm, and the absence of a correlation to the ethyl group. This demonstrates that the ethyl group has migrated faster than the methyl group as is commonly expected for in 1,2 rearrangements in Wagner-Meerwein type processes.[230] The migratory aptitudes of groups in 1,2-rearrangements has been summarised by Winstein.[231] While the relative migratory aptitudes of groups in different classes of rearrangements may vary with the substrate and conditions, it is generally accepted that in migrations to cationic centres, the more electron donating group migrates faster, *i.e.* Et >> Me.[232]

There is no doubt that the scope of the overall transformation from enone to furan requires further investigation but there is considerable proof of concept that this is a viable route to functionalised 2,3,5-trisubstituted furans. This transformation would need to be extended to a broader range of enones; incorporating a study on the effect of the substituted aryl moiety, a broader solvent screen and the potential for other catalysts to be investigated.

2.7 Synthesis of Cyclopentenones

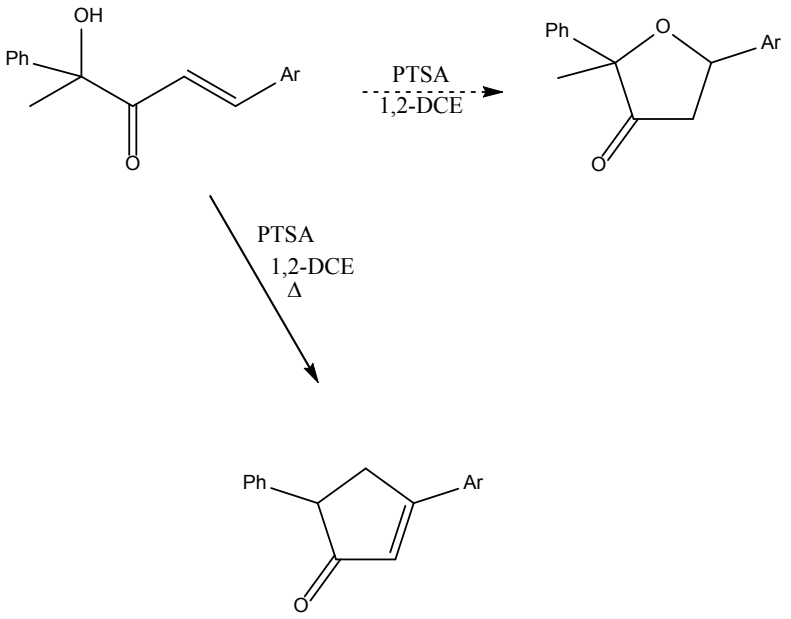
There have been many literature reports of the synthesis of cyclopentenones and the methods employed, including Friedel-Crafts acylation of vinyl chlorides.[233] However, by far the most common route to cyclopentenones is *via* the Nazarov cyclisation (*i.e.* the acid catalysed conversion of a divinyl ketone into a cyclopentenone).[234-236] Activation of the ketone by the acid catalyst generates a pentadienyl cation which undergoes a thermally allowed 4π conrotatory electrocyclisation.[237] This generates an oxyallyl cation which undergoes an elimination reaction to lose a β-hydrogen. Tautomerisation of the resulting enol then produces the cyclopentenone product (Scheme 2.7.1).[238, 239]

Although the Nazarov reaction normally involves a divinyl ketone substrate, we did not detect such a species in the cyclisations that we carried out.



Scheme 2.7.1

As discussed in Section 2.2, the attempted synthesis of an unsymmetrical 4,5-dihydrofuranone (from its enone precursor) containing a phenyl and methyl group at the two-position of the dihydrofuranone ring, led to the exclusive formation of a cyclopentenone-type product as shown in Scheme 2.7.2. This was an attempted extension of the experiment described in the preceding section, however this transformation was not observed with other enone systems employed in our work and was exclusively observed for the examples shown below.



Scheme 2.7.2

Table 2.7.1 shows the yield data and IR carbonyl frequency of the cyclopentones synthesised. All compounds were isolated in good to excellent yields after purification, either by recrystallisation or flash chromatography. The characteristic IR carbonyl stretching frequency was observed *ca*. 1690 cm^{-1}, with the corresponding alkene absorption at *ca*. 1590 cm^{-1}.

Cyclopentenone	Ar*	$\nu_{C=C}$ (cm^{-1})	$\nu_{C=O}$ (cm^{-1})	Yield (%)
419	Ph	1599	1695	84
420	4-FC_6H_4	1599	1691	69
421	4-$NO_2C_6H_4$	1587	1699	81

*Refer to Scheme 2.7.1 for structure of the compounds

Table 2.7.1 Yield and IR data for Cyclopentenones **419 - 421**

^{1}H NMR spectra of **419**, **420** and **421** showed that the readily recognisable pair of alkene proton doublets from the parent enone had collapsed and the appearance of a 1H triplet, that is more correctly assigned as a doublet of doublets (*J*=1.8 Hz) at *ca*. 6.60 ppm

was characteristic of the alkene proton adjacent to the carbonyl group. The presence of diastereotopic protons within the molecular structures led to an ABX spin system (similar in type to those observed in Section 2.2.3). The AB portion resonated as a sixteen-line multiplet (essentially a pair of doublet of doublet of doublets) centred at *ca*. 3.35 ppm with the X portion as a doublet of doublets at *ca*. 3.80 ppm. Assignment of the respective aromatic protons was more difficult for the 3,5-diphenyl compound owing to the similar aryl substituents. Two-dimensional NMR experiments i.e. HBMC and HSQC were employed to aid in the differentiation between the two unsubstituted aryl groups. Identification of the 4-fluoro and 4-nitrophenyl derivatives was much more straightforward; with their respective substitution exhibiting characteristic splitting patterns in the ^{1}H NMR spectra. These aromatic signals were located downfield of those in the unsubstituted aryl ring owing to the deshielding effect of the fluoro- and nitro-substituents. Figure 2.7.1 shows the numbering system of the cyclopentenone ring and Figure 2.7.2 shows a typical ^{1}H NMR spectrum of a representative cyclopentenone, **419**.

Cyclopentenone	$\delta_{C(2)H}$ (ppm)	$\delta_{C(4)H}$ (ppm)	$\delta_{C(4)H}$ (ppm)	$\delta_{C(5)H}$ (ppm)
419	6.60	3.13	3.58	3.80
420	6.67	3.17	3.61	3.81
421	6.77	3.19	3.64	3.86

Table 2.7.2 ^{1}H NMR Chemical Shifts of Non-Aromatic Protons in Cyclopentenones **419 - 421**

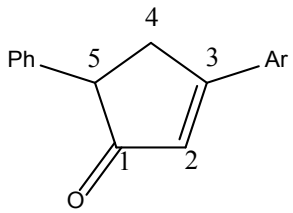


Figure 2.7.1 Numbering System of the Cyclopentenone Ring

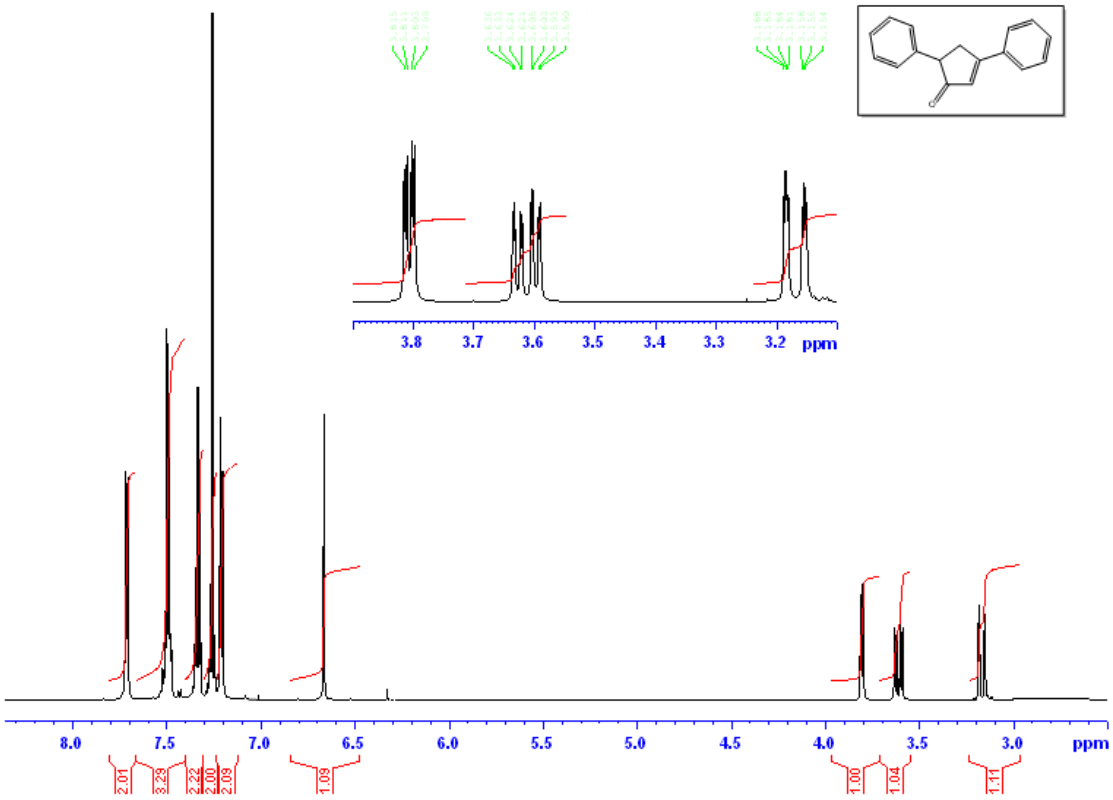


Figure 2.7.2 ^{1}H NMR Spectrum of Cyclopentenone **419** in $CDCl_3$

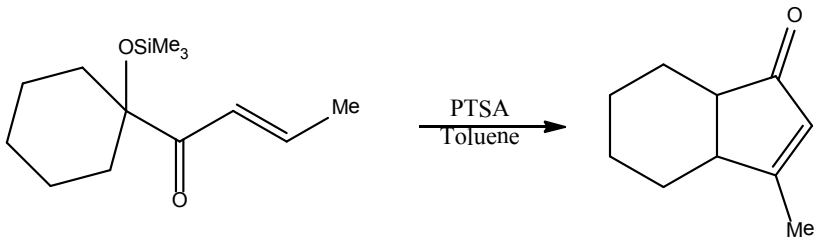
Similarly, assignment of the ^{13}C NMR spectrum of **419** required two-dimensional NMR spectra to distinguish the respective aryl signals. In general for **419**, **420** and **421**, the carbonyl carbon signal space is clearly evident as a resonance at *ca*. 210 ppm. The signal for C(4), as the only CH_2, was observed clearly in the DEPT-135 spectrum at *ca*. 39 ppm with the C(5) signal appearing at *ca*. 52 ppm. The resonances for C(2) and C(3) were observed at *ca*. 126 and 172 ppm respectively. Signals of the aromatic carbons in these spectra were observed from 125 - 135 ppm. As outlined previously, compound **419** required two-dimensional NMR spectra to assign the respective aryl carbon signals with **420** and **421** having signals located downfield of those in the unsubstituted aryl ring owing to the deshielding effect of the fluoro- and nitro substituents.

Cyclopentenone*	$\delta_{C(1)}$	$\delta_{C(2)}$	$\delta_{C(3)}$	$\delta_{C(4)}$	$\delta_{C(5)}$
419	208.42	126.37	172.94	38.48	52.4
420	208.10	126.13	171.48	38.56	52.3
421	207.73	127.32	169.54	38.47	52.4

* ppm in $CDCl_3$

Table 2.7.2 ^{13}C NMR Chemical Shifts of Non-Aromatic Carbons in Cyclopentenones **419 - 421**

Jacobsen[237] reported the conversion of a number of α-hydroxyenones (derived from ethanal) and likewise some α-trimethylsilyloxyenones into cyclopentenones under Nazarov-type conditions (Scheme 2.7.3). It seems however that the process has not been applied to diaryl systems to date, although such compounds have been prepared by other routes[232] involving β-haloenones and boronic acids under Suzuki reaction conditions.



Scheme 2.7.3

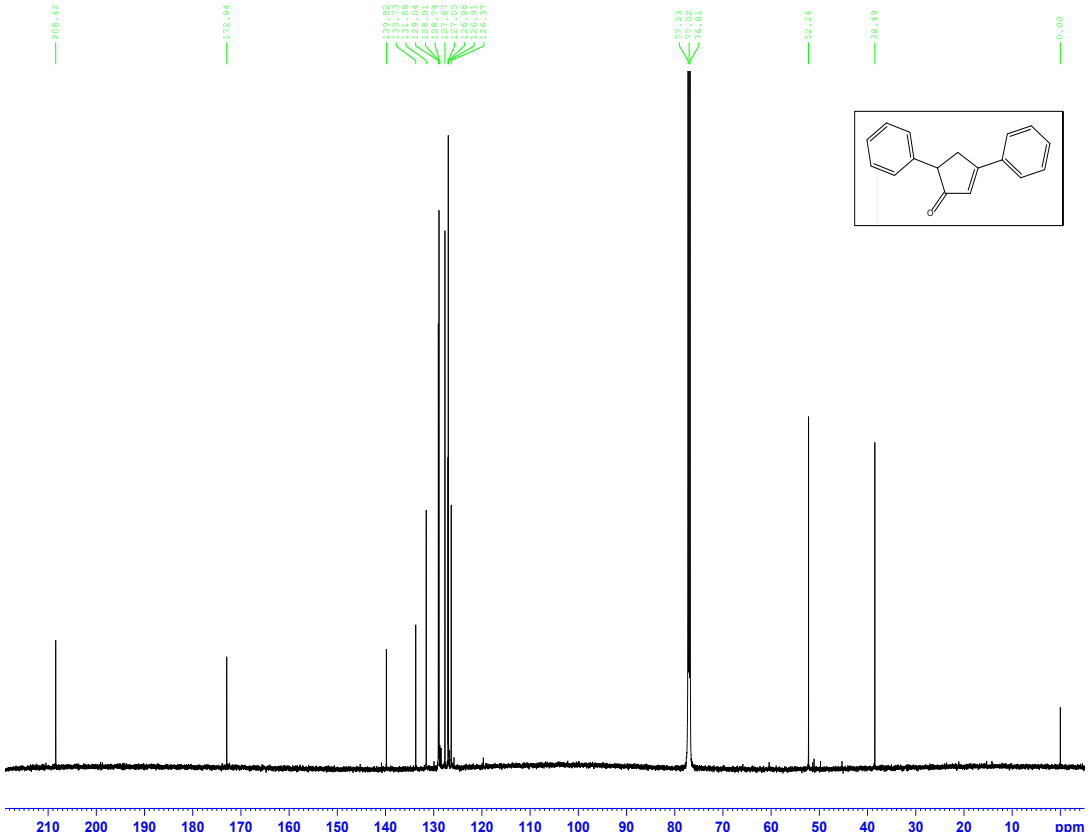


Figure 2.7.3 ^{13}C NMR Spectrum of Cyclopentenone **419** in $CDCl_3$

An X-Ray single crystal structure* of cyclopentenone **419** was also obtained and is shown in Figure 2.7.3.

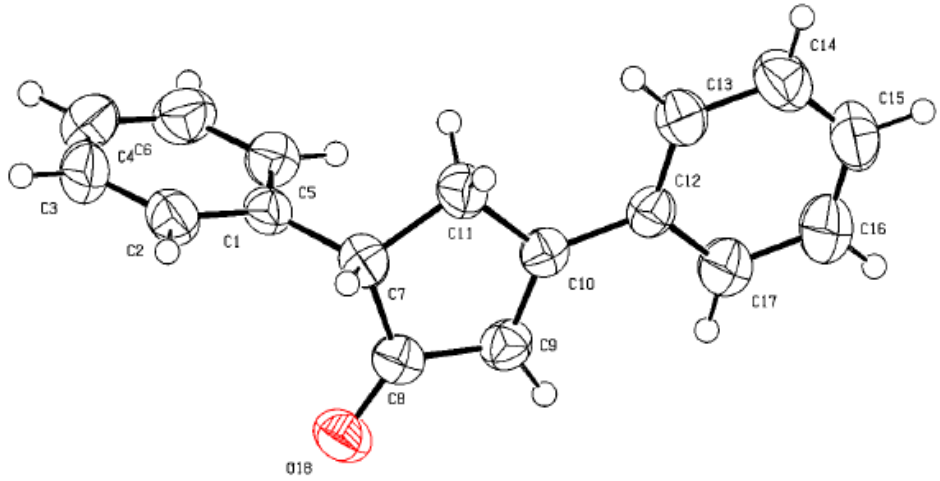


Figure 2.7.4 Crystal Structure of 3,5-Diphenylcyclopent-2-en-1-one **419**

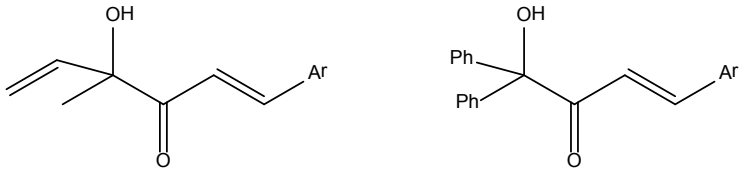
*Structure Determination Carried Out by Dr. Simon Lawrence and Dr. Kevin Eccles, National University of Ireland, Cork.

Conclusions

Our method is suitable for the conversion of aryl substituted α-hydroxyenones into 2,3,5-trisubstituted furans, in synthetically useful quantities when the hydroxyenone contains alkyl groups of the same identity as substituents on the carbon atom contiguous to the carbonyl group, including cyclohexyl derived systems. The latter provide ready access to ring fused furans, which in our view is an advantage over other methods such as the Paal-Knorr or Feist-Benary reactions which require substituted 1,4-diketones and 1,3-dicarbonyl compounds respectively as substrates. The scope of the work described in this section of the thesis was to investigate the viability of this transformation across a range of substituted hydroxyenones/dihydrofuranones and no major optimisation of the process was carried out. This thesis had provided us with proof of concept that this transformation is a viable route, and an interesting investigation to take this transformation forward would be a more in-depth study to determine the impact of the nature of the substituent on the reaction rate. It would also be important to investigate hydroxyenone substrates derived from non-aromatic aldehydes as a route to 2,3,5-trisubstituted furans containing alkyl groups at the five-position of the heterocycle. The compatibility of the furan ring in the product molecular structure with the reaction conditions suggests that α-

hydroxyenones based on heteroaromatic aldehydes would be worth investigating as precursors to more complex furans.

Our observation of competing ethyl and methyl group migrations in an unsymmetrically substituted substrate is clearly a limit but in view of the preferred migration of the ethyl group that we encountered, the process could be useful if the isomeric products can be separated. Our additional observation of a competing process: the conversion of the aryl substituted hydroxyenones into cyclopentenones rather than 4,5-dihydrofuranones or furans is also a disadvantage. It remains to be established how the vinyl **422** and aryl **423** substituted hydroxyenones would behave (Figure 2.7.5).



422 **423**

Figure 2.7.5 Vinyl and Aryl Substituted Hydroxyenones **422** and **423**

Experimental

3.0 Experimental

3.1 General procedures

Solvents were distilled as follows: ethyl acetate from potassium carbonate, dichloromethane from phosphorus pentoxide and hexane was distilled prior to use. THF was freshly distilled from sodium in the presence of benzophenone. Diethyl ether was obtained commercially from Riedel De Haen.

^{1}H NMR spectra were recorded at 300 MHz and 400 MHz on Bruker AVANCE 300 and 400 NMR spectrometers in proton coupled mode. ^{13}C (75.5 MHz) spectra were recorded on a Bruker AVANCE 300 NMR spectrometer with ^{13}C (125 MHz) spectra also recorded on a Bruker AVANCE 600 NMR spectrometer. All spectra were run in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal standard at 20 °C unless otherwise specified. Chemical shifts (δ_H and δ_C) are expressed as parts per million (ppm), positive shifts being downfield from TMS. ^{13}C NMR spectra were assigned with the aid of DEPT experiments. Compounds assigned with the aid of DEPT experiments were assigned by identifying both the carbon type (i.e. CH_3, CH_2, CH or C) and the atom number of the carbon, for example [CH_2, **C**(4)H_2]. Splitting patterns in ^{1}H spectra are designated as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets) and (m) multiplet. Coupling constants are quoted in Hertz (Hz).

Diastereomeric ratios (d.r.) were determined by ^{1}H NMR spectroscopy. When only one diastereomer could be detected, the d.r. is quoted as >98:2.

Where used, a chiral shift study by ^{1}H NMR spectroscopy employed tris-[3-heptafluoropropyl-hydroxymethylene-(+)-camphorato]-europium (III) derivative, [(+)-Eu(hfc)$_3$] as the chiral shift reagent.

Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 and Spectrum-100 instruments. Liquid samples were examined as thin films interspersed between sodium chloride plates. Solid samples were dispersed in potassium bromide and recorded as pressed discs.

The Microanalysis Laboratory, National University of Ireland, Cork, performed elemental analysis using Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers.

Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionisation (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluant; samples were made up in HPLC grade acetonitrile at a concentration of 1 mg/ml and diluted further by the analyst if necessary. High resolution precise mass spectra (HRMS) were recorded on a Waters LCT Premier Tof LC-MS instrument in electrospray ionisation (ESI) mode using 50% acetonitrile-water containing 0.10% formic acid as eluant; samples were made up in HPLC grade acetonitrile.

Melting points were measured on a Thomas Hoover Capillary melting point apparatus. Bulb to bulb distillations were carried out on a Buchi GKR-50 Kugelrohr apparatus and the oven temperature is given as the boiling point of the substrate. Syringe additions were carried out using a Razel Syringe Pump.

Enantiomeric compositions were measured by high performance liquid chromatography (HPLC), using a Chiralpak® AS-H, Chiralcel® OD-H, Chiralcel® OJ-H and Phenomenex® Cellulose-4 column. Details of the column condition and mobile phases are included in Appendix A (Pages 253-258). HPLC analysis was performed on a Waters alliance 2690 separations module. All chiral columns were purchased from Daicel Chemical Industries Limitied. All solvents employed were of HPLC grade. Low temperature chiral HPLC analysis was obtained using an Igloo-Cil® column cooler. PDA detection was used in all cases. When only one single enantiomer could be detected, the enantiomeric excess is quoted as >98%. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at 589 nm in a 10 cm cell; concentrations (*c*) are expressed in g/100 mL. $[\alpha]_D^{20}$ is the specific rotation of a compound and is expressed in units of 10^{-1} deg cm^2 g^{-1}.

Hydrogenation experiments were carried out using a Parr rocking hydrogenator. The hydrogen pressure is quoted for each individual experiment

Single crystal X-ray data was collected by Dr. S. E. Lawrence and Dr. K. S. Eccles, Department of Chemistry, University College Cork. For further details, reference Appendix B.

Organic solutions were dried using magnesium sulphate unless otherwise specified. Thin layer chromatography was performed on precoated silica gel (Merck HF_{254}) plates, compounds were visualised under ultraviolet light (254 nm) and vanillin stain. Wet flash column chromatography was performed using Merck silica gel 60 (typical ratio of silica: crude reaction mixture ~30:1) and the fractions are reported in the order with which they eluted.

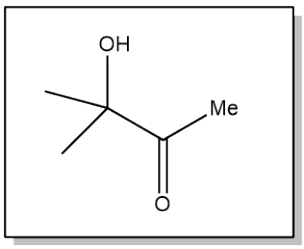
A sample of 1-acetoxybenzotriazole was available from another study in our laboratory. All other materials were commercially available.

3.2 Experimental Procedures

3.2.1 Preparation of 4,5-Dihydro-3(*2H*)-Furanones

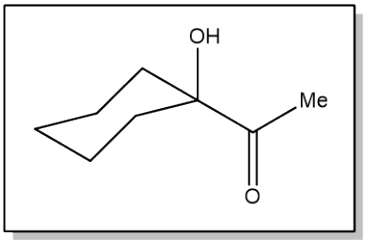
3.2.1.1 α-Hydroxyketones

***3-Hydroxy-3-methylbutan-2-one* 322**



2-Methyl-3-butyne-2-ol (84.10 g, 1.00 mol) was added dropwise to a warm, vigorously stirred mixture of mercuric oxide (13.00 g, 0.06 mol) in water (100 mL) and concentrated sulfuric acid (18 mL), over 1 h at room temperature. The mixture was then heated at 70 °C for 30 min, cooled and filtered through a layer of Celite®. The filter cake was washed with ether (50 mL). The layers from the combined filtrate and washings were separated and the aqueous layer extracted with diethyl ether (5 x 50 mL). The combined organic extracts were washed with water (50 mL) and 5% aqueous sodium bicarbonate (50 mL). The solution was dried, filtered and concentrated to a brown liquid, which was distilled at atmospheric pressure, b.p. 140 °C, (lit.[178] 137-139 °C), to give a clear liquid (29.06 g, 29%). ν_{max}/cm^{-1} (film): 3461, 2981, 1715, 1465, 1139; δ_H (300 MHz): 1.39 [6H, s, (C**H**$_3$)$_2$], 2.26 [3H, s, C**H**$_3$], 3.90 (1H, s, O**H**). Spectroscopic characteristics were in agreement with reported data.[182]

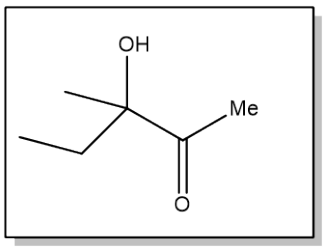
***1-Acetyl-1-cyclohexanol* 323**



1-Ethynyl-1-cyclohexanol (20.00 g, 0.16 mol) was added over 1 h to a vigorously stirred mixture of mercuric oxide (2.07 g, 9.60 mmol) in water (16 mL), 1,4-dioxane (20 mL) and concentrated sulfuric acid (2.90 mL) at room temperature. The mixture was then heated at 70 °C for 30 min, allowed to cool to room temperature and filtered through Celite®. The product was extracted with ether (5 x 40 mL), washed with water (40 mL) and 5% aqueous sodium bicarbonate solution (40 mL). The combined organic extracts were dried and evaporated to a brown oil, which upon vacuum distillation, b.p. 126 °C @ 52 mmHg, (lit.[240] 94 °C @

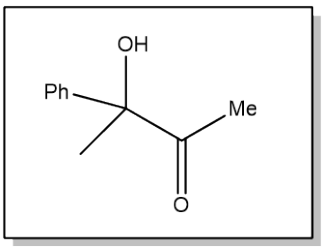
15 mmHg), afforded the product as a clear oil (10.42 g, 46%). ν_{max}/cm^{-1} (film): 3421, 2935, 2859, 1703, 1449, 1150; δ_H (300 MHz): 1.21-1.98 [10H, m, (C**H**$_2$)$_5$], 2.26 [3H, s, C**H**$_3$], 3.50 (1H, s, O**H**). Spectroscopic characteristics were in agreement with reported data.[240]

***3-Hydroxy-3-methylpentan-2-one* 324**



This was prepared following the procedure described for **322**, by dropwise addition of 3-methyl-1-pentyn-3-ol (50.00 g, 0.51 mol) to a vigorously stirred solution of mercuric oxide (10.00 g, 0.05 mol) in water (200 mL) and concentrated sulfuric acid (20 mL). The title compound was isolated as a brown liquid (27.50 g, 46%), used without further purification. ν_{max}/cm^{-1} (film): 3479, 2976, 2938, 1711, 1617, 1460, 1360; δ_H (300 MHz): 0.83 [3H, t, *J*=7.4, C(5)**H**$_3$], 1.36 [3H, s, C(3)C**H**$_3$], 1.74 [2H, q, J=7.4, C(4)**H**$_2$], 2.21 [3H, s, C(1)**H**$_3$], 3.81 (1H, bs, O**H**). Spectroscopic characteristics were in agreement with reported data.[178]

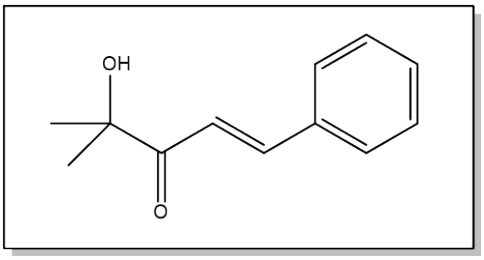
***3-Hydroxy-3-phenylbutan-2-one* 325**



A solution of phenylmagnesium bromide [from magnesium turnings (2.80 g, 0.12 mol) and bromobenzene (16.20 g, 0.10 mol) in ether (80 ml)] was added *via* cannula to an ice cooled solution of diacetyl (8.44 g, 0.10 mol) in dry ether (150 ml) under a nitrogen atmosphere. The reaction was stirred under nitrogen for 16 h and was subsequently quenched with saturated aqueous ammonium chloride (50 mL). The resulting layers were separated and the aqueous layer extracted with ethyl acetate (5 x 50 ml). The combined organic layers were dried and evaporated to yield a dark orange liquid (12.80 g, 78%). ν_{max}/cm^{-1} (film): 3256, 2982, 1713, 1600, 1494, 1355; δ_H (300 MHz): 1.78 [3H, s, C(4)**H**$_3$], 2.08 [3H, s, C(1)**H**$_3$], 4.56 (1H, bs, O**H**), 7.20-7.50 (5H, m, Ar**H**). Spectroscopic characteristics were in agreement with reported data.[185]

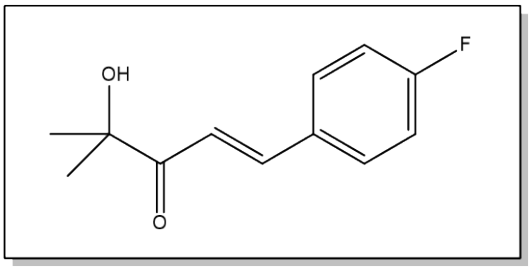
3.2.1.2 α-Hydroxyenones

***E-4-Hydroxy-4-methyl-1-phenylpenten-3-one* 330**



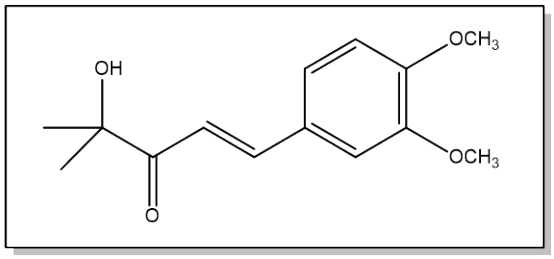
A solution of KOH (21.30 g, 0.38 mol) in ethanol (200 mL) was added dropwise at room temperature over 20 min to a stirring solution of 3-hydroxy-3-methylbutan-2-one **322** (19.40 g, 0.19 mol) and benzaldehyde (20.15 g, 0.19 mol) in the same solvent (100 mL). The mixture was stirred at room temperature for 3 h, after which time IR analysis indicated complete consumption of the starting ketone, and then acidified with 10% aqueous HCl solution. The solvent was evaporated under reduced pressure, and the residue was dissolved in ether (150 mL), washed with water (3 x 100 mL), dried and concentrated *in vacuo* to an orange oil, which was purified by kugelröhr distillation, b.p. 160 °C @ 0.10 mmHg, (lit.[185]160 ºC @ 0.10 mmHg), to yield a yellow oil (25.16 g, 70%). ν_{max}/cm^{-1} (film): 3446, 2976, 1682, 1608, 1070; δ_H (300 MHz): 1.47 [6H, s, (C**H**$_3$)$_2$], 4.17 (1H, bs, O**H**), 7.13 [1H, d, *J*=15.7, C(2)**H**], 7.30-7.70 (5H, m, Ar**H**), 7.83 [1H, d, *J*=15.7, C(1)**H**]. Spectroscopic characteristics were in agreement with reported data.[185]

***E-4-Hydroxy-4-methyl-1-(4-fluorophenyl)-penten-3-one* 331**



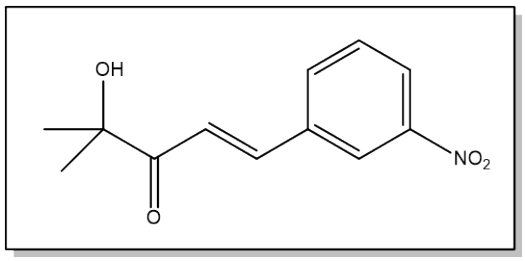
This was prepared following the procedure described for **330**, by adding a solution of KOH (21.30 g, 0.38 mol) in ethanol (300 mL) to **322** (20.00 g, 0.19 mol) and 4-fluorobenzaldehyde (23.58 g, 0.19 mol) in ethanol (100 mL). The *enone* was isolated as a yellow oil (32.47 g, 82%) by flash chromatography, using ethyl acetate/hexane (20:80) as eluant. ν_{max}/cm^{-1} (film): 3441, 2978, 1684, 1614, 1598, 1233, 1159, 1069; δ_H (400 MHz): 1.47 [6H, s, (C**H**$_3$)$_2$], 3.92 (1H, bs, O**H**), 7.01 [1H, d, *J*=15.7, C(2)**H**], 7.11 (2H, t, *J*=8.6, Ar**H**), 7.61 (2H, dd, *J*=5.4, 8.7 Ar**H**), 7.81 [1H, d, *J*=15.7, C(1)**H**]; δ_F (470 MHz): -108.70. Spectroscopic characteristics were in agreement with reported data.[192]

***E*-4-Hydroxy-4-methyl-1-(2,3-dimethoxyphenyl)-penten-3-one 332**



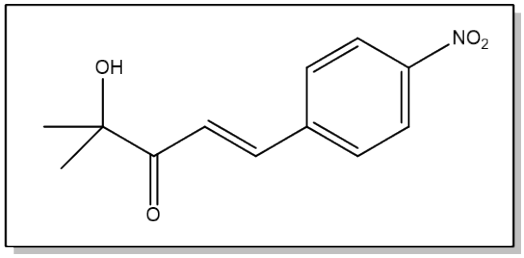
This was prepared following the procedure described for **330**, by adding a solution of KOH (11.22 g, 0.20 mol) in ethanol (200 mL) to **322** (10.50 g, 0.10 mol) and 3,4-dimethoxybenzaldehyde (16.62 g, 0.10 mol) in ethanol (70 mL). The title compound was isolated as a yellow oil (6.92 g, 70%), following kugelröhr distillation b.p. 122 °C @ 0.10 mmHg, (lit.[241] b.p. 120 °C @ 0.10 mmHg). ν_{max}/cm^{-1} (film): 3462, 2975, 1677, 1590, 1512, 1260; δ_H (400 MHz): 1.48 [6H, s, (C**H**$_3$)$_2$], 3.92 [3H, s, OC**H**$_3$], 3.94 [3H, s, OC**H**$_3$], 4.12 (1H, bs, O**H**), 6.89 (1H, d, *J*=8.3, ArC(5)**H**), 6.93 [1H, d, *J*=15.6, C(2)**H**], 7.10 (1H, d, *J*=1.9, ArC(2)**H**), 7.21 (1H, dd, *J*=1.9, 8.3, ArC(6)**H**), 7.80 [1H, d, *J*=15.6, C(1)**H**]. Spectroscopic characteristics were in agreement with reported data.[241]

***E*-4-Hydroxy-4-methyl-1-(3-nitrophenyl)-penten-3-one 333**



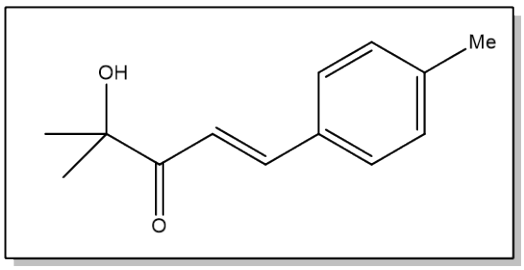
This was prepared following a similar procedure described for **330**, by adding a solution of KOH (10.99 g, 0.20 mol) in 1,4-dioxane (100 mL) and water (50 mL) to **322** (10.00 g, 0.10 mol) and 3-nitrobenzaldehyde (14.81 g, 0.10 mol) in 1,4-dioxane (40 mL). IR analysis indicated reaction completion after 3 h. The reaction mixture was acidified with 10% aqueous HCl solution. The solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (200 mL), washed with water (2 x 75 mL) and brine (100 mL), dried and concentrated to a light brown solid. The title compound was isolated as a pale yellow coloured solid (16.20 g, 70%), following flash chromatography, using ethyl acetate/hexane (10:90) as eluant. m.p.: 80-82 °C (lit.[184] 77-79 ºC); ν_{max}/cm^{-1} (KBr): 3435, 2979, 1690, 1614, 1531, 1350, 1067; δ_H (300 MHz): 1.50 [6H, s, (C**H**$_3$)$_2$], 3.89 (1H, bs, O**H**), 7.19 [1H, d, *J*=15.7, C(2)**H**], 7.62 (1H, t, *J*=8.0, ArC(5)**H**), 7.87 [1H, d, *J*=15.7, C(1)**H**], 7.89 (1H, d, *J*=7.7, ArC(6)**H**), 8.27 (1H, ddd, *J*=0.9, 2.0, 8.0, ArC(4)**H**), 8.47 (1H, t, *J*=2.0, ArC(1)**H**). Spectroscopic characteristics were in agreement with reported data.[184]

***E-4-Hydroxy-4-methyl-1-(4-nitrophenyl)-penten-3-one* 334**



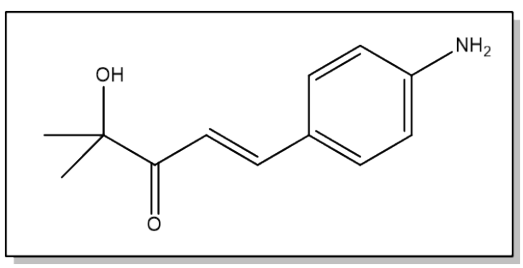
This was prepared following the procedure described for **333**, by adding a solution of KOH (0.54 g, 9.80 mmol) in 1,4-dioxane (15 mL) and water (5 mL) to **1** (0.50 g, 4.90 mmol) and 4-nitrobenzaldehyde (0.74 g, 4.90 mmol) in 1,4-dioxane (10 mL). The title compound was isolated as a mustard coloured solid (0.93 g, 81%), following flash chromatography, using ethyl acetate/hexane (10:90) as eluant. m.p.: 106-109 °C (lit.[184] 101-103 ºC); ν_{max}/cm^{-1} (KBr): 3428, 2979, 1688, 1614, 1596, 1519, 1345, 1067; δ_H (400 MHz): 1.49 [6H, s, (C**H**$_3$)$_2$], 3.45 (1H, s, O**H**), 7.18 [1H, d, *J*=15.8, C(2)**H**], 7.76 (2H, d, *J*=8.7, ArC(2)**H**), 7.85 [1H, d, *J*=15.8, C(1)**H**], 8.28 (2H, d, *J*=8.7, ArC(3)**H**). Spectroscopic characteristics were in agreement with reported data.[184]

***E-4-Hydroxy-4-methyl-1-(p-tolyl)-penten-3-one* 335**



This was prepared following the procedure described for **330**, by adding a solution of KOH (11.00 g, 0.10 mol) in ethanol (100 mL) to **322** (10.00 g, 0.20 mol) and 4-methylbenzaldehyde (11.77 g, 0.20 mol) in ethanol (50 mL). The *enone* was isolated as an orange oil (15.75 g, 79%) by flash chromatography, using ethyl acetate/hexane (10:90) as eluant. ν_{max}/cm^{-1} (film): 3457, 2976, 1683, 1604, 1569, 1325, 1169, 1069; δ_H (300 MHz): 1.47 [6H, s, (C**H**$_3$)$_2$], 2.39 [3H, s, C**H**$_3$], 4.07 (1H, bs, O**H**), 6.99 [1H, d, *J*=15.7, C(2)**H**], 7.22 (2H, d, *J*=8.1, ArC(3)**H**), 7.50 (2H, d, *J*=8.1, ArC(2)**H**), 7.84 [1H, d, *J*=15.7, C(1)**H**]. Spectroscopic characteristics were in agreement with reported data.[243]

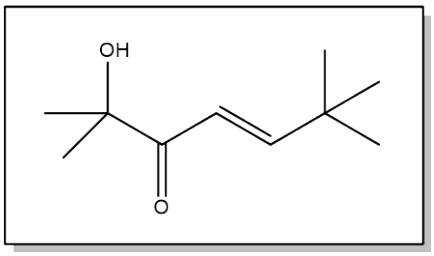
***E-4-Hydroxy-4-methyl-1-(4-aminophenyl)-penten-3-one* 326**



Compound **334** (1.50 g, 5.90 mmol) was dissolved in a mixture of 1,4-dioxane (7.50 mL) and acetic acid (1.10 mL) and the mixture was then brought to a gentle reflux. Iron powder

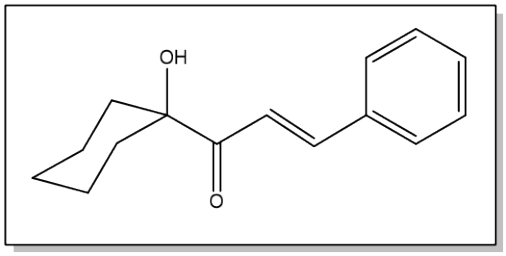
(2.25 g) was added, immediately followed by iron (III) chloride hexahydrate (0.03 g) and the mixture was refluxed for a further 3 h. The mixture was cooled and filtered under vacuum. Ether (50 mL) and water (50 mL) were added to the filtrate and the layers separated. The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic extracts were washed succesively with 5% aqueous sodium bicarbonate (2 x 50 mL), water (2 x 50 mL) and brine (50 mL). The organic layer was dried and concentrated *in vacuo* to yield an orange solid (1.05 g, 87%). m.p.: 86-89 °C; Found C: 69.84, H: 7.21, N: 6.85, $C_{12}H_{15}NO_2$ requires C: 70.22, H: 7.37, N: 6.82; ν_{max}/cm^{-1} (KBr): 3358, 2957, 1663, 1630, 1579, 1517, 1329, 1175, 1072; δ_H (400 MHz): 1.45 [6H, s, (C**H**$_3$)$_2$], 4.06 (2H, bs, N**H**$_2$), 4.18 (1H, s, O**H**), 6.66 (2H, d, *J*=8.5, ArC(3)**H**), 6.81 [1H, d, *J*=15.5, C(2)**H**], 7.44 (2H, d, *J*=8.5, ArC(2)**H**), 7.79 [1H, d, *J*=15.5, C(1)**H**]; δ_C (75.5 MHz): 26.71 [2x**C**H$_3$], 75.27 [**C**(4)], 113.78 (Ar**C**(3)H), 114.79 (Ar**C**(2)H), 124.31 (Ar**C**), 130.82 [**C**(2)H], 146.22 [**C**(1)H], 149.62 (Ar**C**), 202.43 [**C**(3)O]; m/z: 247 $(M+H+CH_3CN)^+$, 206 $(M+H)^+$, 105; HRMS (ES+): Found 206.1182, $C_{12}H_{16}NO_2$ $(M+H)^+$ requires 206.1182. STDEV: 0.50 ppm.

***E-2-Hydroxy-2,6,6-trimethylhept-4-ene-3-one* 328**



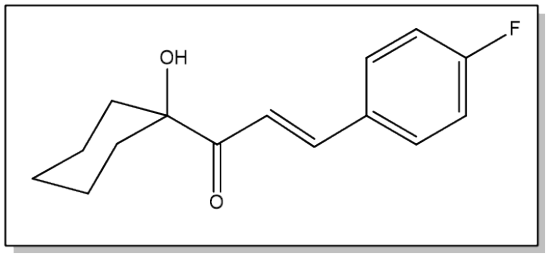
This was prepared following the procedure described for **330**, by adding a solution of KOH (29.17 g, 0.52 mol) in ethanol (150 mL) to a **322** (26.58 g, 0.26 mol) and trimethylacetaldehyde (22.37 g, 0.26 mol) in ethanol (100 mL). The title compound was isolated as a yellow oil (25.11 g, 57%) following flash chromatography using ethyl acetate/hexane (20:80) as eluant. ν_{max}/cm^{-1} (film): 3454, 2967, 2871, 1690, 1619, 1464, 1367; δ_H (300 MHz): 1.13 [9H, s, C(C**H**$_3$)$_3$], 1.46 [6H, s, (C**H**$_3$)$_2$], 4.06 [1H, bs, O**H**], 6.33 [1H, d, *J*=15.0, C(4)**H**], 7.16 [1H, d, *J*=15.0, C(5)**H**]. Spectroscopic characteristics were in agreement with reported data.[241]

***E-1-(1-Hydroxycyclohexyl)-3-phenylprop-2-en-1-one* 336**



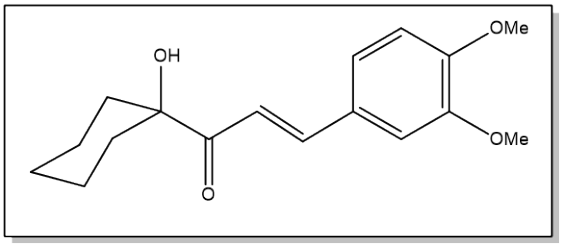
This was prepared following the procedure described for **330**, by adding a solution of KOH (7.85 g, 0.14 mol) in ethanol (150 mL) to 1-acetyl-1-cyclohexanol **323** (10.42 g, 0.07 mol) and benzaldehyde (7.42 g, 0.05 mol) in ethanol (150 mL). The *enone* was purified by flash chromatography using ethyl acetate/hexane (20:80) as eluant, and isolated as a dark gold oil (10.78 g, 69%). ν_{max}/cm^{-1} (film): 3429, 2936, 1674, 1596, 1447, 1119; δ_H (300 MHz): 1.20-2.00 [10H, m, (C**H**$_2$)$_5$], 3.86 [1H, bs, O**H**), 7.10 [1H, d, *J*=15.7, C(2)**H**], 7.30-7.70 (5H, m, Ar**H**), 7.90 [1H, d, *J*=15.7, C(3)**H**]. Spectroscopic characteristics were in agreement with reported data.[185]

***E-1-(1-Hydroxycyclohexyl)-3-(4-fluorophenyl)-prop-2-en-1-one* 337**



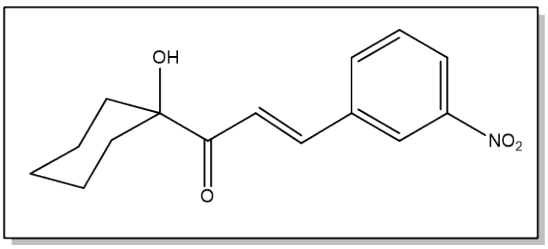
This was prepared following the procedure described for **330**, by adding a solution of KOH (5.50 g, 0.10 mol) in ethanol (50 mL) to a stirred solution of **323** (7.00 g, 0.05 mol) and 4-fluorobenzaldehyde (6.08 g, 0.05 mol) in ethanol (50 mL). The *enone* was purified by flash chromatography using ethyl acetate/hexane (30:70) as eluant, and isolated as a pale yellow solid (10.93 g, 88%). m.p. 70-72 °C; Found C: 72.65, H: 6.89, $C_{15}H_{17}FO_2$ requires C: 72.56, H: 6.90; ν_{max}/cm^{-1} (film): 3449, 2934, 2858, 1679, 1599, 1590, 1448, 1233; δ_H (300 MHz): 1.50-1.85 [10H, m, (C**H**$_2$)$_5$], 3.71 [1H, bs, O**H**), 7.00-7.12 [3H, m, C(2)**H** and ArC(2)**H**], 7.60 (2H, dd, *J*=5.4, 8.7, ArC(3)**H**), 7.78 [1H, d, *J*=15.7, C(3)**H**]; δ_C (75.5 MHz): 21.11, 25.33, 33.76 [3x**C**H$_2$, (**C**H$_2$)$_5$], 77.34 [**C**OH], 116.16 (d, $^2J_{CF}$=22.0, Ar**C**(3)H), 118.50 [**C**(2)H], 130.53 (d, $^3J_{CF}$=8.3, Ar**C**(2)H), 130.72 (d, $^4J_{CF}$=3.8, Ar**C**), 143.91 [**C**(3)H], 164.23 (d, $^1J_{CF}$=252.9, Ar**C**-F), 202.44 [**C**(1)O]; δ_F (470 MHz): -108.90; m/z: 249 $(M+H)^+$, 146, 105, 83; HRMS (ES+): Found 249.1291, $C_{15}H_{18}FO_2$ $(M+H)^+$ requires 249.1290. STDEV: 0.40 ppm.

***E-1-(1-Hydroxycyclohexyl)-3-(3,4-dimethoxyphenyl)-prop-2-en-1-one* 338**



This was prepared following the procedure described for **330**, by adding a solution of KOH (0.80 g, 14.00 mmol) in ethanol (10 mL), **323** (1.00 g, 7.00 mmol) and 3,4-dimethoxybenzaldehyde (1.16 g, 7.00 mmol) in ethanol (10 mL). The *enone* was purified by flash chromatography using ethyl acetate/hexane (30:70) as eluant, and isolated as a yellow oil (1.46 g, 72%). ν_{max}/cm^{-1} (film): 3445, 2978, 1685, 1615, 1590, 1233, 1159, 1068; δ_H (300 MHz): 1.20-1.80 [10H, m, (C**H**$_2$)$_5$], 3.83 [1H, s, O**H**), 3.93 (3H, s, OC**H**$_3$), 3.95 (3H, s, OC**H**$_3$), 7.00-7.12 [3H, m, C(2)**H** and Ar**H**], 7.60 (2H, dd, *J*=5.38, 8.72, Ar**H**), 7.79 [1H, d, *J*=15.7, C(3)**H**]; δ_C (75.5 MHz): 19.25, 23.42, 31.93 [3x**C**H$_2$, (**C**H$_2$)$_5$], 54.11, 54.28 [2xO**C**H$_3$], 75.32 [**C**OH], 108.23 (Ar**C**(2)H), 109.15 (Ar**C**(5)H), 114.51 (Ar**C**(6)H), 121.63 [**C**(2)H], 125.45 (Ar**C**), 143.58 [**C**(3)H], 147.32 (Ar**C**O), 149.79 (Ar**C**O), 200.56 [**C**(1)O]; m/z: 291 $(M+H)^+$, 105; HRMS (ES+): Found 291.1596, $C_{17}H_{23}O_4$ $(M+H)^+$ requires 291.1596. STDEV: 0.00 ppm.

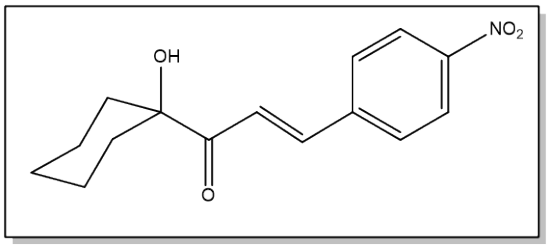
***E-1-(3-(3-Nitrophenylprop-2-enoyl))-1-cyclohexanol* 339**



This was prepared following the procedure described for **333**, by adding a solution of KOH (6.73 g, 0.12 mol) in 1,4-dioxane (100 mL) and water (40 mL) to a solution of **323** (8.50 g, 0.06 mol) and 3-nitrobenzaldehyde (9.07 g, 0.06 mol) in 1,4-dioxane (20 mL). The title compound was isolated as a pale yellow coloured solid (14.35 g, 87%), following flash chromatography, using ethyl acetate/hexane (10:90) as eluant. m.p.: 100-103 °C; Found C: 65.44, H: 6.23, N: 5.06, $C_{15}H_{17}NO_4$ requires C: 65.44, H: 6.22, N: 5.09; ν_{max}/cm^{-1} (KBr): 3462, 2936, 2859, 1683, 1612, 1531, 1353, 1105; δ_H (300 MHz): 1.10-1.90 [10H, s, (C**H**$_2$)$_5$], 3.54 (1H, bs, O**H**) , 7.29 [1H, d, *J*=15.7, C(2)**H**], 7.62 (1H, t, *J*=7.9, ArC(5)**H**), 7.83 [1H, d, *J*=15.7, C(3)**H**], 7.89 (1H, d, *J*=8.0, ArC(6)**H**), 8.27 (1H, ddd, *J*=0.9, 2.1, 8.0, ArC(4)**H**), 8.47 (1H, t, *J*=2.1, ArC(2)**H**); δ_C (75.5 MHz): 21.01, 25.20, 33.55 [3x**C**H$_2$, (**C**H$_2$)$_5$], 76.63 [**C**OH], 121.52 (Ar**C**(6)H), 122.46 [**C**(2)H], 125.10 (Ar**C**(5)H), 130.09 (Ar**C**(4)H), 134.59

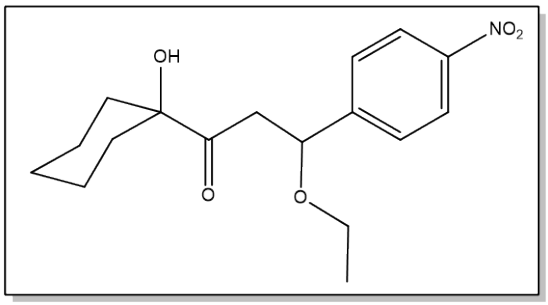
(Ar**C**(2)H), 136.20 (Ar**C**), 142.10 [**C**(3)H], 148.69 (Ar**C**-NO_2), 202.26 [**C**(1)O]; m/z: 276 $(M+H)^+$, 248, 240, 119, 105, 64; HRMS (ES+): Found 276.1236, $C_{15}H_{18}NO_4$ $(M+H)^+$ requires 276.1232. STDEV: 1.40 ppm.

***E-1-(3-(4-Nitrophenylprop-2-enoyl))-1-cyclohexanol* 340**



This was prepared following the procedure described for **330**, by adding a solution of KOH (0.79 g, 14.00 mmol) in 1,4-dioxane (10 mL) and water (5 mL) to **323** (1.00 g, 7.03 mmol) and 4-nitrobenzaldehyde (1.06 g, 7.03 mmol) in 1,4-dioxane (10 mL). The title compound was isolated as bright yellow crystals (1.41 g, 73%), following flash chromatography, using ethyl acetate/hexane (10:90) as eluant. m.p.: 120-122 °C; Found C: 65.46, H: 6.18, N: 5.12, $C_{15}H_{17}NO_4$ requires C: 65.44, H: 6.22, N: 5.09; ν_{max}/cm^{-1} (KBr): 3452, 2935, 2858, 1683, 1613, 1593, 1519, 1345, 1266, 1104; δ_H (400 MHz): 1.20-1.85 [10H, m, $(C\mathbf{H}_2)_5$], 3.43 (1H, bs, O**H**), 7.28 [1H, d, *J*=15.8, C(2)**H**], 7.76 (1H, d, *J*=8.4, ArC(2)**H**), 7.82 [1H, d, *J*=15.8, C(3)**H**], 8.27 (1H, d, *J*=8.4, ArC(3)**H**); δ_C (125 MHz): 21.00, 25.22, 33.72 [3x$\mathbf{C}H_2$, $(\mathbf{C}H_2)_5$], 77.62 [**C**OH], 122.93 [**C**(2)H], 124.18 (Ar**C**(2)H), 129.42 (Ar**C**(3)H), 140.63 (Ar**C**), 141.83 [**C**(3)H], 148.70 (Ar**C**-NO_2), 202.22 [**C**(1)O]; m/z: 276 $(M+H)^+$, 247, 146, 105, 100; HRMS (ES+): Found 276.1236, $C_{15}H_{18}NO_4$ $(M+H)^+$ requires 276.1225. STDEV: 4.00 ppm.

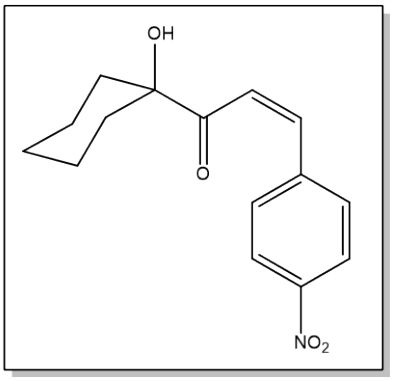
***3-Ethoxy-1-(1-hydroxycyclohexyl)-3-(4-nitrophenyl-)propan-1-one* 347**



This compound (0.73 g) was isolated as an impure sample contaminated with the parent enone in the preparation of **340**, when ethanol was employed as the reaction solvent; δ_H (300 MHz): 1.15 [3H, t, *J*=6.0, $OCH_2C\mathbf{H}_3$], 1.21-1.45 [10H, m, $(CH_2)_5$], 2.69 [2H, 8 lines, AB of ABX, δ_B=3.30, δ_A=2.59, J_{AX}=4.6, J_{BX}=8.9, J_{AB}=15.8, $COC\mathbf{H}_2$], 3.37 [2H, q, *J*=6.0, $OC\mathbf{H}_2CH_3$], 3.48 (1H, bs, O**H**), 4.91 [1H, dd, X of ABX, J_{AX}=4.6, J_{BX}=8.8, C**H**(OEt)], 7.53 (2H, d, *J*=8.7, ArC(2)**H**), 8.22 (2H, d, *J*=8.7, ArC(3)**H**); δ_C(75.5 MHz): 15.17

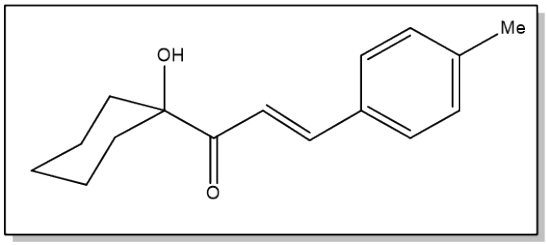
[OCH_2CH_3], 20.91, 33.20, 33.43 [3xCH_2, (CH_2)$_5$], 44.87 [**C**(2)H_2], 65.36 [OCH_2CH_3], 77.54 [**C**(3)H], 78.26 (**C**OH), 123.89 (Ar**C**(3)H), 127.25 (Ar**C**(2)H), 147.61 (Ar**C**), 149.26(Ar**C**-NO_2), 212.26 (**C**(1)O).

***Z-1-(3-(4-Nitrophenylprop-2-enoyl))-1-cyclohexanol* 348**



This compound (0.025 g) was isolated as a bright yellow oil following chromatographic purification of **348**. ν_{max}/cm^{-1} (film): 3425, 2935, 2858, 1686, 1593, 1518, 1353, 1197; δ_H (300 MHz): 1.20-1.85 [10H, m, (CH_2)$_5$], 3.44 (1H, s, O**H**), 6.74 [1H, d, *J*=12.8, C(2)**H**], 7.02 [1H, d, *J*=12.8, C(3)**H**], 7.64 (2H, d, *J*=8.7, ArC(2)**H**), 8.20 (2H, d, *J*=8.7, ArC(3)**H**); δ_C (75.5 MHz): 21.05, 25.21, 33.80 [3xCH_2, (CH_2)$_5$], 78.00 [**C**OH], 123.40 (Ar**C**(2)H), 125.36 [**C**(2)H], 130.15 (Ar**C**(3)H), 140.95 [**C**(3)H], 141.41 (Ar**C**), 147.76 (Ar**C**-NO2), 204.47 [**C**(1)O]; m/z: 276 $(M+H)^+$, 258, 135, 124; HRMS (ES+): Found 276.1232, $C_{15}H_{18}NO_4$ $(M+H)^+$ requires 276.1236. STDEV: 1.40 ppm. The compound isomerises to **340** upon exposure to ambient laboratory conditions.

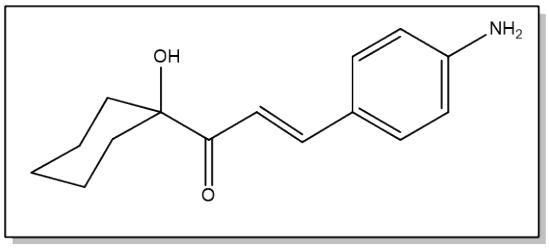
***E-1-(3-(p-Tolylprop-2-enoyl))-1-cyclohexanol* 341**



This was prepared following the procedure described for **330**, by adding a solution of KOH (6.73 g, 0.12 mol) in ethanol (100 mL) to **323** (8.50 g, 0.12 mol) and 4-methylbenzaldehyde (7.20 g, 0.06 mol) in ethanol (50 mL). The *enone* was isolated as a light brown solid (12.63 g, 86%) by flash chromatography, using ethyl acetate/hexane (10:90) as eluant. m.p. 85-87 °C; Found C: 78.56, H: 8.34, $C_{16}H_{20}O_2$ requires C: 78.65, H: 8.25; ν_{max}/cm^{-1} (film): 3459, 2933, 2859, 1674, 1599, 1569, 1325, 1169, 1069; δ_H (300 MHz): 1.50-1.82 [10H, m, (CH_2)$_5$], 2.39 [3H, s, CH_3], 3.84 (1H, bs, O**H**), 7.08 [1H, d, *J*=15.7, C(2)**H**], 7.22 (1H, d, *J*=8.1, ArC(3)**H**), 7.51 (1H, d, *J*=8.1, ArC(2)**H**), 7.82 [1H, d, *J*=15.7, C(3)**H**]; δ_C (75.5 MHz): 21.10, 21.91, 25.37 [3xCH_2, -(CH_2)$_5$-], 33.79 [Ar-CH_3], 76.64 [**C**OH], 117.67 [**C**(2)H],

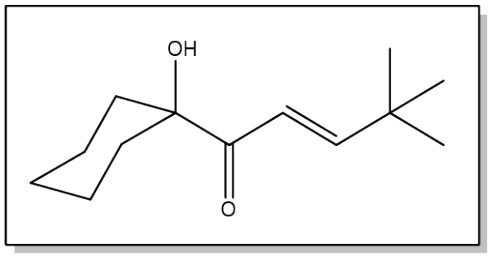
128.66 (Ar**C**(3)H), 129.87 (Ar**C**(2)H), 131.67 (Ar**C**-CH_3), 141.52 [**C**(1)H], 145.43 (Ar**C**), 202.64 [**C**(1)O]; m/z: 246 $(M+H)^+$, 207, 189, 163, 105; HRMS (ES+): Found 246.1589, $C_{16}H_{21}O_2$ $(M+H)^+$ requires 245.1620. STDEV: 2.80 ppm.

***E-1-(3-(4-Aminophenylprop-2-enoyl))-1-cyclohexanol* 327**



This was prepared following the procedure described for **326**, by dissolving **340** (1.00 g, 3.60 mmol) in a mixture of 1,4-dioxane (6.00 mL) and acetic acid (0.69 mL). Subsequent addition of iron powder (1.53 g), immediately followed by iron (III) chloride hexahydrate (0.03 g) and reflux for 3 h led to the title compound being isolated without further purification as an orange solid (0.71 g, 80%). m.p.: 119-122 °C; Found C: 73.52, H: 7.74, N:5.68, $C_{15}H_{19}NO_2$ requires C: 73.44, H: 7.81, N: 5.71; ν_{max}/cm^{-1} (KBr): 3264, 2930, 1664, 1593, 1439, 1258; δ_H (300 MHz): 1.20-1.85 [10H, m, (C**H**$_2$)$_5$], 4.02 (1H, s, O**H**), 4.07 (2H, s, N**H**$_2$), 6.66 [1H, d, *J*=15.5, C(2)**H**], 6.90 (2H, d, *J*=8.6, ArC(3)**H**), 7.44 (2H, d, *J*=8.6, ArC(2)**H**), 7.77 [1H, d, *J*=15.5, C(3)**H**]; δ_C (75.5 MHz): 21.26, 25.40, 33.97 [3x**C**H$_2$, -(**C**H$_2$)$_5$-], 76.64 [**C**OH], 114.07 [**C**(2)H], 114.77 (Ar**C**(3)H), 124.36 (Ar**C**-NH_2), 130.76 (Ar**C**(2)H), 146.47 [**C**(3)H], 149.59 (Ar**C**), 202.53 [**C**(3)O]; m/z: 288, 287 $(M+H+CH_3CN)^+$, 247, 246 $(M+H)^+$; HRMS (ES+): Found 246.1494, $C_{15}H_{20}NO_2$ $(M+H)^+$ requires 246.1492. STDEV: 0.80 ppm.

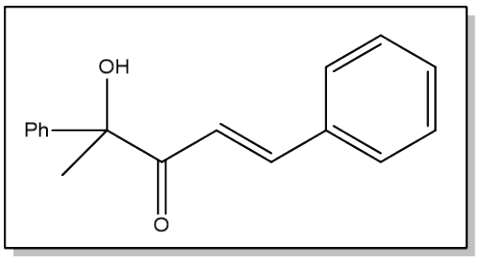
***E-1-Hydroxy-1-cyclohexyl-5,5-dimethyl-hex-3-en-2-one* 329**



This was prepared following the procedure described for **330**, by adding a solution of KOH (3.95 g, 0.04 mol) in ethanol (40 mL) to **323** (5.00 g, 0.08 mol) and trimethylacetaldehyde (3.01 g, 0.04 mol) in ethanol (25 mL). The *enone* was purified by flash chromatography using ethyl acetate/hexane (20:80) as eluant, and isolated as a gold oil (5.09 g, 69%). ν_{max}/cm^{-1} (film): 3459, 2936, 2865, 1683, 1619, 1447, 1302, 1268, 1108; δ_H (300 MHz): 1.11 [9H, s, (C**H**$_3$)$_3$], 1.50-1.80 [10H, m, (C**H**$_2$)$_5$], 3.80

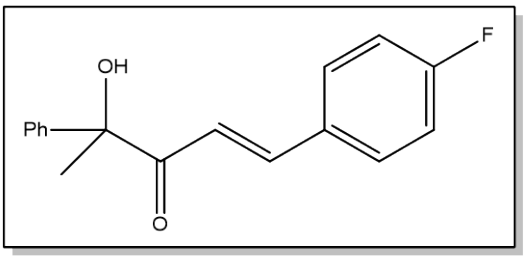
(1H, bs, O**H**), 6.40 [1H, d, *J*=15.6, C(3)**H**], 7.13 [1H, d, *J*=15.6, C(4)**H**]; δ_C (75.5 MHz): 21.11, 25.33, 33.72 [3x**C**H_2, (**C**H_2)$_5$], 28.64 [(**C**H_3)$_3$], 34.14 [**C**(5)], 77.10 [**C**OH], 117.41 [**C**(3)H], 160.27 [**C**(4)H], 203.05 [**C**(1)O]; m/z: 211 $(M+H)^+$, 138, 137; HRMS (ES+): Found 211.1692, $C_{13}H_{23}O_2$ $(M+H)^+$ requires 211.1698. STDEV: 2.8 ppm.

***(±)-E-4-Hydroxy-1,4-diphenyl-1-pent-1-en-3-one* 342**



This was prepared following the procedure described for **330**, by adding a solution of KOH (3.37 g, 0.06 mol) in ethanol (100 mL) to a solution of **325** (5.00 g, 0.03 mol) and benzaldehyde (3.18 g, 0.03 mol) in ethanol (50 mL). The title compound was isolated as a brown oil (6.68 g, 88%). ν_{max}/cm^{-1} (NaCl): 3475, 2958, 1684, 1613, 1500; δ_H (300 MHz): 1.85 [3H, s, C**H**$_3$], 4.73 (1H, s, O**H**), 6.79 [1H, d, *J*=15.7, C(2)**H**], 7.20-7.52 (10H, m, Ar**H**), 7.78 [1H, d, *J*=15.7, C(1)**H**]. Spectroscopic characteristics were in agreement with reported data.[185]

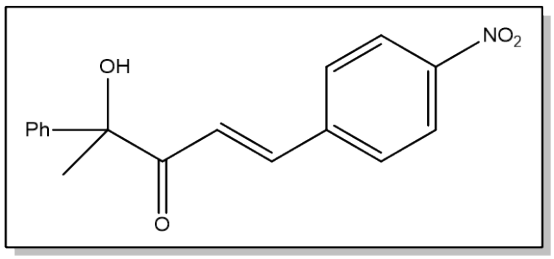
***(±)-E-4-Hydroxy-1-(4-fluorophenyl)-4-phenyl-pent-1-en-3-one* 343**



This was prepared following the procedure described for **330**, by adding a solution of KOH (3.37 g, 0.06 mol) in ethanol (100 mL) to a solution of **325** (5.00 g, 0.03 mol) and benzaldehyde (3.18 g, 0.03 mol) in ethanol (50 mL). The title compound was isolated as a yellow semi-solid (6.31 g, 78%), following flash chromatography, using ethyl acetate/hexane (5:95) as eluant. ν_{max}/cm^{-1} (NaCl): 3461, 3062, 2981, 1679, 1597, 1508, 1319, 1231; δ_H (300 MHz): 1.84 [3H, s, C**H**$_3$], 4.72 (1H, s, O**H**), 6.72 [1H, d, *J*=15.7, C(2)**H**], 7.03 (2H, t, *J*=8.7, ArC(2)**H**-F), 7.25-7.55 (7H, m, Ar**H** and ArC(3)**H**-F), 7.74 [1H, d, *J*=15.7, C(1)**H**]); δ_C (75.5 MHz): 24.27 [**C**(5)H_3], 79.04 [**C**(4)], 116.19 (d, $^2J_{CF}$=22.0, Ar**C**(3)H-F), 118.77 [**C**(2)], 126.30 (Ar**C**H), 128.14 (Ar**C**H), 128.79 (Ar**C**H), 130.44 (d, $^4J_{CF}$=3.3, Ar**C**), 130.61 (d, $^3J_{CF}$=8.6, Ar**C**(2)H-F), 141.35 (Ar**C**(Ph)), 144.06 [**C**(1)], 164.27 (d, $^1J_{CF}$=252.7, Ar**C**-F), 199.54 [**C**(3)O]; δ_F: -

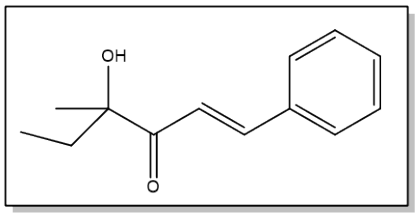
108.12; m/z: 271 $(M+H)^+$, 253, 224, 179, 105, 151, 64; HRMS (ES+): Found 271.1129, $C_{17}H_{16}FO_4$ $(M+H)^+$ requires 271.1134. STDEV: 1.80 ppm.

***(±)-E-4-Hydroxy-1-(4-nitrophenyl)-4-phenyl-pent-1-en-3-one* 344**



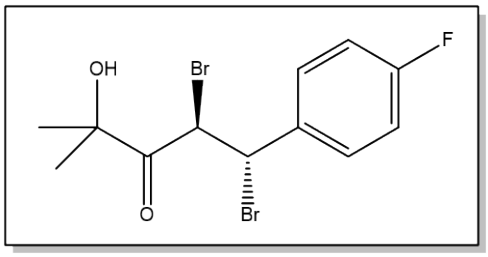
This was prepared following the procedure described for **330**, by adding a solution of KOH (1.35 g, 0.02 mol) in 1,4-dioxane (15 mL) and water (10 mL) to a solution of **325** (2.00 g, 0.01 mol) and 4-nitrobenzaldehyde (1.81 g, 0.01 mol) in 1,4-dioxane (15 mL). The title compound was isolated as a bright yellow oil (2.78 g, 78%), following flash chromatography, using ethyl acetate/hexane (2:98) as eluant. ν_{max}/cm^{-1} (NaCl): 3431, 2979, 1689, 1615, 1597, 1519, 1345, 1049; δ_H (300 MHz): 1.86 [3H, s, C**H**$_3$], 4.41 (1H, s, O**H**), 6.92 [1H, d, *J*=15.8, C(2)**H**], 7.30-7.52 (5H, m, Ar**H**), 7.61 (2H, d, *J*=8.8, ArC(2)**H**-NO_2), 7.77 [1H, d, *J*=15.8, C(1)**H**], 8.21 (2H, d, *J*=8.8, ArC(3)**H**-NO_2); δ_C (75.5 MHz): 24.30 [**C**(5)H_3], 79.36 [**C**(4)], 122.90 [**C**(2)], 124.13 (Ar**C**(2)H-NO_2), 126.22 (Ar**C**H), 128.40 (Ar**C**H), 128.95 (Ar**C**H), 129.15 (Ar**C**(3)H-NO_2), 140.23 (Ar**C**(Ph)), 140.76 (Ar**C**), 142.02 [**C**(1)], 148.71 (Ar**C**-NO_2), 199.13 [**C**(3)O]; m/z: 298 $(M+H)^+$, 280, 251, 244, 196, 151, 122, 105, 64; HRMS (ES+): Found 298.1079, $C_{17}H_{16}NO_4$ $(M+H)^+$ requires 298.1079. STDEV: 0.00 ppm.

***(±)-E-4-Hydroxy-4-methyl-1-phenylhex-1-en-3-one* 345**



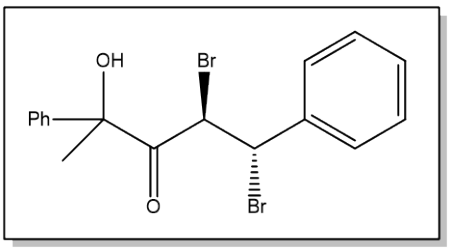
This was prepared following the procedure described for **330**, by adding a solution of KOH (9.65 g, 0.17 mol) in ethanol (100 mL) to a solution of **324** (10.00 g, 0.09 mol) and benzaldehyde (9.13 g, 0.09 mol) in ethanol (50 mL). The title compound was isolated, without purification, as a brown oil (15.12 g, 86%). ν_{max}/cm^{-1} (NaCl): 3466, 2974, 2936, 1682, 1609, 1577, 1450, 1328; δ_H (300 MHz): 0.85 [3H, t, *J*=7.4, C(5)**H**$_3$], 1.44 [3H, s, C(3)C**H**$_3$], 1.83 [2H, q, *J*=7.4, C(4)**H**$_2$], 2.21 [3H, s, C(4)**H**$_3$], 4.32 (1H, bs, O**H**), 7.02 [1H, d, *J*=15.7, C(2)**H**], 7.39-7.44 (3H, m, Ar**H**), 7.57-7.63 (Ar**H**), 7.86 [1H, d, *J*=15.7, C(1)**H**]. Spectroscopic characteristics were in agreement with reported data.[185]

***anti-4,5-Dibromo-2-hydroxy-2-methyl-5-(4-fluorophenyl)-3-pentanone* 366**



Neat bromine (1.15 g, 7.20 mmol) was added dropwise, at room temperature, over 5 min, to a stirring solution of **331** (1.50 g, 7.20 mmol) in dichloromethane (20 mL). The mixture was stirred for 1 h and the solvent evaporated to yield a brown waxy solid (2.11 g, 79%). m.p.: 109-111 °C; ν_{max}/cm^{-1} (KBr): 3432, 2981, 2933, 1721, 1605, 1512, 1228, 1199, 1159; δ_H (300 MHz): 1.53 [3H, s, C**H**$_3$], 1.63 [3H, s, C**H**$_3$], 2.19 (1H, bs, O**H**), 5.41 [1H, d, *J*=11.7, C(5)**H**], 5.63 [1H, d, *J*=11.7, C(4)**H**], 7.09 (2H, t, *J*=8.7, ArC(2)**H**), 7.45 (2H, dd, *J*=5.1, 8.7, ArC(3)**H**); δ_C (75.5 MHz): 27.12 [**C**H$_3$], 28.67 [**C**H$_3$], 44.97 [**C**(5)H], 48.47 [**C**(5)H], 77.22 [**C**(2)], 115.94 (d, $^2J_{CF}$=21.9, Ar**C**(3)H), 130.17 (d, $^3J_{CF}$=8.6, Ar**C**(2)H), 133.86 (d, $^4J_{CF}$=3.4, Ar**C**), 162.92 (d, $^1J_{CF}$=249.5, Ar**C**-F), 205.83 [**C**(3)O]; δ_F: -111.80; m/z: 366 $(M+H)^+$, 331, 295, 223, 171, 95, 81; HRMS (ES+): Found 366.9345, $C_{12}H_{14}{}^{79}Br_2FO_2$ $(M+H)^+$ requires 366.9266. STDEV: 2.50 ppm.

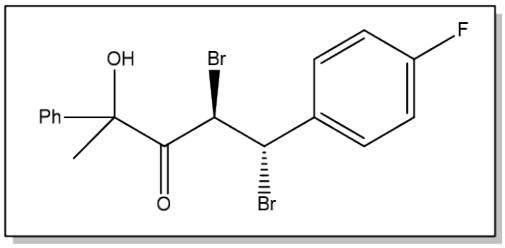
***anti-1,2-Dibromo-4-hydroxy-1,4-diphenyl-3-pentanone* 367**



This was prepared following the procedure described for **366**, by dropwise addition of neat bromine (3.19 g, 0.02 mol) to a stirring solution of **342** (3.90 g, 0.02 mol) in dichloromethane (50 mL). The mixture was stirred for 1 h and the solvent evaporated to yield a brown oil (5.21 g, 82%) in a 71:29 mixture of diastereomers. ν_{max}/cm^{-1} (NaCl): 3501, 3032, 2981, 1723, 1601, 1493, 1208, 1145; δ_H (300 MHz): 1.93 [2.13H, s, C**H**$_3$, major], 1.98 [0.87H, s, C**H**$_3$, major], 3.09 (1H, bs, O**H,** minor), 3.43 (1H, bs, O**H**, major), 5.29 [0.29H, d, *J*=11.6, C(1)**H**, minor], 5.33 [0.71H, d, *J*=11.6, C(1)**H**, major], 5.52 [0.29H, d, *J*=11.6, C(2)**H**, minor], 5.65 [0.71H, d, *J*=11.6, C(2)**H**, major], 7.25-7.50 (10H, m, ArC**H**, both diastereomers); δ_C (75.5 MHz): 26.85 [**C**H$_3$, major], 28.53 [**C**H$_3$, major], 44.15 [**C**(1)H, major], 45.31 [**C**(1)H, minor], 48.49 [**C**(2)H, minor], 49.58 [**C**(2)H, major], 80.59 [**C**(4), major], 80.90 [**C**(4), minor], 125.51 (Ar**C**H, minor), 125.98 (Ar**C**H, major), 126.14 (Ar**C**H, minor), 128.21 (Ar**C**H, major), 128.26 (Ar**C**H, minor), 128.34 (Ar**C**H, major), 128.54 (Ar**C**H, minor), 128.58 (Ar**C**H, major), 128.77 (Ar**C**H, minor), 128.81 (Ar**C**H, major), 129.16 (Ar**C**H, minor), 129.29 (Ar**C**H, major), 137.88 (Ar**C**, major),

138.08 (Ar**C**, minor), 139.68 (Ar**C**, minor), 140.89 (Ar**C**, major), 203.14 [**C**(3)O, minor]. 203.84 [**C**(3)O, major]; m/z: 410 $(M+H)^+$, 372, 320, 235, 142, 83, 60; δ_F: -111.62; HRMS (ES+): Found 410.9595, $C_{17}H_{16}{}^{79}Br_2O_2$ $(M+H)^+$ requires 410.1835. STDEV: 150.00 ppm.

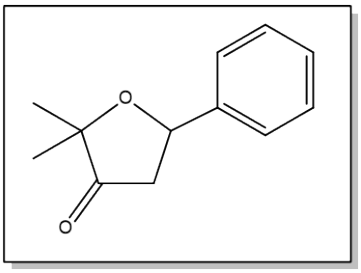
anti-1,2-Dibromo-1-(4-fluorophenyl)-4-hydroxy-4-phenyl-3-pentanone 368



This was prepared following the procedure described for **366**, by dropwise addition of neat bromine (1.76 g, 0.01 mol) to a stirring solution of **343** (3.00 g, 0.01 mol) in dichloromethane (30 mL). The mixture was stirred for 1 h and the solvent evaporated to yield a brown oil (4.41 g, 93%) in a 71:29 mixture of diastereomers. ν_{max}/cm^{-1} (NaCl): 3501, 3032, 2981, 1723, 1601, 1493, 1208, 1145; δ_H (300 MHz): 1.93 [2.13H, s, C**H**$_3$, major], 1.99 [0.87H, s, C**H**$_3$, major], 3.30 (1H, bs, O**H**, both diastereomers), 5.26-5.34 [1H, m, C(1)**H**, both diastereomers], 5.47 [0.29H, d, *J*=11.6, C(2)**H**, minor], 5.59 [0.71H, d, *J*=11.6, C(2)**H**, major], 7.05 (2H, t, *J*=8.7, ArC(2)**H**, both diastereomers), 7.30-7.44 (5H, m, Ar**H**, both diastereomers), 7.56-7.64 (2H, m, Ar**H**, both diastereomers); δ_C (75.5 MHz): 27.45 [**C**H$_3$, major], 28.56 [**C**H$_3$, major], 44.24 [**C**(1)H, major], 45.41 [**C**(1)H, minor], 47.59 [**C**(2)H, minor], 48.68 [**C**(2)H, major], 80.60 [**C**(4), major], 80.92 [**C**(4), minor], 115.85 (d, $^2J_{CF}$=21.9, Ar**C**(3)H, minor), 115.91 (d, $^2J_{CF}$=21.9, Ar**C**(3)H, major), 125.95 (Ar**C**H, major), 126.02 (Ar**C**H, minor), 128.33 (Ar**C**H, minor), 128.42 (Ar**C**H, major), 128.58 (Ar**C**H, minor), 128.63 (Ar**C**H, major), 130.07 (d, $^3J_{CF}$=8.6, Ar**C**(2)H, minor), 130.09 (d, $^3J_{CF}$=8.6, Ar**C**(2)H, major), 133.85 (d, $^4J_{CF}$=3.4, Ar**C**, minor), 134.06 (d, $^4J_{CF}$=3.4, Ar**C**, major), 139.51 (Ar**C**, minor), 140.79 (Ar**C**, minor), 202.98 [**C**(3)O, minor]. 203.78 [**C**(3)O, major]; m/z: 428 $(M+H)^+$, 253, 88, 60; HRMS (ES+): Found 428.9501, $C_{17}H_{16}{}^{79}Br_2O_2$ $(M+H)^+$ requires 428.9505. STDEV: 1.0 ppm.

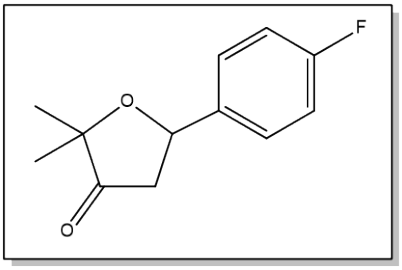
3.2.1.3 Acid Catalysed Cyclisation Reactions Forming 4,5-Dihydrofuran-3-ones

***(±)-2,2-Dimethyl-5-phenyl-4,5-dihydro-3(2H)-furanone* 349**



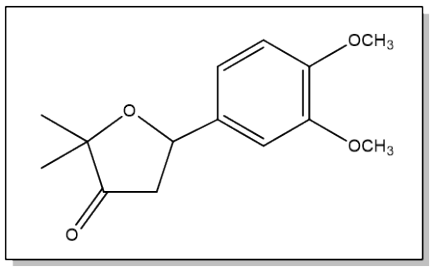
A solution of **330** (25.16 g, 0.13 mol) and PTSA (6.90 g, 0.04 mol) was refluxed in 1,2-dichloroethane (75 mL) for 24 h. The mixture was allowed cool to room temperature, diluted with 1,2-dichloroethane (75 mL), washed with 1M aqueous NaOH (2 x 30 mL), water (2 x 30 mL) and brine (2 x 30 mL). The solution was dried and the solvent evaporated to give a yellow oil (19.64 g). The title compound was isolated as a yellow solid (11.86 g, 48%), by flash chromatography using ethyl acetate/hexane (2:98) as eluant. m.p. 33-35 °C, (lit.[243] 35-36 °C); ν_{max}/cm^{-1} (KBr): 2977, 1756, 1457, 1113; δ_H (300 MHz): 1.32 [3H, s, C**H**$_3$], 1.40 [3H, s, C**H**$_3$], 2.70 [2H, 8 lines, AB of ABX, δ_A=2.50, δ_B=2.90, J_{AX}=6.0, J_{BX}=10.4, J_{AB}=18.2, C(4)**H**$_2$], 5.13 [1H, dd, X of ABX, J_{AX}=6.0, J_{BX}=10.4, C(5)**H**], 7.20-7.50 (5H, m, Ar**H**). Spectroscopic characteristics were in agreement with reported data.[119]

***(±)-2,2-Dimethyl-5-(4-fluorophenyl)-4,5-dihydro-3(2H)-furanone* 350**



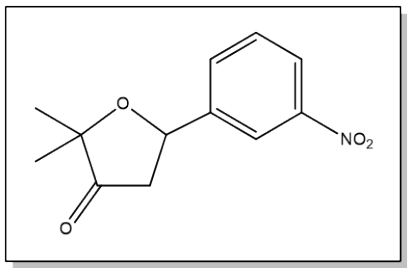
This was prepared following the procedure described for **349,** from **331** (20.00 g, 0.09 mol) and PTSA (3.84 g, 0.04 mol) in 1,2-dichloroethane (200 mL). The title compound was isolated as a brown oil (13.35 g, 67%) by flash chromatography, using ethyl acetate/hexane (20:80) as eluant. ν_{max}/cm^{-1} (film): 2979, 1755, 1607, 1511, 1376, 1222; δ_H (400 MHz): 1.32 [3H, s, C**H**$_3$], 1.40 [3H, s, C**H**$_3$], 2.69 [2H, 8 lines, AB of ABX system, δ_A=2.50, δ_B=2.86, J_{AX}=5.9, J_{BX}=10.5, J_{AB}=18.1, C(4)**H**$_2$], 5.20 [1H, dd, X of ABX, J_{AX}=5.9, J_{BX}=10.5, C(5)**H**], 7.06 (2H, t, *J*=8.6, ArC(2)**H**), 7.39 (2H, dd, *J*=5.4, 8.6, ArC(3)**H**); δ_F (470 MHz): -114.42. Spectroscopic characteristics were in agreement with reported data.[192]

***(±)-2,2-Dimethyl-5-(3, 4-dimethoxyphenyl)-4,5-dihydro-3(2H)-furanone* 351**



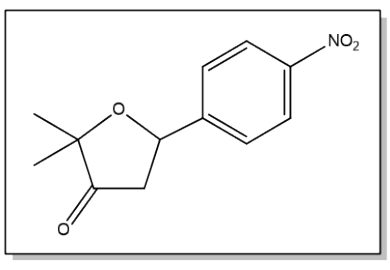
This was prepared following the procedure described for **349** , from **332** (10.00 g, 0.04 mol) and PTSA (0.96 g, 0.01 mmol) in 1,2-dichloroethane (75 mL). Flash chromatography using ethyl acetate/hexane (10:90) as eluant gave (5.80 g, 58%) of dihydrofuranone **351** as a light brown oil. ν_{max}/cm^{-1} (film): 3098, 2973, 1754, 1608, 1556, 1257, 1027; δ_H (300 MHz): 1.32 [3H, s, C**H**$_3$], 1.40 [3H, s, C**H**$_3$], 2.71 [2H, 8 lines, AB of ABX, δ_A=2.57, δ_B=2.85, J_{AX}=5.9, J_{BX}=10.2, J_{AB}=18.2, C(4)**H**$_2$], 3.88 [3H, s, OC**H**$_3$], 3.90 [3H, s, OC**H**$_3$], 5.16 [1H, dd, X, of ABX, J_{AX}=5.9, J_{BX}=10.2, C(5)**H**], 6.70-7.00 (3H, m, Ar**H**). Spectroscopic characteristics were in agreement with reported data.[178]

***(±)-2,2-Dimethyl-5-(3-nitrophenyl)-4,5-dihydro-3(2H)-furanone* 352**



This was prepared following the procedure described for **349**, from **333** (6.50 g, 0.03 mol) and PTSA (3.80 g, 0.02 mol) in 1,2-dichloroethane (150 mL). Flash chromatography using ethyl acetate/hexane (5:95) as eluant gave (3.80 g, 58%) of the title compound as a pale yellow solid. m.p.: 65-66 °C; ν_{max}/cm^{-1} (film): 3082, 2977, 1758, 1603, 1532, 1351, 1112; δ_H (300 MHz): 1.36 [3H, s, C**H**$_3$], 1.44 [3H, s, C**H**$_3$], 2.76 [2H, 8 lines, AB of ABX, δ_A=2.53, δ_B=2.99, J_{AX}=6.1, J_{BX}=10.4, J_{AB}=18.1, C(4)**H**$_2$], 5.34 [1H, dd, X, of ABX, J_{AX} = 6.1, J_{BX} = 10.4, C(5)**H**], 7.59 (1H, t, *J*=7.8, ArC(5)**H**), 7.71 (1H, d, *J*=7.8, ArC(6)**H**), 8.19 (1H, ddd, *J*=0.9, 2.1, 7.8, ArC(4)**H**), 8.30 (1H, t, *J*=2.1, ArC(2)**H**). Spectroscopic characteristics were in agreement with reported data.[184] Furan **91** (1.08 g) was also isolated on purification.

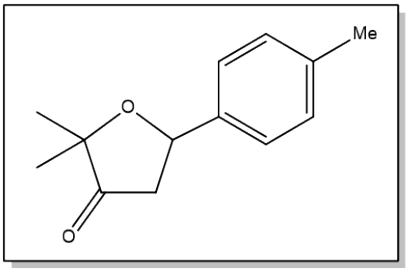
***(±)-2,2-Dimethyl-5-(4-nitrophenyl)-4,5-dihydro-3(2H)-furanone* 353**



This was prepared following the procedure described for **349**, from **334** (20.00 g, 0.08 mol) and methanesulphonic acid (7.70 g, 0.08 mmol) in 1,2-dichloroethane (250 mL). Flash chromatography using ethyl acetate/hexane (10:90)

as eluant gave the title compound (9.78 g, 49%) as an orange solid. m.p.: 55-56 °C; ν_{max}/cm^{-1} (film): 3080, 2979, 1757, 1604, 1521, 1349, 1027; δ_H (400 MHz): 1.35 [3H, s, C**H**$_3$], 1.43 [3H, s, C**H**$_3$], 2.73 [2H, 8 lines, AB of ABX, δ_B=2.97, δ_A=2.49, J_{AX}=6.1, J_{BX}=10.5, J_{AB}=18.1, C(4)**H**$_2$], 5.33 [1H, dd, X, of ABX, J_{AX}=6.1, J_{BX} =10.5, C(5)**H**], 7.59 (2H, d, *J*=8.5, ArC(2)**H**), 8.26 (2H, d, *J*=8.5, ArC(3)**H**). Spectroscopic characteristics were in agreement with reported data.[184] Furan **92** (1.34 g) was also isolated on purification.

***(±)-2,2-Dimethyl-5-(p-tolyl)-4,5-dihydro-3(2H)-furanone* 354**



This was prepared following the procedure described for **349,** from **335** (6.50 g, 0.03 mol) and PTSA (1.90 g, 0.01 mol) in 1,2-dichloroethane (150 mL). The title compound was isolated as a gold oil (4.30 g, 66%) by flash chromatography, using ethyl acetate/hexane (5:95) as eluant. ν_{max}/cm^{-1} (film): 2977, 2928, 1756, 1703, 1606, 1515, 1375, 1171; δ_H (300 MHz): 1.32 [3H, s, C**H**$_3$], 1.39 [3H, s, C**H**$_3$], 2.69 [2H, 8 lines, AB of ABX, δ_A=2.55, δ_B=2.84, J_{AX}=5.9, J_{BX}=10.4, J_{AB}=18.1, C(4)**H**$_2$], 5.17 [1H, dd, X, of ABX, J_{AX}=5.9, J_{BX}=10.4, C(5)**H**], 7.19 (2H, d, *J*=8.0, ArC(3)**H**), 7.30 (2H, d, *J*=8.0, ArC(2)**H**); δ_C (75.5 MHz): 21.21 [Ar-**C**H$_3$], 21.64 [**C**H$_3$], 24.44 [**C**H$_3$], 44.15 [**C**(4)H$_2$], 74.34 [**C**(5)H], 81.37 [**C**(2)], 126.06 (Ar**C**(3)H), 129.35 (Ar**C**(2)H), 137.65 (Ar**C**-Me), 137.97 (Ar**C**), 217.43 [**C**(3)O]; m/z: 244 $(M+H+CH_3CN)^+$, 205 $(M+H)^+$, 203, 187; HRMS (ES+): Found 205.1229, $C_{13}H_{17}O_3$ $(M+H)^+$ requires 205.1224. STDEV: 2.40 ppm.

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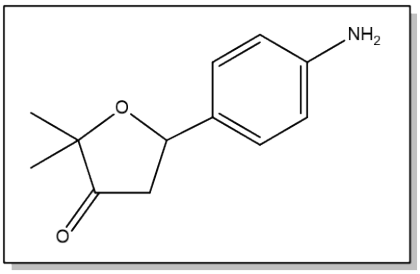
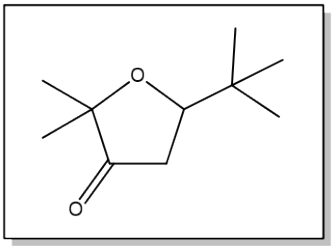
***(±)-2,2-Dimethyl-5-(4-aminophenyl)-4,5-dihydro-3(2H)-furanone* 355**



This was prepared following the procedure described for **326**, by dissolving **353** (0.25 g, 1.06 mmol) in a mixture of 1,4-dioxane (5.00 mL) and acetic acid (0.20 mL). Subsequent addition of iron powder (0.38 g), immediately followed by iron (III) chloride hexahydrate (0.05 g) and reflux for 3 h led to the title compound being isolated as an orange oil (0.21 g, 83%) by flash chromatography, using ethyl acetate/hexane (20:80) as eluant. ν_{max}/cm^{-1}

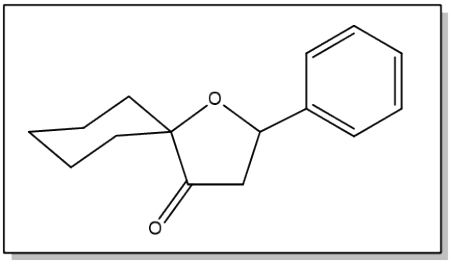
(KBr): 3367, 2976, 2930, 1752, 1626, 1521, 1375, 1170; δ_H (300 MHz): 1.30 [3H, s, C**H**$_3$], 1.37 [3H, s, C**H**$_3$], 2.67 [2H, 8 lines, AB of ABX, δ_A=2.55, δ_B=2.78, J_{AX}=5.9, J_{BX}=10.5, J_{AB}=18.1, C(4)**H**$_2$], 3.73 (2H, bs, N**H**$_2$), 5.09 [1H, dd, X, of ABX, J_{AX}=5.9, J_{BX}=10.5, C(5)**H**], 6.67 (2H, d, J=8.5, ArC(3)**H**), 7.20 (2H, d, J=8.5, ArC(2)**H**); δ_C (75.5 MHz): 21.62 [**C**H$_3$], 24.47 [**C**H$_3$], 44.02 [**C**(4)H$_2$], 74.44 [**C**(5)H], 81.30 [**C**(2)], 115.10 (Ar**C**(3)H), 127.51 (Ar**C**(2)H), 130.01 (Ar**C**-NH$_2$), 146.65 (Ar**C**), 217.97 [**C**(3)O]; m/z: 247 $(M+H+CH_3CN)^+$, 206 $(M+H)^+$, 183, 146, 115, 64; HRMS (ES+): Found 206.1181, $C_{12}H_{16}NO_2$ $(M+H)^+$ requires 206.1182. STDEV: 0.10 ppm.

***(±)-2,2-Dimethyl-5-tert-butyl-4,5-dihydro-3(2H)-furanone* 356**



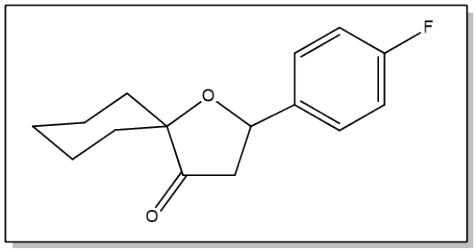
This was prepared following the procedure described for **349** from **328** (25.15 g, 0.14 mol) and PTSA (28.5 g, 0.15 mol) in 1,2-dichloroethane (50 mL) The title compound was isolated as a clear oil (12.77 g, 51%) by vacuum distillation, b.p. 25 °C @ 0.1mmHg (lit.[178] 55 °C @ 4 mmHg). ν_{max}/cm^{-1} (film): 2959, 2870, 1757, 1480, 1194, 1118; δ_H (300 MHz): 0.92 [9H, s, C(C**H**$_3$)$_3$], 1.20 [3H, s, C**H**$_3$], 1.24 [3H, s, C**H**$_3$], 2.34 [2H, dd, AB of ABX system, δ_A=2.32, δ_B=2.35, J_{AX}=7.3, J_{BX}=9.3, J_{AB}=18.3, C(4)**H**$_2$], 3.87 [1H, dd, X of ABX, J_{AX}=7.3, J_{BX}=9.3, C(5)**H**]. Spectroscopic characteristics were in agreement with reported data.[178]

***(±)-2-Phenyl-1-oxaspiro[4.5]decan-4-one* 357**



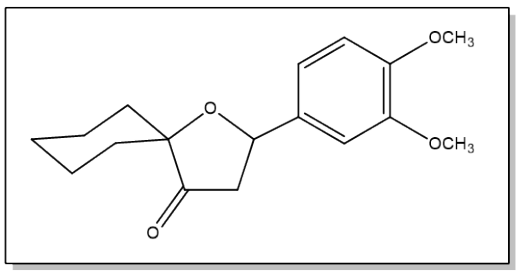
This was prepared following the procedure described for **349**, from **336** (10.78 g, 0.046 mol) and PTSA (4.40 g, 0.023 mol) in 1,2-dichloroethane (100 mL). Compound **357** was isolated as a brown oil (6.93 g, 65%) by flash chromatography, using ethyl acetate/hexane (20:80) as eluant. ν_{max}/cm^{-1} (film): 2939, 1747, 1459, 1048; δ_H (300 MHz): 1.22-1.81 [10H, m, (C**H**$_2$)$_5$], 2.69 [2H, 8 lines, AB of ABX system, δ_A=2.53, δ_B=2.86, J_{AX}=6.1, J_{BX}=10.4, J_{AB}=18.1, C(4)**H**$_2$], 5.20 [1H, dd, X of ABX, J_{AX}=6.1, J_{BX}=10.4, C(5)**H**], 7.25-7.47 (5H, m, Ar**H**). Spectroscopic characteristics were in agreement with reported data.[192]

***(±)-2-(4-Fluorophenyl)-1-oxaspiro[4.5]decan-4-one* 358**



This was prepared following the procedure described for **349**, from **337** (8.09 g, 0.033 mol) and PTSA (6.28 g, 0.033 mol) in 1,2-dichloroethane (75 mL). Compound **358** was isolated as a brown solid (5.57 g, 68%) by flash chromatography, using ethyl acetate/hexane (20:80) as eluant. m.p.: 58-60 °C; Found C: 72.71, H: 6.97, $C_{15}H_{17}FO_2$ requires C: 72.56, H: 6.90; ν_{max}/cm^{-1} (film): 2935, 2858, 1751, 1606, 1511, 1448, 1230; δ_H (300 MHz): 1.30-1.80 [10H, m, (C**H**$_2$)$_5$], 2.66 [2H, 8 lines, AB of ABX system, δ_A=2.48, δ_B=2.84, J_{AX}=6.1, J_{BX}=10.4, J_{AB}=18.0, C(4)**H**$_2$], 5.12 [1H, dd, X of ABX, J_{AX}=6.1, J_{BX}=10.4, C(5)**H**], 7.07 (2H, t, J=8.7, ArC(2)**H**), 7.40 (2H, dd, J=5.4, 8.7, ArC(3)**H**); δ_C (75.5 MHz): 21.10, 21.47, 25.08, 29.32, 33.17 [5xC**H**$_2$, (**C**H$_2$)$_5$], 44.72 [**C**(4)H$_2$], 73.71 [**C**(5)H], 82.98 [**C**(2)], 115.49 (d, $^2J_{CF}$=21.1, Ar**C**(3)H), 127.69 (d, $^3J_{CF}$=8.3, (Ar**C**(2)H), 137.03 (d, $^4J_{CF}$=3.0, Ar**C**), 162.48 (d, $^1J_{CF}$=246.1, Ar**C**-F), 216.61 [**C**(3)O]; δ_F (470 MHz): -114.72; m/z: 247 $(M-H)^-$, 231, 140, 123, 102; HRMS (ES-): Found 247.1134, $C_{15}H_{16}FO_2$ $(M-H)^-$ requires 247.1135. STDEV: 0.40 ppm.

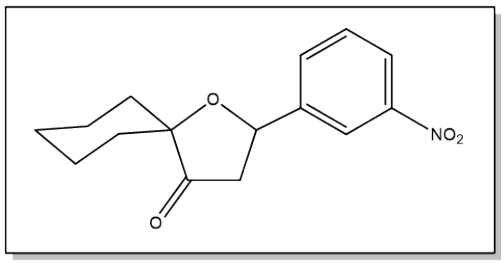
***(±)-2-(3,4-Dimethoxyphenyl)-1-oxaspiro[4.5]decan-4-one* 359**



This was prepared following the procedure described for **349**, from **338** (0.50 g, 1.70 mmol) and PTSA (0.28 g, 1.50 mmol) in 1,2-dichloroethane (20 mL). **359** was isolated as a brown oil (0.18 g, 36%) by flash chromatography, using ethyl acetate/hexane (30:70) as eluant. Found C: 70.00, H: 7.43, $C_{17}H_{22}O_4$ requires C: 70.32, H: 7.64; ν_{max}/cm^{-1} (film): 3090, 2974, 1755, 1610, 1556, 1257, 1030; δ_H (300 MHz): 1.20-1.80 [10H, m, (C**H**$_2$)$_5$], 2.69 [2H, 8 lines, AB of ABX system, δ_A=2.55, δ_B=2.84, J_{AX}=6.1, J_{BX}=10.2, J_{AB}=18.1, C(4)**H**$_2$], 3.89 [3H, s, OC**H**$_3$], 3.91 [3H, s, OC**H**$_3$], 5.15 [1H, dd, X of ABX, J_{AX}=6.1, J_{BX}=10.2, C(5)**H**], 6.85-7.00 (3H, m, Ar**H**); δ_C (75.5 MHz): 21.11, 21.48, 25.11, 29.45, 33.18 [5xC**H**$_2$, (**C**H$_2$)$_5$], 44.65 [**C**(4)H$_2$], 55.91, 56.00, (2xO**C**H$_3$), 74.20 [**C**(5)H], 82.86 [**C**(2)], 109.32 (Ar**C**(2)H), 111.25 (Ar**C**(5)H), 118.45 (Ar**C**(6)H), 148.96 (Ar**C**O), 149.24, (Ar**C**O), 217.08 [**C**(3)O];

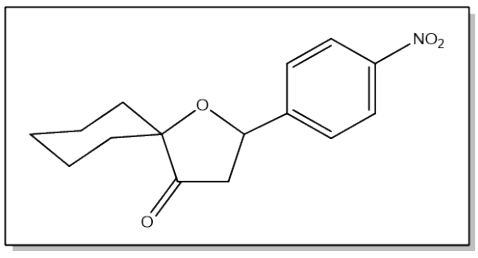
m/z: 291 $(M+H)^+$, 275, 181, 171, 102, HRMS (ES+): Found 291.1590, $C_{17}H_{24}O_4$ $(M+H)^+$ requires 291.1596. STDEV: 2.40 ppm.

***(±)-2-(3-Nitrophenyl)-1-oxaspiro[4.5]decan-4-one* 360**



This was prepared following the procedure described for **349,** from **339** (6.50 g, 0.02 mol), and PTSA (1.90 g, 0.01 mol) in 1,2-dichloroethane (150 mL). The title compound was isolated as a gold oil (4.60 g, 71%) by flash chromatography, using ethyl acetate/hexane (5:95) as eluant. ν_{max}/cm^{-1} (film): 2935, 2860, 1750, 1531, 1448, 1347, 1257; δ_H (300 MHz): 1.32-1.81 [10H, m, (C**H**$_2$)$_5$], 2.73 [2H, 8 lines, AB of ABX system, δ_A=2.51, δ_B=2.96, J_{AX}=6.2, J_{BX}=10.4, J_{AB}=17.9, C(4)**H**$_2$], 5.32 [1H, dd, X of ABX, J_{AX}=6.2, J_{BX}=10.4, C(5)**H**], 7.58 (1H, t, *J*=8.0, ArC(5)**H**), 7.77 (1H, d, *J*=8.0, ArC(6)**H**), 8.19 (1H, ddd, *J*=1.0, 2.1, 8.0, ArC(4)**H**), 8.31 (1H, t, *J*=2.1, C(2)**H**); δ_C (75.5 MHz): 21.09, 21.47, 25.02, 29.30, 33.04 [5xCH_2, (**C**H$_2$)$_5$], 44.33 [**C**(4)H_2], 73.27 [**C**(5)H], 83.33 [**C**(2)], 121.02 (Ar**C**(6)H), 123.00 (Ar**C**(5)H), 129.68 (Ar**C**(4)H), 132.02 (Ar**C**(2)H), 143.54 (Ar**C**-NO_2), 148.47 (Ar**C**), 215.48 [**C**(3)O]; m/z: 276 $(M+H)^+$, 203, 141, 105, 64; HRMS (ES+): Found 276.1243, $C_{15}H_{18}NO_4$ $(M+H)^+$ requires 276.1236 STDEV: 2.5 ppm.

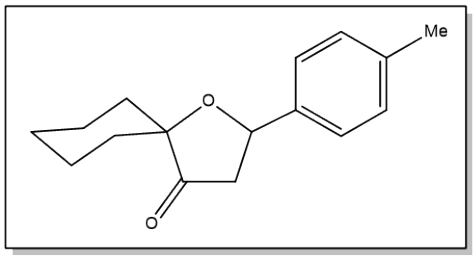
***(±)-2-(4-Nitrophenyl)-1-oxaspiro[4.5]decan-4-one* 346**



This was prepared following the procedure described for **349,** from **340** (12.00 g, 0.04 mol), and methanesulphonic acid (3.27 g, 0.03 mol) in 1,2-dichloroethane (150 mL). The title compound was isolated as an orange solid (8.20 g, 68%) by flash chromatography, using ethyl acetate/hexane (20:80) as eluant. m.p.: 107-110 °C; Found C: 65.71, H: 6.35, N: 4.90, $C_{15}H_{17}NO_4$ requires C: 65.44, H: 6.22, N: 5.09; ν_{max}/cm^{-1} (KBr): 2935, 2860, 1751, 1604, 1521, 1348, 1076; δ_H (400 MHz): 1.30-1.80 [10H, m, (C**H**$_2$)$_5$], 2.71 [2H, 8 lines, AB of ABX system, δ_A=2.47, δ_B=2.95, J_{AX}=6.3, J_{BX}=10.4, J_{AB}=17.9, C(4)**H**$_2$], 5.33 [1H, dd, X of ABX, J_{AX}=6.3, J_{BX}=10.4, C(5)**H**], 7.61

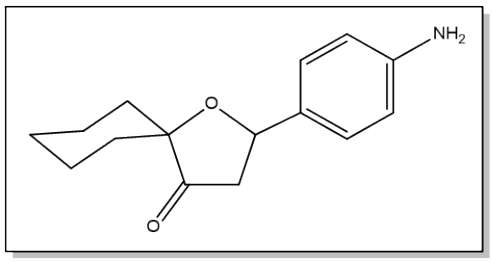
(1H, d, *J*=8.6, ArC(2)**H**), 8.26 (1H, d, *J*=8.6, ArC(3)**H**); δ_C (75.5 MHz): 21.09, 21.47, 25.01, 29.32, 33.16 [5xCH_2, (**C**H_2)$_5$], 44.26 [**C**(4)H_2], 73.31 [**C**(5)H], 83.27 [**C**(2)], 123.91 (Ar**C**(2)H), 126.64 (Ar**C**(3)H), 147.57 (Ar**C**), 148.70 (Ar**C**-NO_2), 215.41 [**C**(3)O]; m/z: 276 $(M+H)^+$, 179, 166, 135, 106, 62; HRMS (ES+): Found 276.1239, $C_{15}H_{17}NO_4$ $(M+H)^+$ requires 276.1236. STDEV: 1.10 ppm. Furan **96** (0.54 g) was also isolated on purification.

***(±)-2-(4-Tolyl)-1-oxaspiro[4.5]decan-4-one* 361**



This was prepared following the procedure described for **349,** from **341** (5.00 g, 0.02 mol), and PTSA (1.90 g, 0.01 mol) in 1,2-dichloroethane (125 mL). The title compound was isolated as a light brown solid (3.40 g, 68%) by flash chromatography, using ethyl acetate/hexane (10:90) as eluant. m.p.: 107-110 °C; Found C: 78.56, H: 8.16, $C_{16}H_{20}O_2$ requires C: 78.65, H: 8.25; ν_{max}/cm^{-1} (film): 2934, 2859, 1750, 1602, 1515, 1447, 1151, 1058; δ_H (300 MHz): 1.20-1.80 [10H, m, (C**H**$_2$)$_5$], 2.36 [3H, s, C**H**$_3$], 2.67 [2H, 8 lines, AB of ABX system, δ_A=2.52, δ_B=2.83, J_{AX}=6.0, J_{BX}=10.4, J_{AB}=18.1, C(4)**H**$_2$], 5.16 [1H, dd, X of ABX, J_{AX}=6.0, J_{BX}=10.4, C(5)**H**], 7.07 (2H, d, *J*=8.0, ArC(3)**H**), 7.40 (2H, d, *J*=8.0, ArC(2)**H**); δ_C (75.5 MHz): 21.19 [ArC-**C**H$_3$], 21.12, 21.49, 25.14, 29.32, 33.18 [5xCH_2, (**C**H_2)$_5$], 44.78 [**C**(4)H_2], 74.24 [**C**(5)H], 82.87 [**C**(2)], 126.04 (Ar**C**(3)H), 129.31 (Ar**C**(2)H), 137.87 (Ar**C**-**C**H$_3$), 138.18 (Ar**C**), 217.39 [**C**(3)O]; m/z: 245 $(M+H)^+$, 224, 182, 163, 100, 77, 46; HRMS (ES+): Found 244.1542, $C_{16}H_{20}O_2$ $(M+H)^+$ requires 244.1546. STDEV: 1.60 ppm.

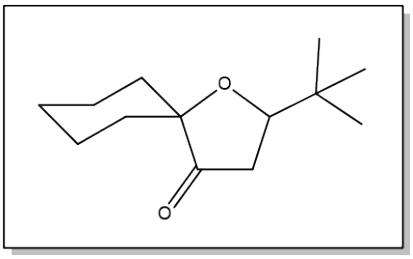
***(±)-2-(4-Aminophenyl)-1-oxaspiro[4.5]decan-4-one* 362**



This was prepared following the procedure described for **326**, by dissolving **346** (0.50 g, 1.82 mmol) in a mixture of 1,4-dioxane (10.00 mL) and acetic acid (0.71 mL). Subsequent addition of iron powder (0.84 g), immediately followed by iron (III) chloride hexahydrate (0.14 g) and reflux for 3 h led to the title compound being

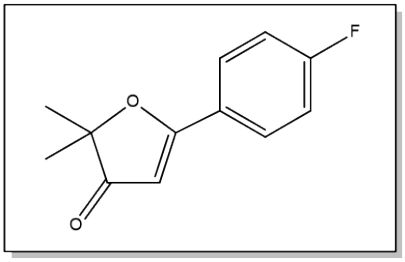
isolated as an orange solid (0.39 g, 87%) by flash chromatography, using ethyl acetate/hexane (20:80) as eluant. m.p.: 80-82 °C; ν_{max}/cm^{-1} (KBr): 3465, 3372, 2933, 2857, 1746, 1622, 1520, 1448, 1347, 1278, 1178; δ_H (300 MHz): 1.39-1.70 [10H, m, (C**H**$_2$)$_5$], 2.64 [2H, 8 lines, AB of ABX, δ_A=2.52, δ_B=2.77, J_{AX}=5.9, J_{BX}=10.4, J_{AB}=18.1, C(4)**H**$_2$], 3.72 (2H, bs, N**H**$_2$), 5.07 [1H, dd, X, of ABX, J_{AX}=5.9, J_{BX}=10.4, C(5)**H**], 6.67 (1H, d, *J*=8.4, ArC(3)**H**), 7.20 (1H, d, *J*=8.4, ArC(2)**H**); δ_C (75.5 MHz): 21.12, 21.49, 25.15, 29.29, 33.20 [5xC**H**$_2$, (**C**H$_2$)$_5$], 44.70 [**C**(4)H$_2$], 74.33 [**C**(5)H], 82.80 [**C**(2)], 115.08 (Ar**C**(3)H), 127.44 (Ar**C**(2)H), 130.66 (Ar**C**-NH$_2$), 146.56 (Ar**C**), 217.82 [**C**(3)O]; m/z: 246 $(M+H)^+$; HRMS (ES+): Found 246.1494, $C_{15}H_{19}NO_2$ $(M+H)^+$ requires 246.1485. STDEV 3.70 ppm.

***(±)-2-tert-Butyl-1-oxaspiro[4.5]decan-4-one* 363**



This was prepared following the procedure described for **349,** from **329** (5.09 g, 0.02 mol) and PTSA (4.50 g, 0.02 mol) in 1,2-dichloroethane (75 mL). The title compound was isolated as a brown oil (4.16 g, 82%) by flash chromatography, using ethyl acetate/hexane (20:80) as eluant; ν_{max}/cm^{-1} (film): 2933, 2859, 1751, 1448, 1364, 1084, 1043; δ_H (300 MHz): 0.94 [9H, s, C(C**H**$_3$)$_3$], 1.40-1.65 [10H, m, (C**H**$_2$)$_5$], 2.31 [2H, d, *J*=8.3, C(4)**H**$_2$], 3.87 [1H, t, *J*=8.3, C(5)**H**]; δ_C (75.5 MHz): 21.09, 21.44, 25.16, 29.25, 32.93 [5xC**H**$_2$, (**C**H$_2$)$_5$], 24.91 [(**C**H$_3$)$_3$], 33.20 [**C**(CH$_3$)$_3$], 80.05 [**C**(5)H], 82.07 [**C**(2)], 218.42 [**C**(3)O]; m/z: 211 $(M+H)^+$, 193, 137, HRMS (ES+): Found 211.1698, $C_{17}H_{23}O_2$ $(M+H)^+$ requires 211.1702. STDEV: 1.90 ppm.

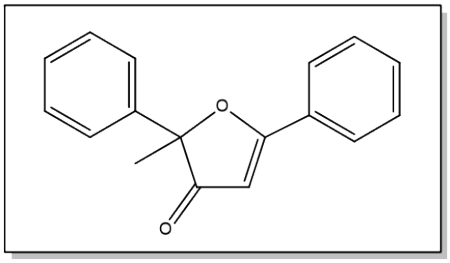
***2,2-Dimethyl-5-(4-fluorophenyl)-3(2H)-furanone* 369**



Sodium hydroxide (0.40 g, 0.01 mol) in ethanol (15 mL) was added dropwise to a stirring solution of **366** (1.93 g, 5.00 mmol) in ethanol (15 mL) and stirred at room temperature for 24 h. The mixture was subsequently acidified with 10% hydrochloric acid and the solvent removed under reduced pressure. The resulting residue was dissolved in ethyl acetate (25

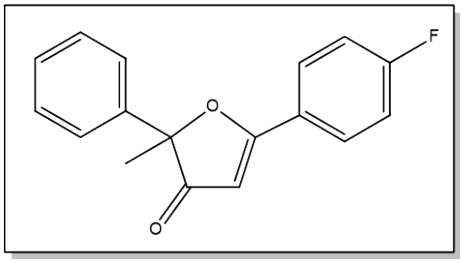
mL), washed with water (3 x 10 mL) and brine (2 x 30 mL). The solution was dried and concentrated under reduced pressure to yield a brown solid. Flash chromatography, using ethyl acetate/hexane (10:90) as eluant yielded the title compound as a brown solid (0.94g, 87%). m.p.: 118-120 °C; Found C: 69.63, H: 5.43, $C_{12}H_{11}FO_2$ requires C: 69.89, H: 5.38; ν_{max}/cm^{-1} (KBr): 3099, 3086, 2980, 2930, 1694, 1610, 1577, 1508, 1419, 1230, 1177, 1158, 1049; δ_H (300 MHz): 1.49 [6H, s, (C**H**$_3$)$_2$, 5.92 [1H, s, C(4)**H**], 7.15 (2H, t, *J*=8.9, ArC(2)**H**), 7.86 (2H, dd, *J*=5.3, 8.9, ArC(3)**H**); δ_C (75.5 MHz): 23.15 [2x**C**H$_3$], 89.17 [**C**(2)], 98.32 [**C**(4)H], 116.14 (d, $^2J_{CF}$=22.2, Ar**C**(3)H), 125.51 (d, $^4J_{CF}$=3.2, Ar**C**), 129.52 (d, $^3J_{CF}$ = 8.9, Ar**C**(2)H), 165.31 (d, $^1J_{CF}$ = 254.4, Ar**C**), 182.22 [**C**(5)], 206.73 [**C**(3)O]; δ_F (470 MHz): -106.00; m/z: 248 $(M+H+CH_3CN)^+$, 207 $(M+H)^+$, 105, 64, HRMS (ES+): Found 207.0827, $C_{12}H_{12}FO_2$ $(M+H)^+$ requires 207.0821. STDEV: 2.90 ppm.

***2-Methyl-2,5-diphenyl-3(2H)-furanone* 370**



This was prepared following the procedure described for **369,** from addition of sodium hydroxide (0.80 g, 0.02 mol) in ethanol (30 mL), to a solution of **367** (4.42 g, 0.01 mol) in ethanol (30 mL). Stirring was continued for 24 h. The title compound was isolated as a yellow oil (1.85 g, 74%) following purification by flash chromatography using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (NaCl): 3062, 3029, 2981, 2931, 1695, 1606, 1568, 1491, 1450, 1356, 1219; δ_H (300 MHz): 1.86 [3H, s, C**H**$_3$], 6.00 [1H, s, C(4)**H**], 7.30-7.40 (5H, m, Ar**H**), 7.50-7.61 (5H, m, Ar**H**); δ_C (75.5 MHz): 24.47 [**C**H$_3$], 90.48 [**C**(2)], 98.76 [**C**(4)H], 124.59 (Ar**C**H), 127.25 (Ar**C**H), 128.12 (Ar**C**H), 128.57 (Ar**C**H), 128.93 (Ar**C**) 128.99 (Ar**C**H), 132.87 (Ar**C**H), 138.40 (Ar**C**), 183.95 [**C**(5)], 204.43 [**C**(3)O]; m/z: 251 $(M+H)^+$, 105, 83, 64, 42, HRMS (ES+): Found 251.1072, $C_{12}H_{15}O_2$ $(M+H)^+$ requires 251.1071. STDEV: 0.40 ppm.

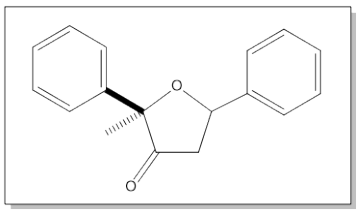
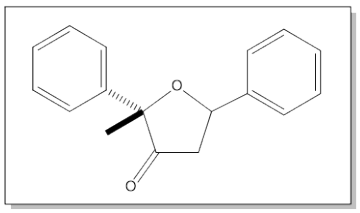
***2-Methyl-2-phenyl-5-(4-fluorophenyl)-3(2H)-furanone* 371**



This was prepared following the procedure described for **369,** from addition of sodium hydroxide (0.80 g,

0.02 mol) in ethanol (40 mL), to a solution of **368** (5.00 g, 0.01 mol) in ethanol (40 mL). Stirring was continued for 24 h. The title compound was isolated as a yellow oil (2.25 g, 69%) following purification by flash chromatography using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (NaCl): 3064, 3028, 2985, 2927, 1693, 1610, 1568, 1453, 1358; δ_H (300 MHz): 1.78 [3H, s, C**H**$_3$], 5.88 [1H, s, C(4)**H**], 7.13 (2H, t, *J*=8.9, ArC(2)**H**), 7.22-7.31 (3H, m, Ar**H**), 7.44-7.49 (2H, m, Ar**H**), 7.86 (2H, dd, *J*=5.3, 8.9, ArC(3)**H**); δ_C (75.5 MHz): 24.46 [**C**H$_3$], 90.64 [**C**(2)], 98.50 [**C**(4)H], 116.35 (d, $^2J_{CF}$=22.1, ArC(3)H), 124.56 (Ar**C**H), 125.21 (d, $^4J_{CF}$=3.3, ArC), 128.20 (Ar**C**H), 128.61 (Ar**C**H), 129.64 (d, $^3J_{CF}$=9.1, Ar**C**), 138.26 (Ar**C**), 165.49 (d, $^1J_{CF}$=254.9, ArC), 182.72 [**C**(5)], 204.18 [**C**(3)O]; δ_F (470 MHz): -106.00; m/z: 269 $(M+H)^+$, 101, 39, HRMS (ES+): Found 269.0978, $C_{17}H_{14}FO_2$ $(M+H)^+$ requires 269.0970. STDEV: 3.00 ppm.

***2-Methyl-2,5-diphenyl-4,5-dihydro-3(2H)-furanone* 365**

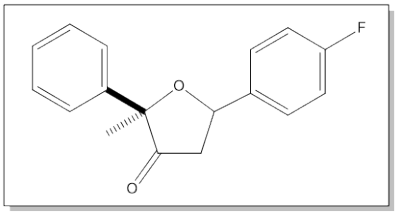
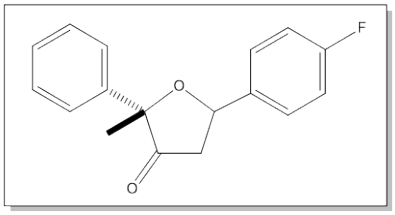



To a solution of chromic acid (4.72 g, 0.04 mol) at 0 °C, was added **372** (1.30 g, 5.11 mmol), in ether (60 mL) and the mixture stirred at this temperature for 30 min, before warming to room temperature with stirring continued for a further 90 min. The mixture was diluted with ether (25 mL), washed with water and saturated sodium bicarbonate solution (2 x 25 mL). The solution was dried and the solvent evaporated to a yellow oil and a mixture of diastereomers, before the title compounds were isolated as gold oils by flash chromatography using ethyl acetate/hexane (2:98) as eluant.

Major Diastereomer **365a**: (0.73 g, 57%); ν_{max}/cm^{-1} (NaCl): 3063, 2975, 2927, 1757, 1683, 1599, 1494, 1360, 1266; δ_H (300 MHz): 1.68 [3H, s, CH_3], 2.72 [2H, 8 lines, AB of ABX, δ_A=2.59, δ_B=2.85, J_{AX}=6.2, J_{BX}=10.1, J_{AB}=18.4, C(4)**H**$_2$], 5.20 [1H, dd, X, of ABX, J_{AX}=6.2, J_{BX}=10.1 C(5)**H**], 7.29-7.60 (10H, m, Ar**H**); δ_C (75.5 MHz): 26.83 [**C**H$_3$], 44.07 [**C**(4)H$_2$], 74.88 [**C**(5)H], 84.84 [**C**(2)], 125.98 (Ar**C**H), 126.31 (Ar**C**H), 127.65 (Ar**C**H), 128.34 (Ar**C**H), 128.60 (Ar**C**H), 128.80 (Ar**C**H), 140.28 (Ar**C**), 141.09 (Ar**C**), 214.25 [**C**(3)O]; m/z: 253 $(M+H)^+$, 235, 143, 64, HRMS (ES+): Found 253.1229, $C_{17}H_{16}FO_2$ $(M+H)^+$ requires 253.1219. STDEV: 4.30 ppm.

Minor Diastereomer **365b**: (0.21 g, 16%); ν_{max}/cm^{-1} (NaCl): 3063, 2975, 2927, 1757, 1683, 1599, 1494, 1360, 1266; δ_H (300 MHz): 1.66 [3H, s, CH_3], 2.79 [2H, 8 lines, AB of ABX, δ_A=2.67, δ_B=2.89, J_{AX}=5.6, J_{BX}=11.2, J_{AB}=17.5, C(4)**H**$_2$], 5.38 [1H, dd, X, of ABX, J_{AX}=5.6, J_{BX}=11.2, C(5)**H**], 7.29-7.70 (10H, m, Ar**H**); δ_C (75.5 MHz): 26.66 [**C**H_3], 44.35 [**C**(4)H_2], 74.73 [**C**(5)H], 84.11 [**C**(2)], 125.14 (Ar**C**H), 126.11 (Ar**C**H), 127.82 (Ar**C**H), 128.35 (Ar**C**H), 128.78 (Ar**C**H), 128.93 (Ar**C**H), 139.02 (Ar**C**), 140.41 (Ar**C**) 213.94 [**C**(3)O]; 253 $(M+H)^+$, 235, 143, 64, HRMS (ES+): Found 253.1229, $C_{17}H_{16}FO_2$ $(M+H)^+$ requires 253.1219. STDEV: 4.00 ppm.

***2-Methyl-2-phenyl-5-(4-fluorophenyl)-4,5-dihydro-3(2H)-furanone* 374**

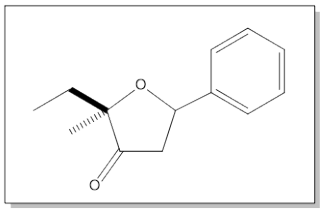
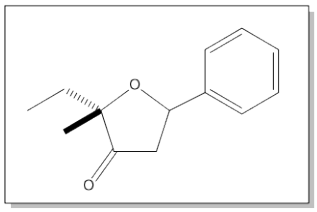
This was prepared following the procedure described for **365**, from addition of **373** (0.27 g, 0.99 mmol), in ether (20 mL) to a solution of chromic acid (0.82 g, 6.93 mmol). The title compounds were isolated as light gold oils following flash chromatography using ethyl acetate:hexane (2:98) as eluant

Major Diastereomer **374a**: (0.16 g, 59%); ν_{max}/cm^{-1} (NaCl): 3061, 2976, 2928, 1758, 1607, 1513, 1447, 1371, 1231; δ_H (300 MHz): 1.66 [3H, s, CH_3], 2.70 [2H, 8 lines, AB of ABX, δ_A=2.55, δ_B=2.85, J_{AX}=6.3, J_{BX}=10.1, J_{AB}=18.5, C(4)**H**$_2$], 5.17 [1H, dd, X, of ABX, J_{AX}=6.3, J_{BX}=10.1, C(5)**H**], 7.11 (2H, t, *J*=8.7, ArC(2)**H**), 7.26-7.42 (3H, m, Ar**H**), 7.49 (2H, dd, *J*=5.3, 8.7, ArC(3)**H**), 7.58 (2H, d, *J*=7.1, Ar**H**); δ_C (75.5 MHz): 26.78 [**C**H_3], 44.07 [**C**(4)H_2], 74.26 [**C**(5)H], 84.91 [**C**(2)], 115.67 (d, $^2J_{CF}$=21.7, Ar**C**(3)H), 125.08 (Ar**C**H), 127.84 (d, $^3J_{CF}$=8.2, Ar**C**(2)H), 127.87 (Ar**C**H), 128.81 (Ar**C**H), 136.17 (d, $^4J_{CF}$=3.1, Ar**C**), 138.82 (Ar**C**), 162.21 (d, $^1J_{CF}$=246.6, Ar**C**-F), 213.58 [**C**(3)O]; δ_F: -104.90; m/z: 271 $(M+H)^+$, 152, 123, 42, HRMS (ES+): Found 271.1134, $C_{17}H_{16}FO_2$ $(M+H)^+$ requires 271.1138. STDEV: 1.50 ppm.

Minor Diastereomer **374b**: (0.05 g, 19%); ν_{max}/cm^{-1} (NaCl): 3061, 2976, 2928, 1758, 1607, 1513, 1447, 1371, 1231; δ_H (300 MHz): 1.67 [3H, s, CH_3], 2.76 [2H, 8 lines, AB of ABX, δ_A=2.62, δ_B=2.88, J_{AX}=5.6, J_{BX}=11.1, J_{AB}=17.5, C(4)**H**$_2$], 5.35 [1H, dd, X, of ABX, J_{AX}=5.6, J_{BX}=11.1, C(5)**H**], 7.11 (2H, t, *J*=8.7, ArC(2)**H**), 7.32-7.42 (3H, m, Ar**H**), 7.44 (2H, dd, *J*=5.5, 8.7, ArC(3)**H**), 7.64 (2H, d, *J*=7.1, Ar**H**); δ_C (75.5 MHz): 23.33

[CH_3], 44.33 [**C**(4)H_2], 74.15 [**C**(5)H], 84.17 [**C**(2)], 115.72 115.15 (d, $^2J_{CF}$=21.7, Ar**C**(3)H), 124.92 (Ar**C**H), 127.72 (Ar**C**H), 128.07 (d, $^3J_{CF}$=8.2, Ar**C**(2)H), 128.39 (Ar**C**H), 136.09 n(d, $^4J_{CF}$=3.0, Ar**C**), 140.96 (Ar**C**), 162.66 (d, $^1J_{CF}$=246.8, Ar**C**-F), 213.92 [**C**(3)O]; δ_F: -113.63; m/z: 271 $(M+H)^+$, 143, 102, 64, 42, HRMS (ES+): Found 271.1134, $C_{17}H_{16}FO_2$ $(M+H)^+$ requires 271.1138. STDEV: 4.80 ppm.

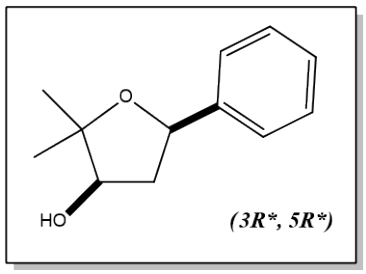
***2-Ethyl-2-methyl-5-phenyl-4,5-dihydro-3(2H)-furanone* 364**

This was prepared following the procedure described for **349,** from **345** (5.00 g, 0.02 mol) and PTSA (0.95 g, 5.00 mmol) in 1,2-dichloroethane (100 mL). The title compound was isolated as a light gold oil (4.20 g, 84%) and a chromatographically inseparable mixture of diastereomers (52:48, major:minor) by flash chromatography, using ethyl acetate/hexane (20:80) as eluant; ν_{max}/cm^{-1} (film): 2975, 2933, 2881, 1755, 1456, 1370, 1113, 1039; δ_H (300 MHz): 0.96 [1.74H, t, *J*=7.4, -$CH_2C\mathbf{H}_3$, major], 0.96 [1.26H, t, *J*=7.4, -$CH_2C\mathbf{H}_3$, minor], 1.27 [1.74H, s, C$\mathbf{H}_3$, major], 1.32 [1.26H, s, C$\mathbf{H}_3$, minor], 1.55-1.84 [2H, m, -$C\mathbf{H}_2CH_3$], 2.35-2.90 [2H, m, C(4)$\mathbf{H}_2$, both diastereomers], 5.14-5.24 [1H, m, C(5)**H**, both diastereomers], 7.25-7.45 [5H, m, Ar**H**].

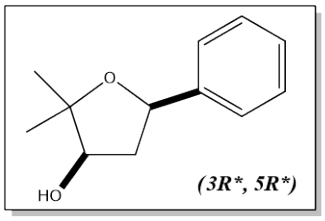
3.2.2 Reduction of 4,5-Dihydro-3(*2H*)-Furanones

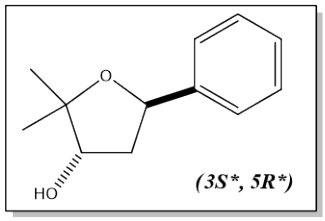
***(±)-2,2-Dimethyl-3-hydroxy-5-phenyltetrahydrofuran* 375**



A flame dried, 100 mL 3-necked flask fitted with septum, thermometer and nitrogen inlet was charged with **349** (1.00 g, 5.28 mmol) in dry THF (40 mL). The solution was cooled to -78 °C. 1M L-Selectride® in THF (11.60 mL, 11.60 mmol) was introduced dropwise to the stirring solution at a rate that ensured the temperature remained at -78 °C. Stirring was continued at -78 °C for 12 h. Saturated aqueous ammonium chloride solution (25 mL) was added and the mixture allowed warm to room temperature. The mixture was then diluted with

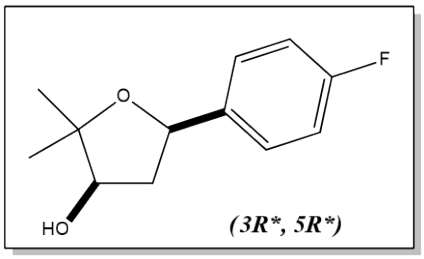
ethyl acetate (75 mL), washed with water (30 mL) and the aqueous layer extracted with ethyl acetate (20 mL). The combined organic layers were washed with 10% aqueous H_2O_2 (3 x 30 mL), water (30 mL), and brine (30 mL). The organic layer was dried, filtered and evaporated to yield a gold oil. Flash chromatography using ethyl acetate/hexane (20:80) as eluant gave the *alcohol* as a pale yellow oil (0.67 g, 66%, d.r. >98:2). ν_{max}/cm^{-1} (film): 3409, 2974, 1457, 1369, 1144, 1096; δ_H (400 MHz): 1.29 [3H, s, CH_3], 1.36 [3H, s, CH_3], 1.89 [1H, ddd, *J*=5.2, 7.6, 13.8, H_A of C(4)**H**$_2$], 2.15 (1H, s, O**H**), 2.68 [1H, ddd, *J*=6.2, 7.6, 13.8, H_B of C(4)**H**$_2$], 4.01 [1H, t, *J*=5.2, C(3)**H**], 4.95 [1H, t, *J*=7.6, C(5)**H**], 7.21-7.43 (5H, m, Ar**H**). Spectroscopic characteristics corresponded directly with those reported for the 3R*, 5R* isomer.[178]





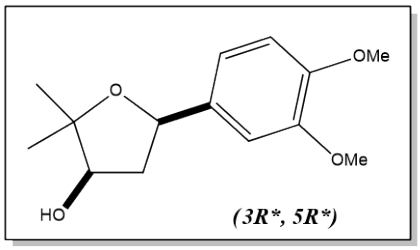
A solution of $NaBH_4$ (0.09 g, 2.60 mmol) in water (5 mL) was added dropwise to a solution of **349** (0.25 g, 1.30 mmol) in methanol (20 mL). The resulting mixture was stirred at room temperature for 1 h, at which time TLC analysis indicated consumption of the starting furanone. Water (40 mL) was added and the resulting cloudy solution extracted with dichloromethane (3 x 40 mL). The combined dichloromethane extracts were washed with water (3 x 50 mL), dried and evaporated to a yellow oil, which was purified by flash chromatography using ethyl acetate/hexane (20:80) as eluant. The *alcohol*, a yellow oil, was isolated along with a chromatographically inseparable mixture of diastereomers (0.30 g, 87%, d.r. 86:14). (Major diastereomer (3R*, 5R*), minor diastereomer (3S*, 5R*)). ν_{max}/cm^{-1} (film): 3414, 2973, 1457, 1368, 1142, 1093; δ_H(300 MHz): 1.26 [3H, s, C**H**$_3$], 1.32 [3H, s, C**H**$_3$], 1.88 [0.86H, ddd, *J*=5.6, 7.9 and 13.8, H_A of C(4)**H**$_2$, major], 2.05-2.25 [1.28H, m, C(3)O**H**, both diastereomers and C(4)**H**$_2$, minor], 2.67 [0.86H, ddd, *J*=6.6, 7.9 and 13.8, H_B of C(4)**H**$_2$, major], 4.01 [1H, t, *J*=5.6, C(3)**H** both diastereomers], 4.94 [0.86H, t, *J*=7.9, C(5)**H**, major], 5.09 [0.14H, dd, *J*=6.6 and 9.2, C(5)**H**, minor], 7.20-7.40 (5H, m, Ar**H**). Spectroscopic characteristics corresponded directly with those reported for the 3R*, 5R* isomer.[178]

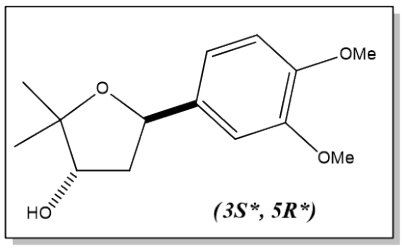
***(±)-2,2-Dimethyl-3-hydroxy-5-(4-fluorophenyl)-tetrahydrofuran* 376**



This compound was prepared following the procedure described for **375**, from 1M L-Selectride® in THF (11.20 mL, 11.20 mmol) and **350** (1.00 g, 4.80 mmol) in THF (25 mL). The title *alcohol* was isolated as a light gold oil (0.72 g, 71%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (20:80) as eluant. ν_{max}/cm^{-1} (film): 3412, 2974, 2933, 1606, 1511, 1461, 1368, 1224, 1155; δ_H (400 MHz): 1.29 [3H, s, C**H**$_3$], 1.36 [3H, s, C**H**$_3$], 1.59 (1H, s, O**H**), 1.89 [1H, ddd, *J*=4.8, 7.4, 13.7, H_A of C(4)**H**$_2$], 2.75 [1H, ddd, *J*=6.3, 7.5, 13.7, H_B of C(4)**H**$_2$], 4.10 [1H, q, *J*=5.7, 10.9, C(3)**H**], 4.96 [1H, t, *J*=7.5, C(5)**H**], 7.01 (2H, t, *J*=8.7, ArC(2)**H**), 7.36 (2H, dd, *J*=5.7, 8.7, ArC(3)**H**); δ_F (470 MHz): -116.11; Spectroscopic characteristics corresponded directly with those reported for the 3R*, 5R* isomer.[178]

***(±)-2,2-Dimethyl-3-hydroxy-5-(3, 4-dimethoxyphenyl)-tetrahydrofuran* 377**



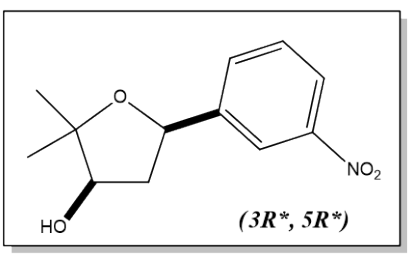


This compound was prepared following the procedure described for **375,** from dropwise addition of $NaBH_4$ (0.15 g, 4.00 mol) in water (50 mL) to a stirring solution of **351** (0.86 g, 3.40 mmol) in methanol (50 mL) at -20 °C. The title *alcohol* was isolated as a gold oil and as a chromatographically inseparable mixture of diastereomers (0.75 g, 87%, d.r. 74:26) by flash chromatography, using ethyl acetate:hexane (40:60) as eluant. The title compound was subsequently dried under high vacuum and recrystallised from ethyl acetate:hexane in an attempt to isolate the major diastereomer, however this was unsuccessful. Compound **377** was finally isolated as a yellow solid and mixture of diastereomers (0.52 g, 61%, d.r. 80:20). (Major diastereomer: (3R*, 5R*), minor diastereomer: (3S*, 5R*)). m.p. 46-48 °C; Found C: 66.70, H: 7.75, $C_{14}H_{20}O_4$ requires C: 66.65, H: 7.99; ν_{max}/cm^{-1} (film): 3414, 2970, 2936, 1594, 1517, 1464, 1379, 1262, 1160; δ_H (300 MHz): 1.29 [2.40H, s, C**H**$_3$, major], 1.35 [0.60H, s, C**H**$_3$, minor], 1.36 [0.60H, s, C**H**$_3$, minor], 1.38 [2.40H, s, C**H**$_3$, major], 1.60 (1H, bs, O**H**, both diastereomers), 1.96 [0.80H, ddd, *J*=4.8,

7.5, 13.5, H_A of C(4)**H**$_2$, major], 2.08-2.32 [0.40H, m, C(4)**H**$_2$, minor], 2.74 [0.80H, ddd, *J*=6.3, 7.5, 13.5, H_B of C(4)**H**$_2$, major], 3.85 [3H, s, OC**H**$_3$, both diastereomers], 3.88 [3H, s, OC**H**$_3$, both diastereomers], 4.06-4.16 [1H, m, C(3)**H** both diastereomers], 4.95 [0.80H, t, *J*=7.5, C(5)**H**, major], 5.16 [0.20H, dd, *J*=9.2 and 6.3, C(5)**H**, minor], 6.83 (1H, d, *J*=8.3, ArC(5)**H**, both diastereomers), 6.92 (1H, dd, *J*=1.8, 8.3, ArC(6)**H**, both diastereomers), 6.99 (1H, d, *J*=1.8, ArC(2)**H**, both diastereomers); δ_C (75.5 MHz): 21.69 [**C**H$_3$, minor], 22.67 [**C**H$_3$, major], 25.82 [**C**H$_3$, major], 28.27 [**C**H$_3$, minor], 43.23 [**C**(4)H$_2$, major], 43.47 [**C**(4)H$_2$, minor], 55.78, 55.93 (2xO**C**H$_3$), 76.73 [**C**(3)H, major], 78.27 [**C**(3)H, minor], 78.37 [**C**(5)H, major], 78.49 [**C**(5)H, minor], 83.12 [**C**(2), major], 83.65 [**C**(2), minor], 109.07 (Ar**C**(2)H, minor), 109.31 (Ar**C**(2)H, major), 110.95 (Ar**C**(5)H, major), 111.03 (Ar**C**(5)H, minor), 117.98 (Ar**C**(6)H, minor), 118.16 (Ar**C**(6)H, major), 135.61 (Ar**C**, minor), 135.77 (Ar**C**, major), 148.22 (Ar**C**O, minor), 148.28 (Ar**C**O, major), 148.90 (Ar**C**O, minor), 148.98 (Ar**C**O, major); m/z: 253 $(M+H)^+$, 235, 146, 105, 59. HRMS (ES+): Found 253.1448, $C_{14}H_{21}O_4$ $(M+H)^+$ requires 253.1440. STDEV: 3.20 ppm.

This compound was prepared following the procedure described for **375**, from L-Selectride® (12.00 mL, 12.00 mmol) and **351** (1.00 g, 3.99 mmol) in THF (25 mL). The alcohol was isolated as a light gold oil and a chromatographically inseparable mixture of diastereomers (0.70 g, 70%, d.r. 85:15) by flash chromatography, using ethyl acetate/hexane (40:60) as eluant. (Major diastereomer: (3R*, 5R*), minor diastereomer: (3S*, 5R*)). ν_{max}/cm^{-1} (film): 3414, 2970, 2936, 1594, 1517, 1464, 1379, 1262, 1160; δ_H (300MHz): 1.27 [3H, s, C**H**$_3$], 1.34 [3H, s, C**H**$_3$], 1.92 [0.85H, ddd, *J*=5.2, 7.6, 13.6, H_A of C(4)**H**$_2$, major], 2.08-2.28 [1.30H, m, O**H** both diastereomers and C(4)**H**$_2$, minor] 2.67 [0.85H, ddd, *J*= 6.2, 7.6, 13.6, H_B of C(4)**H**$_2$, major], 3.85 (3H, s, OC**H**$_3$), 3.88 (3H, s, OC**H**$_3$), 4.04 [1H, t, *J*= 6.2, C(3)**H** both diastereomers], 4.91 [0.85H, t, *J*=7.6, C(5)**H**, major], 5.13 [0.15H, dd, *J*=6.2, 9.2, C(5)**H**, minor], 6.83 (1H, d, *J*=8.3, ArC(5)**H**), 6.92 (1H, dd, *J*=1.8, 8.3, ArC(6)**H**), 6.98 (1H, d, *J*=1.8, ArC(2)**H**).

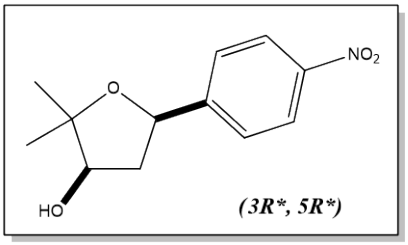
***(±)-2,2-Dimethyl-3-hydroxy-5-(3-nitrophenyl)-tetrahydrofuran* 378**

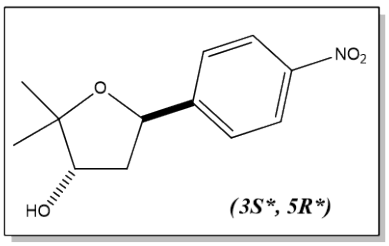


This compound was prepared following the procedure described for **377**, from dropwise addition of $NaBH_4$

(0.76 g, 0.02 mol) in water (50 mL) to a stirring solution of **352** (3.00 g, 13.00 mmol) in methanol (125 mL) at -20 °C. The title alcohol was isolated as a pale yellow solid (2.38 g, 77%, d.r. >98:2) by recrystallisation from ethyl acetate and hexane. m.p. 86-87 °C; Found C: 60.41, H: 6.32, N: 5.47, $C_{12}H_{15}NO_4$ requires C: 60.75, H: 6.37, N: 5.90; ν_{max}/cm^{-1} (KBr): 3427, 2975, 2934, 1529, 1350; δ_H (300 MHz): 1.32 [3H, C**H**$_3$, major], 1.41 [3H, C**H**$_3$, major], 1.62 (1H, d, *J*=5.2, O**H**), 1.92 [1H, ddd, *J*=4.4, 6.9, 13.6, H_A of C(4)**H**$_2$], 2.86 [1H, ddd, *J*=6.1, 8.0, 13.6, H_B of C(4)**H**$_2$], 4.15 [1H, m, C(3)**H**], 5.09 [1H, t, *J*=7.5, C(5)**H**], 7.51 (1H, t, *J*=7.9, ArC(5)**H**), 7.75 (1H, d, *J*=7.7, ArC(6)**H**), 8.11 (1H, ddd, *J*=1.0, 2.2, 8.2, ArC(4)**H**), 8.27 (1H, t, *J*=1.8, ArC(2)**H**); δ_C (75.5 MHz): 22.40 [**C**H$_3$], 25.68 [**C**H$_3$], 43.18 [**C**(4)H$_2$], 76.07 [**C**(5)H], 78.08 [**C**(3)H], 84.07 [**C**(2)], 121.04 (Ar**C**(5)H), 122.29 (Ar**C**(6)H), 129.36 (Ar**C**(4)H), 132.13 (Ar**C**(2)H), 145.92 (Ar**C**), 148.30 (Ar**C**-NO$_2$); m/z: 238 $(M+H)^+$, 208, 153, 105, 64. HRMS (ES+): Found 238.1079, $C_{12}H_{16}NO_4$ $(M+H)^+$ requires 238.1057. STDEV: 9.20 ppm

***(±)-2,2-Dimethyl-3-hydroxy-5-(4-nitrophenyl)-tetrahydrofuran* 379**

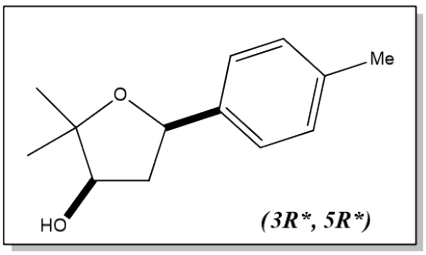




This compound was prepared following the procedure described for **377**, from dropwise addition of $NaBH_4$ (0.34 g, 9.00 mmol) in water (40 mL) to a stirring solution of **353** (2.06 g, 8.76 mmol) in methanol (80 mL) at -20 °C. The alcohol was isolated as a light yellow oil (1.60 g, 77%, d.r. 80:20) by flash chromatography, using ethyl acetate:hexane (20:80) as eluant. (Major diastereomer: (3R*, 5R*), minor diastereomer: (3R*, 5S*)). ν_{max}/cm^{-1} (film): 3432, 2975, 1602, 1520, 1640, 1348, 1140, 1047; δ_H (300 MHz): 1.31 [2.40H, s, C**H**$_3$, major], 1.34 [0.60H, s, C**H**$_3$, minor], 1.39 [3H, s, C**H**$_3$, both diastereomers], 1.82-1.93 [1.60H, m, H_A of C(4)**H** major and O**H**, both diastereomers], 2.06-2.50 [0.20H, m, C(4)**H**$_2$, minor], 2.84 [0.80H, ddd, *J*=6.1, 8.2, 13.6, H_B of C(4)**H**, major], 4.13 [1H, m, C(3)**H**, both], 5.09 [0.80H, t, *J*=7.5, C(5)**H**, major], 5.31 [0.80H, dd, *J*=6.6, 9.6, C(5)**H**, minor], 7.50 (0.40H, d, *J*=8.6, ArC(2)**H**, minor), 7.56 (1.60H, d, *J*=8.6, Ar(2)**H**, major), 8.15-8.21 (2H, m, ArC(3)**H**, both diastereomers); δ_C(75.5 MHz): 21.72 [**C**H$_3$, minor], 22.37 [**C**H$_3$, major], 25.71 [**C**H$_3$, major], 28.13 [**C**H$_3$, minor], 43.18 [**C**(4)H$_2$, major], 43.47 [**C**(4)H$_2$, minor],

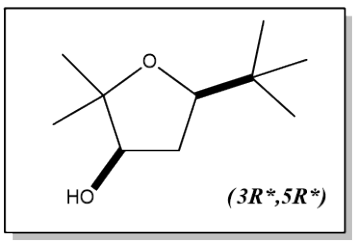
76.12 [**C**(5)H, major], 77.58 [**C**(5)H, minor], 78.01 [**C**(3)H, minor], 78.15 [**C**(3)H, minor], 84.14 [**C**(2), major], 84.68 [**C**(2), minor], 123.67 (Ar**C**(2)H, both diastereomers), 126.56 (Ar**C**(3)H, both diastereomers), 147.05 (Ar**C**), 151.37 (Ar**C**-NO_2); m/z: 236 $(M-H)^-$, 166, 86. HRMS (ES-): Found 236.0924, $C_{12}H_{14}NO_4$ $(M-H)^-$ requires 236.0923 STDEV: 0.40 ppm.

***(±)-2,2-Dimethyl-3-hydroxy-5-(p-tolyl)-tetrahydrofuran* 380**



This compound was prepared following the procedure described for **375**, from 1M L-Selectride® in THF (5.00 mL, 5.00 mmol) and **354** (0.10 g, 0.05 mmol) in THF (20 mL). The title alcohol was isolated as a light gold oil that solidified at room temperature (65.00 mg, 63%, d.r. >98:2) following flash chromatography, using ethyl acetate:hexane (5:95) as eluant. m.p. 73-75 °C; Found C: 76.08, H: 9.01, $C_{13}H_{18}O_2$ requires C: 75.69, H: 8.80; ν_{max}/cm^{-1} (KBr): 3412, 2973, 1516, 1456, 1368, 1145. 1070; δ_H (300 MHz): 1.29 [3H, s, C**H**$_3$], 1.35 [3H, s, C**H**$_3$], 1.68 (1H, bs, O**H**), 1.92 [1H, ddd, *J*=5.1, 7.5, 13.5, H_A of C(4)**H**$_2$], 2.33 [3H, s, C**H**$_3$], 2.72 [1H, ddd, *J*=6.3, 7.6, 13.7, H_B of C(4)**H**$_2$], 4.07 [1H, m, C(3)**H**], 4.95 [1H, t, *J*=7.6, C(5)**H**], 7.17 (2H, t, *J*= 8.0, ArC(3)**H**), 7.28 (2H, d, *J*=8.0, ArC(2)**H**); δ_C (75.5 MHz): 21.13 [Ar-**C**H$_3$], 22.66 [**C**H$_3$], 25.84 [**C**H$_3$], 43.37 [**C**(4)H$_2$], 76.63 [**C**(5)H], 78.53 [**C**(3)H], 83.05 [**C**(2)], 125.83 (Ar**C**(3)H), 129.25 (Ar**C**(2)H), 136.97 (Ar**C**-CH_3), 140.17 (Ar**C**); m/z: 207 $(M+H)^+$, 203, 189, 171, 115, 101; HRMS (ES+): Found 207.1390, $C_{113}H_{19}O_2$ $(M+H)^+$ requires 207.1385. STDEV: 2.40 ppm

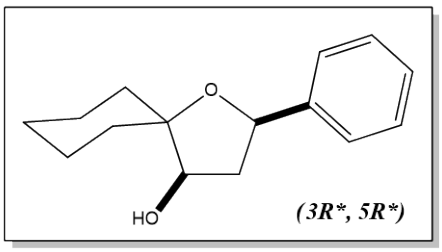
***(±)-2,2-Dimethyl-3-hydroxy-5-tertbutyltetrahydrofuran* 381**



This compound was prepared following the procedure described for **377**, from $NaBH_4$ (0.28 g, 7.40 mmol) in water (15 mL) and **356** (0.64 g, 3.70 mmol) in methanol (30 mL). The title alcohol was isolated as a clear oil (0.47 g, 71%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (20:80) as eluant. ν_{max}/cm^{-1} (film): 3401, 2960, 2869, 1480, 1465, 1396, 1364, 1263, 1088; δ_H: 0.89 [9H, s, (C**H**$_3$)$_3$], 1.19 [6H, s, (C**H**$_3$)$_2$], 1.50 (1H, bs, O**H**), 1.68 [1H, ddd,

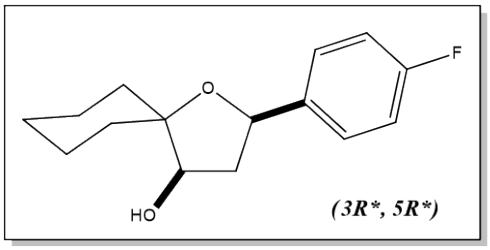
J=4.9, 8.4, 13.6, H_A of C(4)$\mathbf{H}_2$], 2.21 [1H, ddd, *J*=6.3, 7.0, 13.6, H_B of C(4)$\mathbf{H}_2$], 3.62 [1H, dd, *J*=7.0, 8.4, C(3)**H**], 3.95 [1H, dd, *J*=5.3, 6.3, C(5)**H**]. Spectroscopic characteristics corresponded directly with those reported for the 3R*, 5R* isomer.[178]

***(±)-2-Phenyl-1-oxaspiro[4.5]decan-4-ol* 382**



This compound was prepared following the procedure described for **375**, from 1M L-Selectride® in THF (13.00 mL, 13.00 mmol) and **357** (1.00 g, 2.90 mmol) in THF (40 mL). The alcohol was isolated as a gold oil (0.71 g, 71%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (40:60) as eluant. ν_{max}/cm^{-1} (film): 3415, 2930, 2855, 1496, 1450, 1345, 1145; δ_H: 1.21-1.72 [10H, m, (C$\mathbf{H}_2$)$_5$], 1.84 [1H, ddd, *J*=4.1, 6.8, 13.6, H_A of C(4)$\mathbf{H}_2$], 2.50 (1H, s, O**H**), 2.68 [1H, ddd, *J*=6.3, 7.7, 13.6, H_B of C(4)$\mathbf{H}_2$], 3.98 [1H, m, C(3)**H**], 4.93 [1H, t, *J*=7.7, C(5)**H**], 7.18-7.40 (5H, m, Ar**H**). Spectroscopic characteristics corresponded directly with those reported for the 3R*, 5R* isomer.[178]

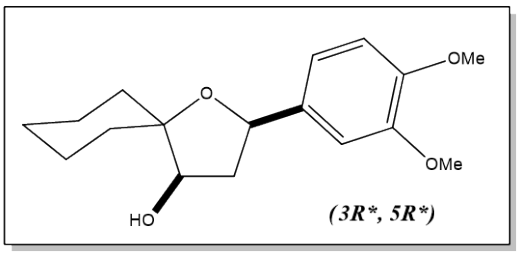
***(±)-2-(4-Fluorophenyl)-1-oxaspiro[4.5]decan-4-ol* 383**



This compound was prepared following the procedure described for **375**, from 1M L-Selectride® in THF (10.00 mL, 10.00 mmol) and **358** (0.25 g, 1.00 mmol) in THF (50 mL). The title alcohol was isolated as a gold solid (0.15 g, 60%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (20:80) as eluant. m.p. 105-107 °C; Found C: 71.60, H: 7.78, $C_{17}H_{24}O_4$ requires C: 71.98, H: 7.65; ν_{max}/cm^{-1} (film): 3429, 2934, 2959, 1645, 1509, 1449, 1224, 1013; δ_H (400 MHz): 1.45 (1H, d, *J*=6.25, O**H**), 1.30-1.80 [10H, m, (C$\mathbf{H}_2$)$_5$], 1.87 [1H, ddd, *J*=3.9, 6.5, 13.8, H_A of C(4)$\mathbf{H}_2$], 2.68 [1H, ddd, *J*=6.3, 8.0, 13.8, H_B of C(4)$\mathbf{H}_2$], 4.12 [1H, m, C(3)**H**], 4.96 [1H, t, *J*=7.3, C(5)**H**], 7.01 (2H, t, *J*=8.8, ArC(2)**H**), 7.38 (2H, m, ArC(2)**H**); δ_C (75.5 MHz): 22.82, 22.96, 25.79, 31.42, 34.43 [5x**C**H_2, (**C**H_2)$_5$], 43.44 [**C**(4)H_2], 76.03 [**C**(5)H], 77.27 [**C**(3)H], 84.87 [**C**(2)], 115.15 (d, $^2J_{CF}$=21.4, Ar**C**(2)H), 127.55 (d, $^3J_{CF}$=8.1, Ar**C**(3)H), 139.52 (d, $^4J_{CF}$=3.1, Ar**C**), 162.05 (d, $^1J_{CF}$=244.8, Ar**C**-F); δ_F (470 MHz): -116.37; m/z:

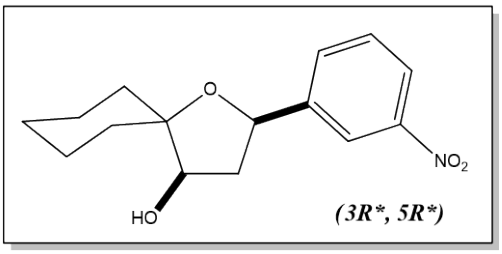
251 $(M+H)^+$, 249, 231, 207, 141, 126, 80. HRMS (ES+): Found 251.1447, $C_{15}H_{20}FO_2$ requires $(M+H)^+$ 251.1436. STDEV: 4.40 ppm

***(±)-2-(3,4-Dimethoxyphenyl)-1-oxaspiro[4.5]decan-4-ol* 384**



This compound was prepared following the procedure described for **377**, from dropwise addition of $NaBH_4$ (0.38 g, 19.00 mmol) in water (75 mL) to a stirring solution of **359** (5.00 g, 17.00 mmol) in methanol (80 mL) at -20 °C. The title alcohol was isolated as a white solid (3.20 g, 64%, d.r. >98:2) by recrystallisation, from ethyl acetate and hexane. m.p.: 71-73 °C; Found C: 70.00, H: 8.27 $C_{17}H_{24}O_4$ requires C: 69.84, H: 8.27; ν_{max}/cm^{-1} (KBr): 3432, 2933, 2857, 1516, 1464, 1262; δ_H (300 MHz): 1.30-1.80 [10H, m, (C**H**$_2$)$_5$], 1.94 [1H, ddd, *J*=3.9, 6.5, 13.7, H_A of C(4)**H**$_2$], 2.75 [1H, ddd, *J*=6.3, 8.0, 13.7, H_B of C(4)**H**$_2$], 3.67 [3H, s, OC**H**$_3$], 3.89 [3H, s, OC**H**$_3$], 4.07-4.15 [1H, m, C(3)**H**], 4.96 [1H, t, *J*=7.2, C(3)**H**], 6.83 (1H, d, *J*=8.2, ArC(5)**H**), 6.93 (1H, dd, *J*=1.9, 8.2, ArC(6)**H**), 7.01 (1H, d, *J*=1.9, ArC(2)**H**); δ_C (75.5 MHz): 22.88, 23.05, 25.81, 31.53, 34.59 [5xC**H**$_2$, (**C**H$_2$)$_5$], 43.27 [**C**(4)H$_2$], 55.78, 55.95, (2xO**C**H$_3$), 76.47 [**C**(5)H], 77.24 [C(3)**H**], 84.80 [**C**(2)], 109.24 (Ar**C**(2)H), 111.00 (Ar**C**(5)H), 117.99 (Ar**C**(6)H), 136.45 (Ar**C**), 148.20 (Ar**C**O), 149.02 (Ar**C**O); m/z: 293 $(M+H)^+$, 275, 257, 165, 155, 105, 64. HRMS (ES+): Found 293.1753, $C_{17}H_{25}O_4$ $(M+H)^+$ requires 293.1751. STDEV: 0.70 ppm

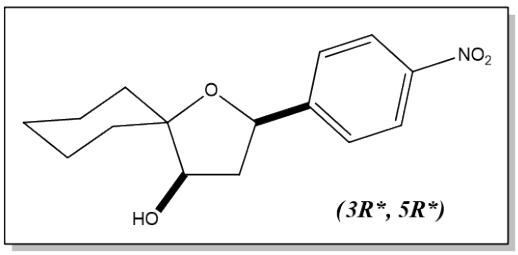
***(±)-2-(3-Nitrophenyl)-1-oxaspiro[4.5]decan-4-ol* 385**



This compound was prepared following the procedure described for **377**, from dropwise addition of $NaBH_4$ (0.57 g, 15.00 mmol) in water (50 mL) to a stirring solution of **360** (2.80 g, 12.00 mmol) in methanol (125 mL) at -20 °C. The title alcohol was isolated as a gold coloured solid (2.18 g, 77%, d.r. >98:2) by recrystallisation, from ethyl acetate and hexane. m.p.: 99-101 °C; Found C: 64.50, H: 7.41, N: 4.76, $C_{15}H_{19}NO_4$ requires C: 64.97, H: 6.91, N: 5.05; ν_{max}/cm^{-1} (film): 3419,

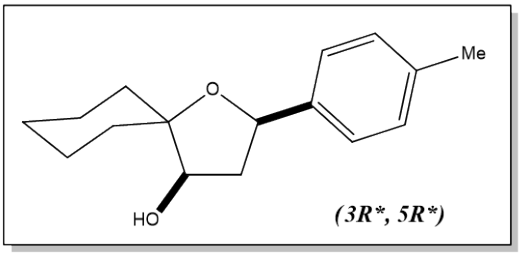
2934, 1528, 1447, 1349, 1059; δ_H (300 MHz): 1.30-1.85 [11H, m, (C**H**$_2$)$_5$ and O**H**], 1.91 [1H, ddd, *J*=3.6, 6.3, 13.6, H_A of C(4)**H**], 2.86 [1H, ddd, *J*=6.2, 8.3, 13.6, H_B of C(4)**H**], 4.13-4.19 [1H, m, C(3)**H**], 5.08 [1H, dd, *J*=6.2, 8.3, C(5)**H**], 7.50 (1H, t, *J*=7.8, ArC(5)**H**), 7.76 (1H, d, *J*=7.8, Ar(6)**H**), 8.10 (1H, ddd, *J*=1.0, 3.2, 8.1, ArC(4)**H**), 8.28 (1H, t, *J*=2.1, ArC(2)**H**); δ_C (75.5 MHz): 22.88, 22.95, 25.73, 31.23, 34.40 [5x**C**H$_2$, (**C**H$_2$)$_5$], 43.13 [**C**(4)H$_2$], 75.86 [**C**(5)H], 76.99 [**C**(3)H], 85.64 [**C**(2)], 121.05 (Ar**C**(5)H), 122.18 (Ar**C**(6)H), 129.32 (Ar**C**(4)H), 132.12 (Ar**C**(2)H), 146.39 (Ar**C**), 148.31 (Ar**C**-NO$_2$); m/z: 278 $(M+H)^+$, 260, 186, 153, 132, 64. HRMS (ES+): Found 278.1392, $C_{16}H_{20}NO_4$ $(M+H)^+$ requires 278.1392. STDEV: 0.00 ppm

***(±)-2-(4-Nitrophenyl)-1-oxaspiro[4.5]decan-4-ol* 386**



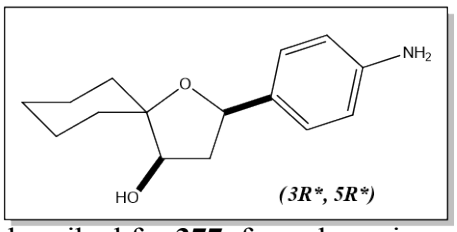
This compound was prepared following the procedure described for **377**, from dropwise addition of $NaBH_4$ (1.13 g, 0.03 mol) in water (80 mL) to a stirring solution of **346** (4.50 g, 0.02 mol) in methanol (150 mL) at -20 °C. The title alcohol was isolated as a pale yellow solid (3.24 g, 71%, d.r. >98:2) by recrystallisation, from ethyl acetate and hexane. m.p.: 107-108 °C; Found C: 64.63, H: 6.86, N: 5.05, $C_{15}H_{19}NO_4$ requires C: 64.97, H: 6.91, N: 5.05; ν_{max}/cm^{-1} (film): 3429, 2934, 2857, 1519, 1447, 1348, 1063; δ_H (300 MHz): 1.30-1.80 [11H, m, (C**H**$_2$)$_5$ and O**H**], 1.89 [1H, ddd, *J*=3.7, 6.3, 13.6, H_A of C(4)**H**], 2.85 [1H, ddd, *J*=6.3, 8.4, 13.6, H_B of C(4)**H**], 4.15 [1H, m, C(3)**H**], 5.08 [1H, dd, *J*=6.3, 8.4, C(5)**H**,], 7.57 (1H, d, *J*=8.6, ArC(2)**H**), 8.19 (1H, d, *J*=8.6, ArC(3)**H**); δ_C (75.5 MHz): 22.87, 22.94, 25.72, 31.23, 34.48 [5x**C**H$_2$, (**C**H$_2$)$_5$], 43.16 [**C**(4)H$_2$], 75.91 [**C**(5)H], 77.01 [**C**(3)H], 85.65 [**C**(2)], 123.65 (Ar**C**(2)H), 126.51 (Ar**C**(3)H), 147.07 (Ar**C**), 151.77 (Ar**C**-NO$_2$); m/z: 278 $(M+H)^+$, 262, 141, 105. HRMS (ES+): Found 278.1392, $C_{15}H_{20}NO_4$ $(M+H)^+$ requires 278.1379. STDEV: 4.70 ppm

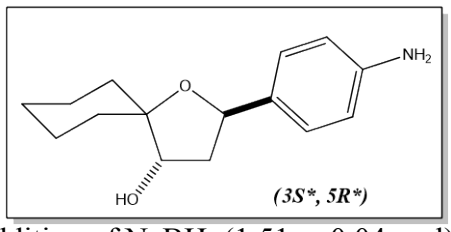
***(±)-2-(p-Tolyl)-1-oxaspiro[4.5]decan-4-ol* 387**



This compound was prepared following the procedure described for **375**, from 1M L-Selectride® in THF (60 mL, 60.00 mmol) and **361** (3.00 g, 12.00 mmol) in THF (150 mL). The title alcohol was isolated as a white solid (1.65 g, 55%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. m.p.: 94-96 °C; Found C: 78.19, H: 9.14, $C_{16}H_{22}O_2$ requires C: 78.01, H: 9.00; ν_{max}/cm^{-1} (KBr): 3433, 2931, 2858, 1645, 1515, 1448, 1182; δ_H (300 MHz): 1.20-1.70 [10H, m, (C**H**$_2$)$_5$], 1.83 [1H, ddd, *J*=4.9, 7.5, 13.8, H_A of C(4)**H**$_2$], 2.18 (1H, d, *J*=6.3, O**H**), 2.30 [3H, s, C**H**$_3$], 2.60 [1H, ddd, *J*=6.4, 7.6, 13.8, H_B of C(4)**H**$_2$], 3.94 [1H, t, *J*=8.7, C(3)**H**], 4.88 [1H, t, *J*=7.5, C(5)**H**], 7.10 (2H, t, *J*=8.0, ArC(3)**H**), 7.26 (2H, d, *J*=8.0, ArC(2)**H**); δ_C (75.5 MHz): 21.20 [Ar-**C**H$_3$], 22.79, 23.11, 25.91, 31.54, 34.71 [5x**C**H$_2$, (**C**H$_2$)$_5$], 43.32 [**C**(4)H$_2$], 76.45 [**C**(5)H], 77.36 [**C**(3)H], 84.46 [**C**(2)], 125.94 (Ar**C**(3)H), 129.11 (Ar**C**(2)H), 140.74 (Ar**C**-CH$_3$), 143.75 (Ar**C**); m/z: 247 (M+H), 229, 211, 124, 119, HRMS (ES+): Found 247.1698, $C_{15}H_{13}O_2$ $(M+H)^+$ requires 247.1620. STDEV: 1.20 ppm

***(±)-2-(4-Aminophenyl)-1-oxaspiro[4.5]decan-4-ol* 388**



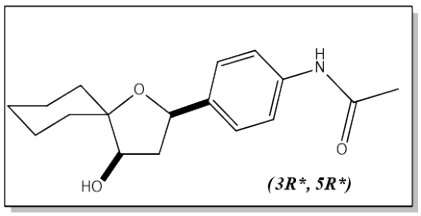


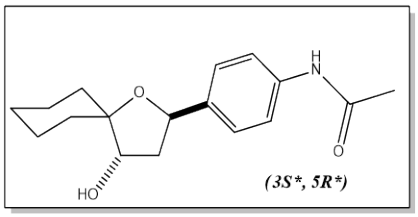
This compound was prepared following the procedure described for **377**, from dropwise addition of $NaBH_4$ (1.51 g, 0.04 mol) in water (175 mL) to a stirring solution of **362** (7.10 g, 0.03 mol) in methanol (150 mL) at -20 °C. The alcohol was isolated as a brown semi-solid (5.80 g, 78%, d.r. 78:22) by flash chromatography, using ethyl acetate:hexane (10:90) as eluant. Found C: 72.50, H: 8.36, N:5.62, $C_{15}H_{21}NO_2$ requires C: 72.84, H: 8.56, N:5.66; ν_{max}/cm^{-1} (film): 3399, 2931, 2856, 1615, 1518, 1448, 1179; δ_H (300 MHz): 1.30-1.80 [10H, m, (C**H**$_2$)$_5$, both diastereomers], 1.89 [0.78H, ddd, *J*=4.2, 6.9, 13.7, H_A of C(4)**H**$_2$, major], 2.08-2.25 (0.44H, m, C(4)**H**$_2$, minor), 2.69 [0.78H, ddd, *J*=6.3, 7.7, 13.7, H_B of C(4)**H**$_2$, major], 3.63 (2H, bs, N**H**$_2$, both diastereomers), 4.08 [1H, dd, *J*=4.1, 6.3, C(3)**H**, both], 4.88 [0.78H, t,

J=7.3, C(5)**H,** major], 5.10 [0.22H, dd, *J*=6.1, 10.0, C(5)**H**, minor], 6.65 (2H, t, *J*=8.5, ArC(3)**H**), 7.19 (2H, d, *J*=8.5 ArC(2)**H**); δ_C(75.5MHz): 22.84, 23.37, 25.69, 30.85, 37.66 [5xCH2, (**C**H2)5, major], 23.01, 23.58, 25.85, 31.58, 34.49 [5xCH2, (**C**H_2)$_5$, minor], 43.34 [**C**(4)H_2, minor], 43.64 [**C**(4)H_2, major], 76.39 [**C**(5)H, major], 77.28 [**C**(5)H, minor], 77.30 [**C**(3)H, minor], 43.64 [**C**(3)H, major], 84.9 [**C**(2), both diastereomers], 115.06 (Ar**C**(3)H, major), 115.13 (Ar**C**(3)H, minor), 127.09 (Ar**C**(2)H, major), 127.17 (Ar**C**(2)H, minor), 133.13 (Ar**C**-NH_2, both diastereomers), 145.62 (Ar**C**, both diastereomers); m/z: 248 $(M+H)^+$, 230, 100, 69, HRMS (ES+): Found 248.1658, $C_{15}H_{22}NO_2$ $(M+H)^+$ requires 248.1651. STDEV: 2.80 ppm.

Attempts to access **388** *via* iron mediated reduction of the parent nitro-substituted hydroxyfuran **386** proved unsuccessful.

(±)-2-(4-Acetamidophenyl)-1-oxaspiro[4.5]decan-4-ol 389

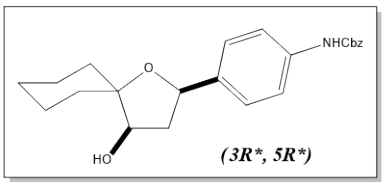


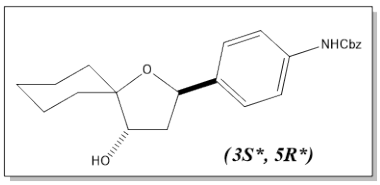


To a solution of **392** (0.10 g, 0.30 mmol, d.r. 38:62 [(3R*, 5R*):(3S*, 5R*)]), in methanol (10 mL) was added potassium carbonate (0.06 g, 0.40 mmol) in water (4 mL). The reaction mixture was stirred at room temperature overnight before addition of 10% HCl solution. The solution was extracted with ether (5 x 10 mL, washed with water (15 mL), dried and evaporated to a light brown oil and a chromatographically inseparable mixture of diastereomers (0.05 g, 60%, d.r. 33:67). (Major diastereomer: (3R*, 5S*), minor diastereomer: (3R*, 5R*)). ν_{max}/cm^{-1} (film): 3305, 2934, 2858, 1669, 1605, 1539, 1516, 1318; δ_H (400 MHz): 1.30-1.83 [10H, m, C**H**$_2$)$_5$, both diastereomers], 1.83 [0.33H, ddd, *J*=4.5, 6.9, 13.5, H_A of C(4)**H**$_2$, minor], 2.08-2.30 [1.34H, m, C(4)**H**$_2$, major], 2.16 [3H, s, NHCOC**H**$_3$, both diastereomers], 2.73 [0.33H, ddd, *J*=7.0, 7.4, 13.5, H_B of C(4)**H**$_2$, minor], 2.75 (1H, bs, O**H**, both diastereomers), 4.07 [1H, t, *J*=4.5, C(3)**H**, both diastereomers], 4.95 [0.33H, t, *J*=7.4, C(5)**H,** minor], 5.17 [0.67H, dd, *J*=6.0, 10.0, C(5)**H**, major], 7.26 (2H, d, *J*=8.4, ArC(3)**H,** both diastereomers), 7.44 (2H, d, *J*=8.4, ArC(2)**H,** both diastereomers), 7.58 (1H, bs, N**H**, both diastereomers); δ_C (125 MHz): 21.13 [CO**C**H_3, major], 21.16 [CO**C**H_3, minor], 22.58, 22.70, 25.62, 31.57, 33.84 [5xCH_2, (**C**H_2)$_5$, major], 22.94, 22.70, 25.45, 31.14, 37.52 [5xCH_2, (**C**H_2)$_5$, major], 24.57

[NHCO**C**H_3, both diastereomers], 41.12 [**C**(4)H_2, major], 41.53 [**C**(4)H_2, minor], 76.44 [**C**(5)H, major], 78.44 [**C**(5)H, minor], 78.53 [**C**(3)H, major], 78.95 [**C**(5)H, minor], 84.16 [**C**(2), major], 84.64 [**C**(2), minor], 119.83 (Ar**C**(3)H, major), 119.95 (Ar**C**(3)H, minor), 126.42 (Ar**C**(2)H, minor), 126.77 (Ar**C**(2)H, major), 137.11 (Ar**C**, both diastereomers), 138.61 (Ar**C**-NH, minor), 139.14 (Ar**C**-NH, major), 168.37 [NH**C**OCH_3, both diastereomers], 170.55 [**C**OCH_3, minor], 170.67 [**C**OCH_3, major]; m/z: 332 $(M+H)^+$, 272, 254, 230, 105; HRMS (ES+): Found 332.1856, $C_{19}H_{26}NO_4$ $(M+H)^+$ requires 332.1862. STDEV: 1.80 ppm.

***(±)-Benzyl-(4-(4-hydroxy-1-oxaspiro[4.5]-decan-2-yl)phenyl)-carbamate* 390**

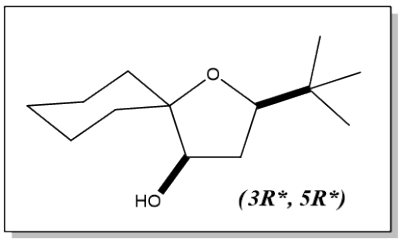




Benzylchloroformate (0.34 mL, 2.42 mmol) was added dropwise to a stirring solution of **388** (0.30 g, 1.21 mmol, d.r. 78:22 [(3R*, 5R*):(3S*, 5R*)]), triethylamine (0.67 mL, 4.84 mmol) and 10 mol% DMAP (14.00 mg) in dichloromethane (40 mL) at room temperature. Stirring was continued overnight where reaction completion was indicated by TLC analysis. The reaction mixture was diluted with dichloromethane (15 mL) and washed successively with saturated sodium bicarbonate (20 mL), water (20 mL) and brine (20 mL). The organic solution was dried and concentrated *in vacuo* to yield the crude product as a brown oil. Purification by flash chromatography using ethyl acetate:hexane (20:80) produced the protected *alcohol* as a yellow oil (0.35 g, 76%, d.r. 30:70) and chromatographically inseparable mixture of diastereomers. (Major diastereomer: (3R*, 5S*), minor diastereomer: (3R*, 5R*)). ν_{max}/cm^{-1} (film): 3321, 2933, 2858, 1707, 1602, 1538, 1314, 1223; δ_H (300 MHz): 1.30-1.95 [11.30H, m, (C**H**$_2)_5$ and O**H**, both diastereomers and C(4)**H**$_2$, minor], 2.00-2.25 [1.40H, m, C(4)**H**$_2$, major], 2.71 [0.30H, ddd, *J*=6.3, 7.8, 14.1, H_B of C(4)**H**$_2$, minor], 4.00-4.20 [1H, m, C(3)**H**, both diastereomers], 4.92 [0.30H, t, *J*=7.8, C(5)**H,** minor], 5.10-5.20 [2.70H, m, C(5)**H**, major and OC**H**$_2$Ph, both diastereomers], 6.80 (1H, bs, N**H**, both diastereomers), 7.20-7.40 (9H, Ar**H**, both diastereomers); δ_C (75.5 MHz): 22.83, 23.03, 25.82, 31.46, 34.52 [5xCH2, (**C**$H_2)_5$, minor], 23.36, 23.59, 25.66, 30.85, 37.53 [5xCH_2, (**C**$H_2)_5$, major], 43.33 [**C**(4)H_2, minor], 43.67 [**C**(4)H_2, major], 67.02 [O**C**H_2Ph, both diastereomers], 76.18 [**C**(5)H,

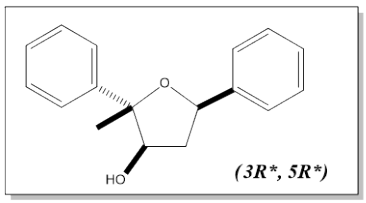
minor], 77.05 [**C**(5)H, major], 77.30 [**C**(3)H, minor], 77.97 [**C**(3)H, major], 84.75 [**C**(2), minor], 85.46 [**C**(2), both diastereomers] 126.51 (Ar**C**H, both diastereomers), 126.65 (Ar**C**H, both diastereomers), 128.34 (Ar**C**H, both diastereomers), 128.37 (Ar**C**H, both diastereomers), 128.64 (Ar**C**H, both diastereomers), 136.07 (Ar**C**, both diastereomers), 136.80 (Ar**C**, both diastereomers), 138.62 (Ar**C**, both diastereomers), 153.42 [**C**O_2Bn]; m/z: 382 $(M+H)^+$, 290, 261, 196, HRMS (ES+): Found 382.2018, $C_{23}H_{28}NO_4$ $(M+H)^+$ requires 382.2035. STDEV: 4.40 ppm.

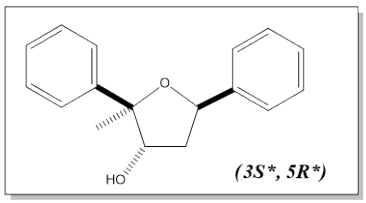
***(±)-2-Tertbutyl-1-oxaspiro[4.5]decan-4-ol* 391**



This compound was prepared following the procedure described for **377**, from dropwise addition of $NaBH_4$ (0.20 g, 5.00 mmol) in water (40 mL) to a stirring solution of **363** (1.20 g, 4.80 mmol) in methanol (25 mL) at -20 °C. The alcohol was isolated as a gold oil (3.24 g, 71%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (film): 3407, 2933, 2861, 1448, 1362, 1149; δ_H(300 MHz): 0.89 [9H, s, (C**H**$_3$)$_3$], 1.25-1.70 [12H, m, (C**H**$_2$)$_5$, H_A of C(4)**H**$_2$ and O**H**], 2.19 [1H, ddd, *J*=6.8, 7.1, 14.0, H_B of C(4)**H**$_2$], 3.56 [1H, dd, *J*=7.1, 8.2, C(3)**H**], 3.94 [1H, dd, *J*= 7.1, 11.8, C(5)**H**]; δ_C (75.5 MHz): 22.60, 22.90, 25.98, 31.33, 33.86 [5x**C**H$_2$, (**C**H$_2$)$_5$], 25.71 [(**C**H$_3$)$_3$], 33.14 [**C**(CH$_3$)$_3$], 37.78 [**C**(4)H$_2$], 77.20 [**C**(5)H], 82.21 [**C**(3)H], 82.79 [**C**(2)]; m/z: 213 $(M+H)^+$, 195, 193, 177, 109, HRMS (ES+): Found 213.1847, $C_{13}H_{25}O_2$ $(M+H)^+$ requires 213.1855. STDEV: 3.80 ppm.

***2-Methyl-2,5-diphenyl-3-hydroxytetrahydrofuran* 372**

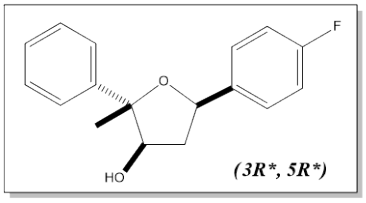


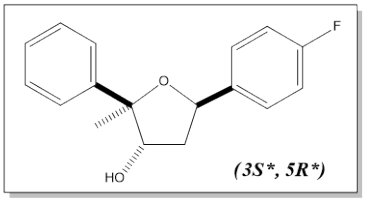


This compound was prepared following the procedure described for **377**, from dropwise addition of $NaBH_4$ (1.51 g, 0.04 mmol) in water (30 mL) to a stirring solution of **370** (2.00 g, 7.99 mmol) in methanol (100 mL) at room temperature. The reaction was stirred overnight at room temperature, where TLC analysis showed the presence of remaining starting material. The

reaction mixture was heated to a gentle reflux for 24 h where reaction completion was indicated by TLC analysis. **372** was obtained as a light gold oil (1.66 g, 82%, d.r. 85:15) by flash chromatography using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (film): 3410, 2929, 2850, 1499, 1452, 1344; δ_H (400 MHz): 1.48 [3H, s, C**H**$_3$, both diastereomers], 1.95 [0.85H, ddd, *J*=5.6, 7.8, 14.1, one of C(4)**H**$_2$, major], 2.10-2.40 [0.30H, m, C(4)H$_2$, minor], 2.75 [0.85H, ddd, *J*=5.6, 8.8, 14.1, one of C(4)**H**$_2$, major], 4.20-4.40 [1H, m, C(3)**H**, both diastereomers], 5.11 [0.85H, dd, *J*=6.4, 7.8, C(5)**H**, major], 5.22 [0.81H, dd, *J*=5.6. 8.8, C(5)**H**, minor], 7.10-7.50 (10H, m, Ar**H**); δ_C (125 MHz): 23.60 [**C**H$_3$, both diastereomers], 40.49 [**C**(4)H2, major diastereomers], 41.18 [**C**(4)H2, minor diastereomers], 77.47 [**C**(5)H, minor], 77.74 [**C**(5)H, major], 78.42 [**C**(3)H, major], 78.87 [**C**(3)H, minor], 86.81 [**C**(2), both diastereomers], 124.50 (Ar**C**H, both diastereomers), 125.52 (Ar**C**H, both diastereomers), 126.85 (Ar**C**H, both diastereomers), 140.46 (Ar**C**, both diastereomers), 141.58 (Ar**C**, both diastereomers); m/z: 255 $(M+H)^+$, 237, 167, 105, 83, HRMS (ES+): Found 255.1377, $C_{17}H_{19}O_2$ $(M+H)^+$ requires 255.1385. STDEV: 3.10 ppm.

***2-Methyl-2-phenyl-5-(4-fluorophenyl)-3-hydroxytetrahydrofuran* 373**



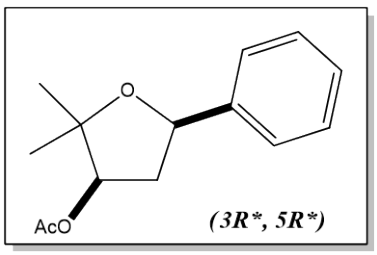


This compound was prepared following the procedure described for **377**, from dropwise addition of $NaBH_4$ (1.90 g, 0.05 mmol) in water (35 mL) to a stirring solution of **369** (2.80 g, 0.01 mol) in methanol (100 mL) at room temperature. The reaction was stirred overnight at room temperature, where TLC analysis showed the presence of remaining starting material. The reaction mixture was heated to a gentle reflux for 24 h where reaction completion was indicated by TLC analysis. **373** was obtained as a gold oil (2.28 g, 84%, d.r. 81:19) by flash chromatography using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (film): 3430, 2930, 2960, 1647, 1510, 1447, 1012; δ_H (300 MHz): 1.57 [3H, s, C**H**$_3$, both diastereomers], 2.07 [0.81H, ddd, *J*=5.7, 7.9, 14.2, one of C(4)**H**$_2$, major], 2.10-2.50 [0.38H, m, C(4)H$_2$, minor], 2.85 [0.81H, ddd, *J*=5.7, 8.9, 14.2, one of C(4)**H**$_2$, major], 4.30-4.50 [1H, m, C(3)**H**, both diastereomers], 5.08 [0.19H, dd, *J*=6.5, 7.9, C(5)**H**, minor], 5.19 [0.81H, dd, *J*=5.7. 8.9, C(5)**H**, minor], 7.03 (2H, d, *J*=8.8, Ar**H**, both), 7.25-

7.50 (7H, m, Ar**H**, both); δ_C (75.5 MHz): 25.22 [**C**H_3, both diastereomers], 42.13 [**C**(4)H2, both diastereomers], 76.98 [**C**(5)H, minor], 77.38 [**C**(5)H, major], 78.23 [**C**(3)H, major], 78.78 [**C**(3)H, minor], 88.91 [**C**(2), both diastereomers], 115.19 (d, $^2J_{CF}$=21.4, Ar**C**(2)H, both diastereomers), 126.00 (Ar**C**H), 127.46 (Ar**C**H), 128.31 (d, $^3J_{CF}$=8.1, Ar**C**(3)H, both diastereomers), 128.80 (Ar**C**H), 138.96 (d, $^4J_{CF}$=2.9, Ar**C**), 141.92 (Ar**C**), 162.17 (d, $^1J_{CF}$=245.2, Ar**C**-F); δ_F: -115.87; m/z: 273 $(M+H)^+$, 197, 178, 163, 80, HRMS (ES+): Found 273.1249, $C_{17}H_{17}FO_2$ $(M+H)^+$ requires 273.1246. STDEV: 2.80 ppm.

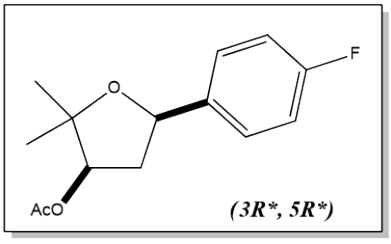
3.2.3 3-Acetoxytetrahydrofurans

***(±)-2,2-Dimethyl-3-acetoxy-5-phenyltetrahydrofuran* 394**



To a stirring solution of **375** (0.59 g, 3.00 mmol, d.r. >98:2) and DMAP (0.02 g, 0.20 mmol), in dichloromethane (50 mL), was added acetic anhydride (1.5 mL) dropwise over 5 min. The mixture was stirred at room temperature for 6 h, at which time TLC analysis indicated consumption of the starting material. The reaction mixture was diluted with dichloromethane (50 mL), washed with water (50 mL) and brine (50 mL), was subsequently dried and evaporated to yield the crude product as a yellow coloured oil. The product (0.47 g, 67%, d.r. >98:2) was isolated as a light gold oil by flash chromatography using ethyl acetate:hexane (15:85) as eluant. ν_{max}/cm^{-1} (film): 2979, 1738, 1375, 1241; δ_H (400 MHz): 1.33 [3H, s, C**H**$_3$], 1.34 [3H, s, C**H**$_3$], 1.94 [1H, ddd, *J*=4.2, 7.5, 13.9, H_A of C(4)**H**$_2$], 2.05 [3H, s, OCOC**H**$_3$], 2.85 [1H, ddd, *J*=6.6, 7.5, 14.2, H_B C(4)**H**$_2$], 5.00 [1H, t, *J*=7.5, C(5)**H**], 5.11 [1H, dd, *J*=4.2, 6.6, C(3)**H**], 7.22-7.42 (5H, m, Ar**H**). Spectroscopic characteristics corresponded directly with those reported for the 3R*, 5R* isomer.[178]

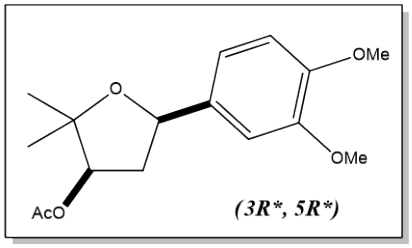
***(±)-2,2-Dimethyl-3-acetoxy-5-(4-fluorophenyl)-tetrahydrofuran* 395**

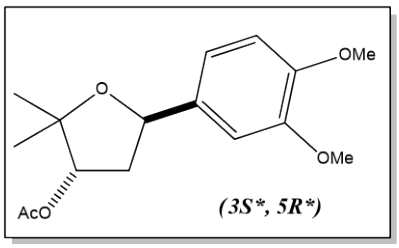


This compound was prepared following the procedure described for **394**, using DMAP (9.00 mg, 0.07 mmol), acetic anhydride (1.00 mL), and **376** (0.25 g, 1.10 mmol, d.r. >98:2) in dichloromethane (20 mL). The *ester* was

isolated as a light gold oil (0.24 g, 85%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (15:85) as eluant. ν_{max}/cm^{-1} (film): 2979, 1740, 1607, 1512, 1466, 1375, 1244, 1146, 1047; δ_H (300 MHz): 1.33 (3H, s, C**H**$_3$), 1.34 [3H, s, C**H**$_3$], 1.89 [3H, ddd, *J*=4.0, 7.3, 14.0, H_A of C(4)**H**$_2$], 2.06 [3H, s, OCOC**H**$_3$], 2.84 [1H, ddd, *J*=6.8, 7.6, 14.0, H_B of C(4)**H**$_2$], 4.97 [1H, t, *J*=7.6, C(5)**H**], 5.11 [1H, dd, *J*=4.0, 6.8, C(3)**H**], 7.01 (2H, t, *J*=8.8, ArC(2)**H**), 7.28-7.40 (2H, m, ArC(3)**H**); δ_F (470 MHz): -115.86, -115.77. Spectroscopic characteristics corresponded directly with those reported for the 3R*, 5R* isomer.[178]

***(±)-2,2-Dimethyl-3-acetoxy-5-(3, 4-dimethoxyphenyl)-tetrahydrofuran* 396**

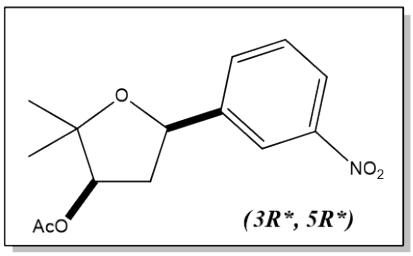




This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.04 mmol), acetic anhydride (3 mL), and **377** (0.09 g, 0.36 mmol, d.r. 80:20) in dichloromethane (10 mL). The *ester* was isolated as a light gold oil (0.09 g, 84%, d.r 74:26) by flash chromatography, using ethyl acetate:hexane (15:85) as eluant. (Major diastereomer: (3R*, 5R*), minor diastereomer: (3S*, 5R*)). ν_{max}/cm^{-1} (film): 2974 1736, 1593, 1517, 1465, 1374, 1328, 1208; δ_H (300 MHz): 1.31 [0.78H, s, C**H**$_3$, minor], 1.33 [2.22H, s, C**H**$_3$, major], 1.34 [0.78H, s, C**H**$_3$, major], 1.40 [0.78H, s, C**H**$_3$, minor], 1.94 [0.74H, ddd, *J*=4.1, 7.5, 14.0, H_A of C(4)**H**$_2$, major], 2.08 [2.22H, s, COC**H**$_3$, major], 2.14 [0.74H, s, COC**H**$_3$, minor], 2.22-2.29 [0.52H, m, C(4)**H**$_2$, minor], 2.83 [0.74H, ddd, *J*=6.8, 7.5, 14.0, H_A of C(4)**H**$_2$, major], 3.86 [3H, s, OC**H**$_3$, both diastereomers], 3.90 [3H, s, OC**H**$_3$, both diastereomers], 4.95 [0.74 H, t, *J*=7.5, C(5)**H**, major] 5.10-5.19 [1.26 H, m, C(3)**H,** major, C(3)**H** and C(5)**H**, minor], 6.83 (1H, d, *J*=8.2, ArC(5)**H**, both diastereomers), 6.89 (1H, dd, *J*=1.8, 7.5, ArC(6)**H**, both diastereomers), 6.98 (1H, d, *J*=1.8, ArC(2)**H**, both diastereomers); δ_C (75.5 MHz): 21.07 [CO**C**H$_3$], 22.22 [**C**H$_3$, minor], 22.79 [**C**H$_3$, major], 23.35 [**C**H$_3$, major], 28.46 [**C**H$_3$, minor], 41.00 [**C**(4)H$_2$, major], 41.31 [**C**(4)H$_2$, minor], 55.74, 55.94, (2xO**C**H$_3$), 76.06 [**C**(5)H, major], 78.78 [**C**(5)H, minor], 79.45 [**C**(3)H, major], 79.99 [**C**(3)H, minor], 82.51 [**C**(2), major], 83.01 [**C**(2), minor], 109.04 (Ar**C**(5)H, minor), 109.36 (Ar**C**(5)H, major), 110.88 (Ar**C**(6)H, major), 111.05

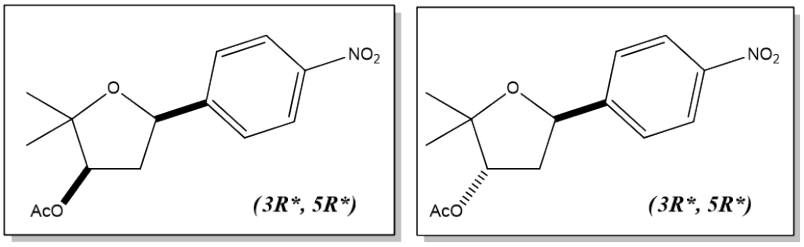
(Ar**C**(6)H, minor), 118.06 (Ar**C**(2)H, minor), 118.53 (Ar**C**(2)H, major), 134.67 (Ar**C**, minor), 135.07 (Ar**C**, major), 148.22 (Ar**C**O, both diastereomers), 148.28 (Ar**C**O, both diastereomers), 170.48 [**C**OCH$_3$]; m/z: 235 (M+H−OAc)$^+$, 217, 123; HRMS (ES+): Found 235.1334, $C_{14}H_{19}O_3$ (M+H−OAc)$^+$ requires 235.1335. STDEV: 0.40 ppm

***(±)-2,2-Dimethyl-3-acetoxy-5-(3-nitrophenyl)-tetrahydrofuran* 397**



This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.04 mmol), acetic anhydride (5 mL) and **378** (0.10 g, 0.42 mmol, d.r. >98:2) in dichloromethane (15 mL). The *ester* was isolated as a gold oil (0.09 g, 77%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (10:90) as eluant. ν_{max}/cm^{-1} (film): 2973, 1738, 1644, 1531, 1350, 1241; δ_H (300 MHz): 1.36 [3H, s, (C**H**$_3$)], 1.39 [3H, s, (C**H**$_3$)], 1.94 [1H, ddd, *J*=3.2, 6.4, 14.4, H_A of C(4)**H**$_2$], 2.08 [3H, s, COC**H**$_3$], 2.96 [1H, ddd, *J*=6.4, 8.3, 14.4, H_B of C(4)**H**$_2$], 5.08-5.21 [2H, m, C(3)**H** and C(5)**H**], 7.51 (1H, t, *J*=7.9, ArC(5)**H**), 7.69 (1H, d, *J*=7.7, ArC(6)**H**), 8.13 (1H, ddd, *J*=1.0, 2.2, 8.2, ArC(4)**H**), 8.33 (1H, t, *J*=2.2, ArC(2)**H**); δ_C (75.5 MHz): 20.99 [CO**C**H$_3$], 22.54 [**C**H$_3$], 25.38 [**C**H$_3$], 40.99 [**C**(4)H$_2$], 76.38 [**C**(5)H], 78.99 [**C**(3)H], 83.70 [**C**(2)], 121.33 (Ar**C**(5)H), 122.31 (Ar**C**(6)H), 129.27 (Ar**C**(4)H), 132.21 (Ar**C**(2)H), 145.38 (Ar**C**), 148.44 (Ar**C**-NO$_2$), 170.45 [**C**OCH$_3$]; m/z: 280 (M+H)$^+$, 258, 218, 167; HRMS (ES+): Found 280.1187, $C_{14}H_{18}NO_5$ (M+H)$^+$ requires 280.1185. STDEV: 0.70 ppm

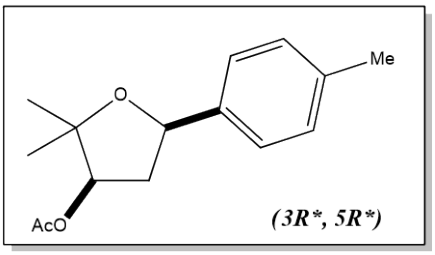
***(±)-2,2-Dimethyl-3-acetoxy -5-(4-nitrophenyl)-tetrahydrofuran* 398**



This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.04 mmol), acetic anhydride (5 mL), and **379** (0.10 g, 0.42 mmol, d.r. 80:20) in dichloromethane (15 mL). The *ester* was isolated as a light gold oil (0.10 g, 85%, d.r. 82:18) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. (Major diastereomer: (3R*,

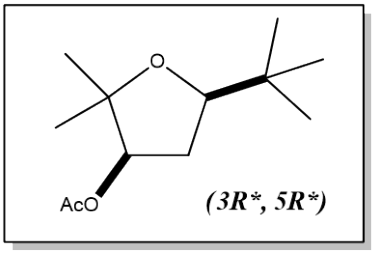
5R*), minor diastereomer: (3S*, 5R*)). ν_{max}/cm^{-1} (film): 2979, 1740, 1604, 1522, 1454, 1375, 1349, 1243, 1144, 1048; δ_H (300 MHz): 1.34 [0.60H, s, C**H**$_3$, minor], 1.36 [2.40H, s, C**H**$_3$, major], 1.38 [2.40H, s, C**H**$_3$, major], 1.40 [0.60H, s, C**H**$_3$, minor], 1.90 [0.80H, ddd, *J*=3.6, 6.6, 14.1, H_A of C(4)**H**$_2$, major], 2.03 [2.40H, s, COC**H**$_3$, major], 2.15 [0.60H, s, COC**H**$_3$, minor], 2.17-2.44 [0.40H, m, C(4)**H**$_2$, minor], 2.96 [0.80H, ddd, *J*=6.4, 8.3, 14.1, H_B of C(4)**H**, major], 5.10-5.30 [2H, m, C(3)**H** and C(5)**H**, both], 7.49-7.58 (2H, m, ArC(2)**H**, both diastereomers), 8.17-8.25 (2H, m, ArC(3)**H**, both diastereomers); δ_C (75.5 MHz): 20.99 [CO**C**H$_3$], 22.20 [**C**H$_3$, minor], 22.59 [**C**H$_3$, major], 22.52 [**C**H$_3$, major], 28.30 [**C**H$_3$, minor], 41.02 [**C**(4)H$_2$, major], 41.34 [**C**(4)H$_2$, minor], 76.28 [**C**(5)H, major], 77.91 [**C**(5)H, minor], 78.99 [**C**(3)H, major], 79.51 [**C**(3)H, minor], 83.56 [C(2), major], 83.99 [C(2), minor], 123.67 (Ar**C**(2)H, major), 123.78 (Ar**C**(2)H, minor), 126.26 (Ar**C**(3)H, minor), 126.54 (Ar**C**(3)H, major), 147.20 (Ar**C**, both), 150.68 (Ar**C**-NO$_2$, both), 170.39 [**C**OCH$_3$]; m/z: 280 $(M+H)^+$, 220, 182, 143; HRMS (ES+): Found 280.1189, $C_{14}H_{18}NO_5$ $(M+H)^+$ requires 280.1185. STDEV: 1.40 ppm.

***(±)-2,2-Dimethyl-3-acetoxy -5-(4-tolyl)-tetrahydrofuran* 399**



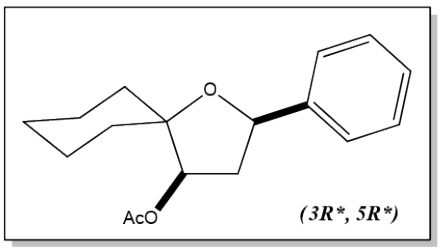
This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.05 mmol), acetic anhydride (3 mL), and **380** (0.25 g, 1.21 mmol, d.r. >98:2) in dichloromethane (30 mL). The *ester* was isolated as a light gold oil (0.26 g, 87%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (film): 2975, 1736, 1366, 1226, 1169; δ_H (300 MHz): 1.33 [6H, s, (C**H**$_3$)$_2$], 1.92 [1H, ddd, *J*=4.4, 7.6, 13.9, H_A of C(4)**H**], 2.06 [3H, s, COC**H**$_3$], 2.33 [3H, s, C**H**$_3$], 2.81 [1H, ddd, *J*=6.9, 7.6, 13.9, H_B of C(4)**H**], 4.96 [1H, t, *J*=7.6, C(5)**H**], 5.10 [1H, dd, *J*=4.4, 6.9, C(3)**H**], 7.13 (1H, d, *J*=8.0, ArC(3)**H**), 7.27 (1H, d, *J*=8.0, ArC(2)**H**); δ_C (75.5 MHz): 21.05 [CO**C**H$_3$], 21.12 [Ar-**C**H$_3$], 22.83 [**C**H$_3$], 25.47 [**C**H$_3$], 41.07 [**C**(4)H$_2$], 77.01 [**C**(5)H], 79.54 [**C**(3)H], 82.40 [**C**(2)], 126.08 (Ar**C**(3)H), 129.25 (Ar**C**(2)H), 137.10 (Ar**C**-CH$_3$), 139.53 (Ar**C**), 170.58 [**C**OCH$_3$]; m/z: 249 $(M+H)^+$, 205, 203, 189, 187, 171, 123; HRMS (ES+): Found 249.1484, $C_{15}H_{21}O_3$ $(M+H)^+$ requires 249.1491. STDEV: 2.80 ppm

***(±)-2,2-Dimethyl-3-acetoxy-5-tertbutyltetrahydrofuran* 400**



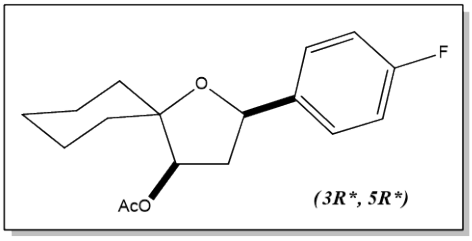
This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.04 mmol), acetic anhydride (15 mL), and **381** (0.64 g, 3.70 mmol, d.r. >98:2) in pyridine (50 mL). The *ester* was isolated as a light gold oil (0.49 g, 63%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (15:85) as eluant. ν_{max}/cm^{-1} (film): 2958, 1739, 1596, 1479, 1374, 1247, 1150; δ_H (300 MHz): 0.88 [9H, s, (C**H**$_3$)$_3$], 1.18 [3H, s, C**H**$_3$], 1.21 [3H, s, C**H**$_3$], 1.90 [1H, ddd, *J*=4.3, 8.2, 13.8, H_A of C(4)**H**$_2$], 2.06 [3H, s, OCOC**H**$_3$], 2.29 [1H, m, H_B of C(4)**H**$_2$], 3.66 [1H, t, *J*=7.6, C(5)**H**], 4.94 [1H, dd, *J*=4.3, 7.0, C(3)**H**]. Spectroscopic characteristics corresponded directly with those reported for the 3R*, 5R* isomer.[178]

***(±)-2-Phenyl-1-oxaspiro[4.5]decan-4-yl acetate* 401**



This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.04 mmol), acetic anhydride (2 mL), and **382** (0.10 g, 0.40 mmol, d.r. >98:2) in pyridine (10 mL). The *ester* was isolated as a light gold oil (0.11 g, 89%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (15:85) as eluant. ν_{max}/cm^{-1} (film): 2979, 1739, 1607, 1511, 1467, 1375, 1244, 1147, 1047; δ_H (400 MHz): 1.20-1.80 [10H, m, (C**H**$_2$)$_5$], 1.89 [1H, ddd, *J*=3.5, 6.8, 14.2, H_A of C(4)**H**$_2$], 2.03 [3H, s, OCOC**H**$_3$], 2.85 [1H, ddd, *J*=6.8, 7.6, 14.2, H_B of C(4)**H**$_2$], 4.99 [1H, t, *J*=7.6, C(5)**H**], 5.13 [1H, dd, *J*=4.0, 6.8, C(3)**H**], 7.10-7.65 (5H, m, Ar**H**). Spectroscopic characteristics corresponded directly with those reported for the 3R*, 5R* isomer.[178]

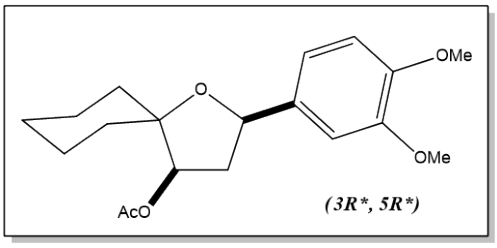
***(±)-2-(4-Fluorophenyl)-1-oxaspiro[4.5]decan-4-yl acetate* 402**



This compound was prepared following the procedure described for **394**, using DMAP (16.00 mg, 0.13 mmol), acetic anhydride (5 mL), and **383** (0.50 g, 1.99 mmol, d.r. >98:2) in dichloromethane

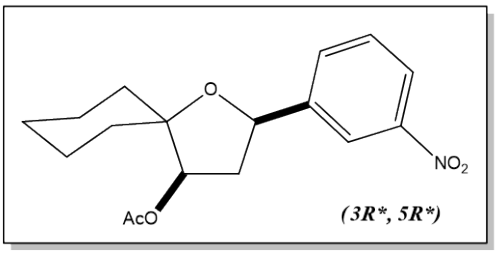
(40 mL). The *ester* was isolated as a light gold oil (0.48 g, 83%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (film): 2936, 2861, 1734, 1650, 1510, 1242, 1157; δ_H (300 MHz): 1.30-1.78 [10H, m, (C**H**$_2$)$_5$], 1.85 [1H, ddd, *J*= 3.3, 6.7, 14.1, H_A of C(4)**H**$_2$], 2.04 [3H, s, COC**H**$_3$], 2.84 [1H, ddd, *J*=6.7, 8.0, 14.1, H_B of C(4)**H**$_2$], 4.98 [1H, t, *J*=7.3, C(5)**H**], 5.14 [1H, dd, *J*=3.3, 6.7, C(3)**H**], 7.01 (2H, t, *J*=8.6, ArC(2)**H**), 7.38 (2H, dd, *J*=5.5, 8.6, ArC(3)**H**); δ_C (75.5 MHz): 21.12 [CO**C**H$_3$], 22.58, 22.72, 25.62, 31.58, 33.84 [5x**C**H$_2$, (**C**H$_2$)$_5$], 41.30 [**C**(4)H$_2$], 76.26 [**C**(5)H], 78.50 [**C**(3)H], 84.31 [**C**(2)], 115.12 (d, $^2J_{CF}$=21.4, Ar**C**(3)H), 127.71 (d, $^3J_{CF}$=8.0, Ar**C**(2)H), 138.96 (d, $^4J_{CF}$=3.1, Ar**C**), 162.10 (d, $^1J_{CF}$=245.1, Ar**C**-F), 170.60 [**C**OCH$_3$]; δ_F (470 MHz): -114.24, -116.12; m/z: 293 $(M+H)^+$, 247, 194, 153, 85; HRMS (ES+): Found 293.1553, $C_{17}H_{21}FO_3$ $(M+H)^+$ requires 293.1556. STDEV: 0.70 ppm.

***(±)-2-(3,4-Dimethoxyphenyl)-1-oxaspiro[4.5]decan-4-yl acetate* 403**



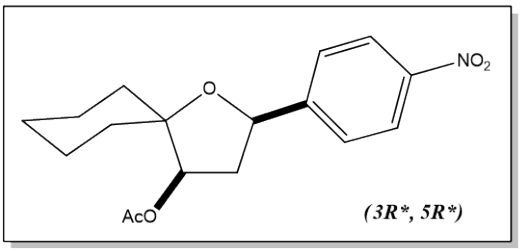
This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.04 mmol), acetic anhydride (3 mL), and **384** (0.06 g, 0.19 mmol, >98:2) in dichloromethane (10 mL). The *ester* was isolated as a light gold oil (0.05 g, 80%, >98:2) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (film): 2935, 2859, 1737, 1517, 1241; δ_H (300 MHz): 1.30-1.80 [10H, m, (C**H**$_2$)$_5$], 1.89 [1H, ddd, *J*=3.5, 6.8, 14.3, H_A of C(4)**H**$_2$], 2.06 [3H, s, COC**H**$_3$], 2.83 [1H, ddd, *J*=6.8, 7.9, 14.3, H_B of C(4)**H**$_2$], 3.87 [3H, s, OC**H**$_3$], 3.90 [3H, s, OC**H**$_3$], 4.95 [1H, t, *J*=7.4, C(5)**H**], 5.15 [1H, dd, *J*=3.5, 6.8, C(3)**H**], 6.82 (1H, d, *J*=8.2, ArC(5)**H**), 6.91 (2H, dd, *J*=1.9, 8.2, ArC(6)**H**), 6.99 (1H, d, *J*=1.9, ArC(2)**H**); δ_C (75.5 MHz): 21.08 [CO**C**H$_3$], 22.57, 22.68, 25.63, 31.63, 33.85 [5xC**H**$_2$, (**C**H$_2$)$_5$], 40.15 [**C**(4)H$_2$], 55.74, 55.95, (2xO**C**H$_3$), 76.69 [**C**(5)H], 77.58 [C(3)**H**], 84.04 [**C**(2)], 109.45 (Ar**C**(5)H), 110.97 (Ar**C**(6)H), 118.43 (Ar**C**(2)H), 135.77 (Ar**C**), 148.36 (Ar**C**O), 148.98 (Ar**C**O), 170.50 [**C**OCH$_3$]; m/z: 335 $(M+H)^+$, 289, 275, 257, 223, 167; HRMS (ES+): Found 335.1783, $C_{19}H_{27}O_5$ $(M+H)^+$ requires 335.1858. STDEV: 22.40 ppm

***(±)-2-(3-Nitrophenyl)-1-oxaspiro[4.5]decan-4-yl acetate* 404**



This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.05 mmol), acetic anhydride (5 mL), and **385** (0.10 g, 0.36 mmol, d.r. >98:2) in dichloromethane (15 mL). The *ester* was isolated as a light gold oil (0.10 g, 83%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (10:90) as eluant. ν_{max}/cm^{-1} (film): 2935, 2860, 1738, 1530, 1350, 1242; δ_H (300 MHz): 1.30-1.80 [10H, m, (C**H**$_2$)$_5$], 1.89 [1H, ddd, *J*=2.7, 5.8, 14.5, H_A of C(4)**H**], 2.05 [3H, s, COC**H**$_3$], 2.95 [1H, ddd, *J*=6.3, 8.5, 14.5, H_B of C(4)**H**], 5.12 [1H, dd, *J*=5.8, 8.5, C(5)**H**], 5.18 [1H, dd, *J*=2.7, 6.3, C(3)**H**], 7.50 (1H, t, *J*=7.9, ArC(5)**H**), 7.69 (1H, d, *J*=7.7, Ar(6)**H**), 8.12 (1H, ddd, *J*=1.0, 3.4, 8.2, ArC(4)**H**), 8.34 (1H, t, *J*=2.1, ArC(2)**H**); δ_C (75.5 MHz): 21.02 [CO**C**H$_3$], 22.57, 22.76, 25.54, 31.38, 33.88 [5x**C**H$_2$, (**C**H$_2$)$_5$], 41.02 [**C**(4)H$_2$], 76.05 [**C**(5)H], 78.06 [**C**(3)H], 85.29 [**C**(2)], 121.36 (Ar**C**(5)H), 122.32 (Ar**C**(6)H), 129.20 (Ar**C**(4)H), 132.23 (Ar**C**(2)H), 145.88 (Ar**C**), 148.44 (Ar**C**-NO$_2$), 170.49 (**C**OCH$_3$); m/z: 320 $(M+H)^+$, 258, 209, 167, 109; HRMS (ES+): Found 320.1510, $C_{17}H_{22}NO_5$ $(M+H)^+$ requires 320.1498. STDEV: 3.70 ppm

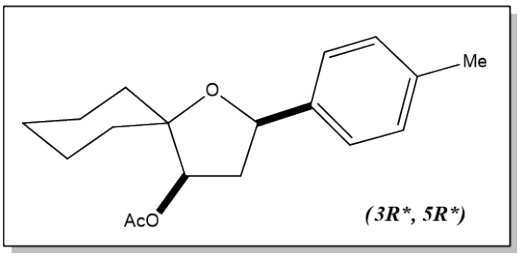
***(±)-2-(4-Nitrophenyl)-1-oxaspiro[4.5]decan-4-yl acetate* 405**



This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.05 mmol), acetic anhydride (2 mL), and **386** (0.25 g, 0.90 mmol, d.r. >98:2) in dichloromethane (30 mL). The *ester* was isolated as a light gold oil (0.23 g, 82%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. Found C: 64.35, H: 6.34, N: 4.39, $C_{17}H_{21}NO_5$ requires C: 63.94, H: 6.63, N: 4.39; ν_{max}/cm^{-1} (film): 2935, 1738, 1642, 1521, 1348, 1242; δ_H (300 MHz): 1.35-1.80 [10H, m, (C**H**$_2$)$_5$], 1.87 [1H, ddd, *J*=3.0, 6.2, 14.2, H_A of C(4)**H**$_2$], 1.99 [3H, s, COC**H**$_3$], 2.94 [1H, ddd, *J*=6.2, 8.5, 14.2, H_B of C(4)**H**$_2$], 5.09-5.18 [2H, m, C(5)**H** and C(3)**H**], 7.56 (2H, d, *J*=8.6, ArC(2)**H**), 8.19 (2H, d, *J*=8.6, ArC(3)**H**); δ_C (75.5 MHz): 20.93 [CO**C**H$_3$], 22.55, 22.70, 25.22, 31.44, 34.04 [5x**C**H$_2$, (**C**H$_2$)$_5$], 40.99 [**C**(4)H$_2$], 75.96 [**C**(5)H], 78.13 [**C**(3)H], 85.05 [**C**(2)], 123.55 (Ar**C**(2)H), 126.52 (Ar**C**(3)H),

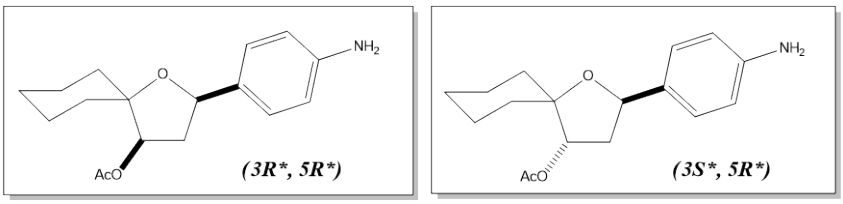
147.11 (Ar**C**), 151.21 (Ar**C**-NO_2), 170.34 (**C**OCH_3); m/z: 320 $(M+H)^+$, 258, 243, 209, 152, 109; HRMS (ES+): Found 320.1492, $C_{17}H_{22}NO_5$ $(M+H)^+$ requires 320.1498. STDEV: 1.90 ppm.

***(±)-2-(p-Tolyl)-1-oxaspiro[4.5]decan-4-yl acetate* 406**



This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.05 mmol), acetic anhydride (5 mL), and **387** (0.15 g, 0.60 mmol, d.r. >98:2) in dichloromethane (15 mL). The *ester* was isolated as a light gold oil (0.15 g, 87%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (film): 2934, 2860, 1737, 1514, 1244; δ_H (300 MHz): 1.25-1.80 [10H, m, $(CH_2)_5$], 1.87 [1H, ddd, *J*=3.6, 6.9, 14.2, H_A of C(4)**H**], 2.04 [3H, s, $COCH_3$], 2.33 [3H, s, CH_3], 2.62 [1H, ddd, *J*=6.9, 7.6, 14.2, H_B of C(4)**H**], 4.95 [1H, t, *J*=7.6, C(5)**H**], 5.13 [1H, dd, *J*=3.6, 6.9, C(3)**H**], 7.13 (1H, d, *J*=8.0, ArC(3)**H**), 7.28 (1H, d, *J*=8.0, ArC(2)**H**); δ_C (75.5 MHz): 21.13 [CO**C**H_3], 21.15 [Ar-**C**H_3], 22.59, 22.70, 25.68, 31.63, 33.84 [5xCH_2, **C**H_2]$_5$, 41.21 [**C**(4)H_2], 77.66 [**C**(5)H], 79.12 [**C**(3)H], 83.93 [**C**(2)], 125.17 (Ar**C**(3)H), 129.28 (Ar**C**(2)H), 137.37 (Ar**C**-CH_3), 140.11 (Ar**C**), 170.68 [**C**OCH_3]; m/z: 289 $(M+H)^+$, 243, 230, 211, 123; HRMS (ES+): Found 289.1815, $C_{18}H_{25}O_3$ $(M+H)^+$ requires 289.1804. STDEV: 3.80 ppm.

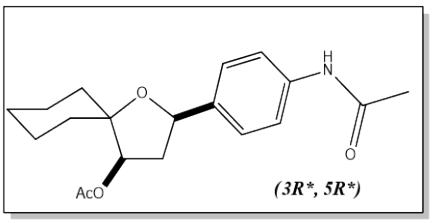
***(±)-2-(4-Aminophenyl)-1-oxaspiro[4.5]decan-4-yl acetate* 407**

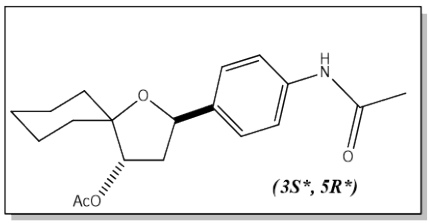


This compound was prepared by hydrogenolysis of **393** (0.06 g, 0.14 mmol, d.r. 30:70 [(3R*, 5R*):(3S*, 5R*)]) with 10% Pd-C (6.00 mg, 10% w/w) in ethanol (3 mL). The mixture was shaken overnight at room temperature under a pressure of 60 psi. The resulting mixture was filtered through Celite® to remove the catalyst and the filter cake washed with ethanol (10 mL), before concentrating the filtrate under reduced pressure to yield the deprotected *ester* (35.00 mg, 88%, d.r. 30:70) as a light gold oil.

(Major diastereomer: (3R*, 5S*), minor diastereomer: (3R*, 5R*)). ν_{max}/cm^{-1} (film): 3390, 2940, 2932, 1739, 1640, 1410; δ_H (300 MHz):1.20-1.85 [10.30H, m, (C**H**$_2$)$_5$, both diastereomers and H_A of C(4)H_2, major], 1.95-2.20 [4.40H, m, C(4)**H**$_2$, minor and COC**H**$_3$, both diastereomers], 2.74 [0.30H, ddd, *J*=6.8, 7.9, 14.3, H_B of C(4)**H**$_2$, major], 3.55 (2H, bs, N**H**$_2$, both diastereomers), 4.80 [0.30H, t, *J*=7.4, C(5)**H**, major], 4.97 [0.70H, t, *J*=7.9, C(5)**H**, minor], 5.05 [0.30H, dd, *J*=3.6, 6.8, C(3)**H**, major], 5.15 [0.70H, t, *J*=2.9, C(3)**H**, minor], 6.58 (2H, d, *J*=8.3, Ar**H**, both diastereomers), 7.07 (2H, d, *J*=8.3, Ar**H**, both diastereomers); δ_C (75.5 MHz): 20.13 [CO**C**H$_3$, both diastereomers], 21.55, 21.66, 24.66, 30.67, 32.78 [5xCH2, (**C**H$_2$)$_5$, major], 21.93, 22.10, 24.49, 30.14, 36.63 [5xCH$_2$, (**C**H$_2$)$_5$, minor], 40.16 [**C**(4)H$_2$, major], 40.44 [**C**(4)H$_2$, minor], 76.65 [**C**(5)H, both diastereomers], 77.70 [**C**(3)H, minor], 78.11 [**C**(3)H, major], 82.64 [**C**(2), major], 83.16 [**C**(2), minor], 113.99 (Ar**C**H, major), 114.04 (Ar**C**H, minor), 126.12 (Ar**C**H, minor), 126.45 (Ar**C**H, minor), 131.32 (Ar**C**, both diastereomers), 135.99 (Ar**C**, both diastereomers), 144.82 (Ar**C**, both diastereomers), 169.52 [**C**OCH$_3$, minor], 169.65 [**C**OCH$_3$, major]; m/z: 424 $(M+H)^+$, 364, 290, 230, 137; HRMS (ES+): Found 424.2115, $C_{25}H_{30}NO_5$ $(M+H)^+$ requires 424.2124. STDEV: 2.10 ppm.

***(±)-2-(4-Acetamidophenyl)-1-oxaspiro[4.5]decan-4-yl acetate* 392**

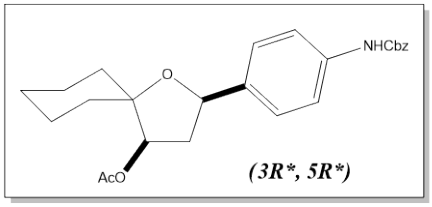


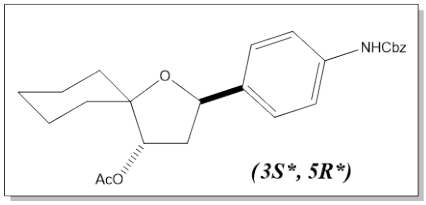


This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.04 mmol), acetic anhydride (0.12 mL, 1.22 mmol), and **388** (0.15 g, 0.61 mmol, d.r. 78:22 [(3R*, 5R*):(3S*, 5R*)]) in dichloromethane (20 mL). The *ester* was isolated as a light brown oil and an inseparable mixtue of diastereomers (0.16 g, 80%, d.r. 38:62) by flash chromatography, using ethyl acetate:hexane (10:90) as eluant. (Major diastereomer: (3R*, 5S*), minor diastereomer: (3R*, 5R*)). ν_{max}/cm^{-1} (film): 3308, 2920, 2851, 1737, 1669, 1604, 1537, 1516, 1374, 1247; δ_H (300 MHz): 1.20-1.80 [10H, m, C**H**$_2$)$_5$, both diastereomers], 1.85 [0.38H, ddd, *J*=3.4, 6.8, 14.2, H_A of C(4)**H**$_2$, minor], 2.05-2.30 [1.24H, m, C(4)**H**$_2$, major], 2.05 [1.14H, s, COC**H**$_3$, minor], 2.13, [1.86H, s, COC**H**$_3$, major], 2.16 [3H, s, NHCOC**H**$_3$, both diastereomers], 2.82 [0.38H, ddd, *J*=6.8, 7.6, 14.2, H_B of C(4)**H**$_2$, minor], 4.96 [0.38H, t, *J*=7.6, C(5)**H**, minor], 5.08-

5.16 [1H, m, C(3)**H** minor and C(5)**H** major], 5.23 [0.62H, dd, *J*=1.2, 5.0, C(3)**H** major], 7.29 (2H, d, *J*=8.5, ArC(3)**H**, both diastereomers), 7.40 (1H, bs, N**H**, both diastereomers), 7.46 (2H, d, *J*=8.5, ArC(2)**H**, both diastereomers); δ_C (75.5 MHz): 21.13 [CO**C**H_3, major], 21.16 [CO**C**H_3, minor], 22.58, 22.70, 25.62, 31.57, 33.84 [5xCH_2, (**C**H_2)$_5$, major], 22.94, 22.70, 25.45, 31.14, 37.52 [5xCH_2, (**C**H_2)$_5$, major], 24.57 [NHCO**C**H_3, both diastereomers], 41.12 [**C**(4)H_2, major], 41.53 [**C**(4)H_2, minor], 76.44 [**C**(5)H, major], 78.44 [**C**(5)H, minor], 78.53 [**C**(3)H, major], 78.95 [**C**(5)H, minor], 84.16 [**C**(2), major], 84.64 [**C**(2), minor], 119.83 (Ar**C**(3)H, major), 119.95 (Ar**C**(3)H, minor), 126.42 (Ar**C**(2)H, minor), 126.77 (Ar**C**(2)H, major), 137.11 (Ar**C**, both diastereomers), 138.61 (Ar**C**-NH, minor), 139.14 (Ar**C**-NH, major), 168.37 [NH**C**OCH_3, both diastereomers], 170.55 [**C**OCH_3, minor], 170.67 [**C**OCH_3, major]; m/z: 332 $(M+H)^+$, 272, 254, 230, 105; HRMS (ES+): Found 332.1856, $C_{19}H_{26}NO_4$ $(M+H)^+$ requires 332.1862. STDEV: 1.80 ppm.

***(±)-Benzyl-(4-(4-acetoxy-1-oxaspiro[4.5]-decan-2-yl)phenyl)-carbamate* 393**

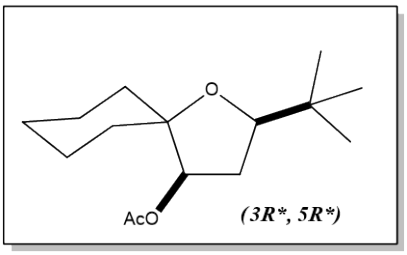




This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.05 mmol), acetic anhydride (1.50 mL), and **390** (0.11 g, 0.29 mmol, d.r. 30:70 [(3R*, 5R*):(3S*, 5R*)]) in dichloromethane (20 mL). The *ester* was isolated as a light gold oil (98.00 mg, 80%, d.r. 30:70) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. (Major diastereomer: (3R*, 5S*), minor diastereomer: (3R*, 5R*)). ν_{max}/cm^{-1} (film): 3328, 2934, 2859, 1736, 1712, 1615, 1601, 1537, 1314, 1221; δ_H (300 MHz): 1.20-1.85 [10.30H, m, (C**H**$_2$)$_5$, both diastereomers and H_A of C(4)**H**$_2$, minor], 1.95-2.20 [4.40H, m, C(4)**H**$_2$, major and COC**H**$_3$, both diastereomers], 2.74 [0.30H, ddd, *J*=6.8, 7.9, 14.4, H_B of C(4)**H**$_2$, minor], 4.87 [0.30H, t, *J*=6.8, C(5)**H**, minor], 5.00-5.20 [3.70H, m, C(3)**H**, both diastereomers, C(5)**H**, major and OC**H**$_2$Ph, both diastereomers], 6.70 (1H, bs, N**H**, both diastereomers), 7.18-7.38 (9H, Ar**H**, both diastereomers); δ_C (75.5 MHz): 21.54, 21.66, 24.43, 30.10, 36.49 [5xCH2, (**C**H_2)$_5$, minor], 21.91, 22.07, 24.59, 30.54, 32.80 [5xCH_2, (**C**H_2)$_5$, major], 40.11 [**C**(4)H_2, minor], 40.49 [**C**(4)H_2, major], 65.97 [O**C**H_2Ph, both diastereomers], 76.45 [**C**(5)H,

minor], 77.38 [**C**(5)H, major], 77.51 [**C**(3)H, minor], 77.94 [**C**(3)H, major], 83.09 [**C**(2), minor], 83.55 [**C**(2), major] 125.50 (Ar**C**H, both diastereomers), 125.84 (Ar**C**H, both diastereomers), 127.29 (Ar**C**H, both diastereomers), 127.33 (Ar**C**H, both diastereomers), 127.59 (Ar**C**H, both diastereomers), 135.01 (Ar**C**, both diastereomers), 135.99 (Ar**C**, both diastereomers), 138.75 (Ar**C**, both diastereomers), 152.32 [**C**O_2Bn, both diastereomers], 169.51 [**C**OCH_3, major], 169.63 [**C**OCH_3, minor]; m/z: 424 $(M+H)^+$, 364, 290, 230, 137; HRMS (ES+): Found 424.2115, $C_{25}H_{30}NO_5$ $(M+H)^+$ requires 424.2124. STDEV: 2.10 ppm.

***(±)-2-Tert-butyl-1-oxaspiro[4.5]decan-4-yl acetate* 408**



This compound was prepared following the procedure described for **394**, using DMAP (5.00 mg, 0.04 mmol), acetic anhydride (2 mL), and **391** (0.25, g, 1.17 mmol, d.r. >98:2) in dichloromethane (30 mL). The *ester* was isolated as a light gold oil (0.24 g, 80%, d.r. >98:2) by flash chromatography, using ethyl acetate:hexane (10:90) as eluant. ν_{max}/cm^{-1} (film): 2935, 2862, 1739, 1364, 1244; δ_H (300 MHz): 0.88 [9H, s, (C**H**$_3$)$_3$], 1.25-1.70 [11H, m, (C**H**$_2$)$_5$ and H_A of C(4)**H**$_2$], 2.04 [3H, s, COC**H**$_3$], 2.19 [1H, quintet, *J*=7.2, 14.0, H_B of C(4)**H**$_2$], 3.59 [1H, t, *J*=7.6, C(5)**H**], 4.97 [1H, dd, *J*=4.1, 7.2, C(3)**H**]; δ_C (75.5 MHz): 22.60, 22.90, 25.98, 31.33, 33.86 [5x**C**H$_2$, (**C**H$_2$)$_5$], 25.66 [(**C**H$_3$)$_3$], 33.14 [**C**(CH$_3$)$_3$], 37.78 [**C**(4)H$_2$], 77.20 [**C**(5)H], 82.21 [**C**(3)H], 82.79 [**C**(2)]; m/z: 255 $(M+H)^+$, 225, 195, 177, 109; HRMS (ES+): Found 255.1956, $C_{15}H_{27}O_3$ $(M+H)^+$ requires 255.1960. STDEV: 1.60 ppm

3.2.4 Lipase Mediated Kinetic Resolution of 3-Hydroxytetrahydrofurans

3.2.4.1 General Procedure for Enzymatic Screens and Optimisation Experiments

The respective racemic alcohols were dissolved in diisopropylther and dispensed into 20 mL screw-top test-tubes with a pipettor, such that there was ~20 mg of substrate per test-tube. Vinyl acetate (1 eq.) and lipase (spatula tip) were subsequently added and the test-tubes stirred at room temperature at 750 rpm for 24 h. The enzyme was removed by fitration, washed with ethyl acetate and the combined filtrate and washings concentrated under reduced pressure. The extent of conversion, if any, to the acetate was determined by ^{1}H NMR spectroscopy. The enantiomeric compositions of the products of these reactions were determined by chiral HPLC analysis at a later point (Reference Appendix A: Pages 253-258, for the conditions developed for each listed compound).

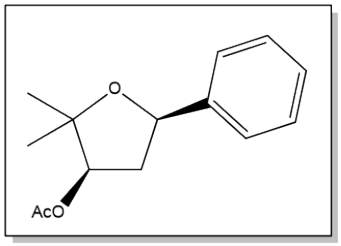
Screens to determine the optimal amount of lipase to be used in the preparative scale reactions were carried out in a similar manner to above, with **375** (20.00 mg, 0.10 mmol) in diisopropyl ether (3 mL) and vinyl acetate (8.60 mg, 0.10 mmol) stirred with the respective amount of *Pseudomonas stutzeri* lipase at room temperature and 750 rpm for 24 h. The respective crude products were isolated as per the procedure previously described and extent of conversion determined by ^{1}H NMR spectroscopy.

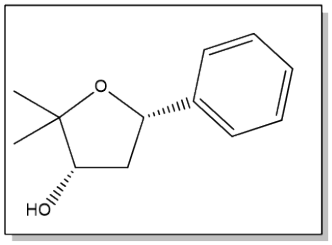
Enzyme (% w/w)	% Conversion
10	7
25	18
50	40
75	41

Table 3.2.4.2

3.2.4.2 Preparative Scale Resolution of 3-Hydroxytetrahydrofurans

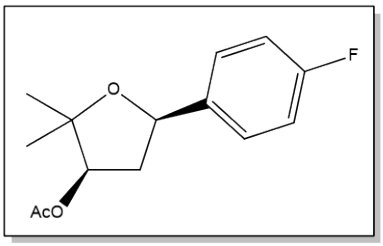
***Resolution of (±)-2,2-Dimethyl-3-hydroxy-5-phenyltetrahydrofuran* 375**

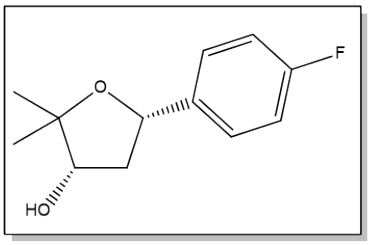




A racemic mixture of **375** (0.15 g, 0.80 mmol), diisopropylether (20 mL), vinyl acetate (0.14 g, 1.60 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where, ^{1}H NMR analysis indicated 48% conversion after 24 h. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl acetate:hexane (5:95) yielded (-)-(3R*,5R*)-2,2-dimethyl-3-acetoxy-5-phenyltetrahydrofuran **394** as a light gold oil (56.00 mg, 30%, d.r. >98:2), $[\alpha]_D^{20}$ = -1.02 (c = 0.39, $CHCl_3$), >99% ee, and (-)-(3S*,5S*)-2,2-dimethyl-3-hydroxy-5-phenyltetrahydrofuran **375** as a light gold oil (60.00 mg, 40%, d.r. >98:2), $[\alpha]_D^{20}$ = -3.96 (c = 0.51, $CHCl_3$), 91% ee. Spectroscopic characteristics of both products correspond with those of the racemic compounds.

***Resolution of (±)-2,2-Dimethyl-3-hydroxy-5-(4-flurorphenyl)-tetrahydrofuran* 376**

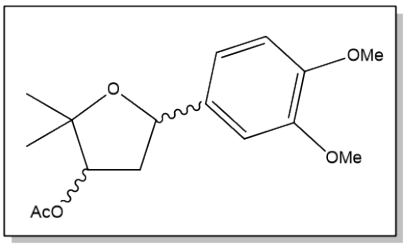


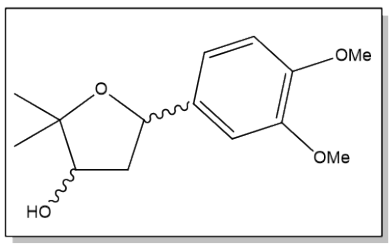


A racemic mixture of **376** (0.15 g, mmol), diisopropylether (20 mL), vinyl acetate (0.12 g, 1.40 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 47% conversion after 40 h. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl acetate:hexane (5:95) yielded (-)-(3R*, 5R*)-2,2-dimethyl-3-acetoxy-5-(4-fluoro)-phenyltetrahydrofuran **395** as a light gold oil (48.00 mg, 27%, d.r. >98:2), $[\alpha]_D^{20}$ = -20.37 (c = 0.56, $CHCl_3$), >99% ee, and (-)-(3S*, 5S*)-2,2-dimethyl-3-hydroxy-5-(4-fluoro)-phenyltetrahydrofuran **376** as a light gold oil (56.00 mg, 37 %, d.r. >98:2), $[\alpha]_D^{20}$ = -8.74 (c = 0.47, $CHCl_3$), 92% ee.

Spectroscopic characteristics of both products correspond with those of the racemic compounds.

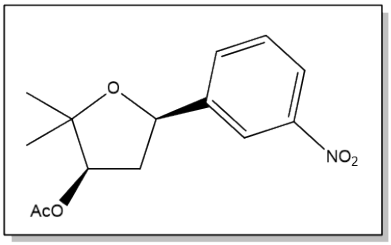
***Resolution of (±)-2,2-Dimethyl-3-hydroxy-5-(3,4-dimethoxyphenyl)-tetrahydrofuran* 377**

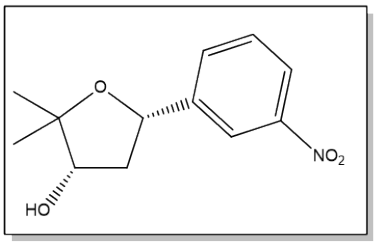




A racemic mixture of **377** (0.15 g, 0.59 mmol), diisopropylether (20 mL), vinyl acetate (0.30 g, 3.54 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 50% conversion after 24 h. The enzyme was filtered off, w ashed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl acetate:hexane (5:95) yielded 2,2-dimethyl-3-acetoxy-5-phenyltetrahydrofuran as a light gold oil and inseparable mixture of diastereomers (52.00 mg, 31%, d.r. 80:20), > 99% ee major, >99% ee minor and (3S*, 5S*)-2,2-dimethyl-3-hydroxy-5-phenyltetrahydrofuran as a light gold oil and inseparable mixture of diastereomers (41.00 mg, 24%, 80:20), >99% ee, >99% ee minor. Spectroscopic characteristics of both products correspond with those of the racemic compounds.

***Resolution of (±)-2,2-Dimethyl-3-hydroxy-5-(3-nitrophenyl)-tetrahydrofuran* 378**

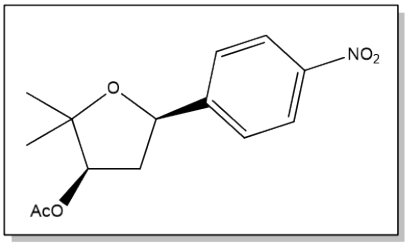


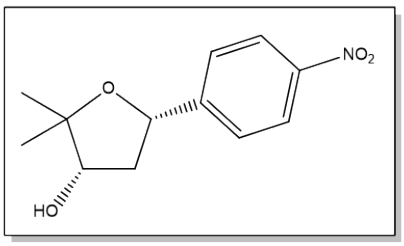


A racemic mixture of **378** (0.15 g, mmol), diisopropylether (20 mL), vinyl acetate (0.26 g, 3.00 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 50% conversion after 48 h. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl acetate:hexane (5:95) yielded (-)-(3R*,5R*)-2,2-dimethyl-3-acetoxy-5-(3-nitro)-phenyltetrahydrofuran **378** as an orange oil (62.00 mg, 37%, d.r. >98:2), $[\alpha]_D^{20}$ = -24.55 (c = 0.77, $CHCl_3$), >99% ee, and (-)-

(3S*,5S*)-2,2-dimethyl-3-hydroxy-5-(3-nitro)-phenyltetrahydrofuran **378** as an orange oil (57.00 mg, 38%, d.r. >98:2), $[\alpha]_D^{20}$ = -2.58 (c = 0.47, $CHCl_3$), >99% ee. Spectroscopic characteristics of both products correspond with those of the racemic compounds.

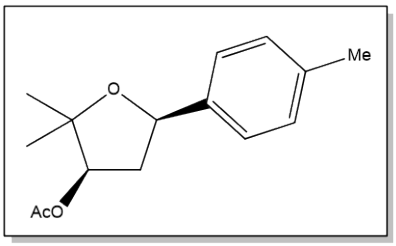
***Resolution of (±)-2,2-Dimethyl-3-hydroxy-5-(4-nitrophenyl)-tetrahydrofuran* 379**

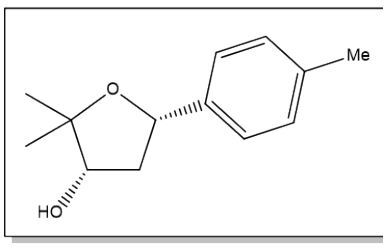




A racemic mixture of **379** (0.15 g, 0.63 mmol), diisopropylether (20 mL), vinyl acetate (0.26 g, 3.00 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 50% conversion after 28 h. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl acetate:hexane (5:95) yielded 2,2-dimethyl-3-acetoxy-5-(4-nitrophenyl)-tetrahydrofuran as an orange oil and inseparable mixture of diastereomers (48.00 mg, 27%, d.r. 80:20), >99% ee major, >99% ee minor, and (3S*, 5S*)-2,2-dimethyl-3-hydroxy-5-(4-nitrophenyl)-tetrahydrofuran as a dark gold oil and inseparable mixture of diastereomers (37.00 mg, 25%, d.r. 80:20), >99% ee major, >99% ee minor. Spectroscopic characteristics of both products correspond with those of the racemic compounds.

***Resolution of (±)-2,2-Dimethyl-3-hydroxy-5-(4-tolyl)-tetrahydrofuran* 380**

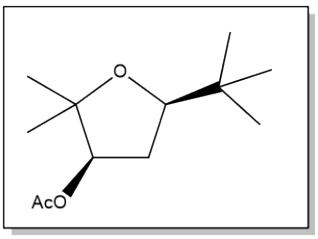


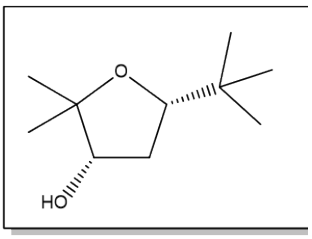


A racemic mixture of **380** (0.15 g, mmol), diisopropylether (20 mL), vinyl acetate (0.37 g, 4.30 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 50% conversion after 24 h. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl acetate:hexane (5:95) yielded (-)-

(3R*,5R*)-2,2-dimethyl-3-acetoxy-5-(4-nitro)-phenyltetrahydrofuran **399** as a clear oil (61.00 mg, 34%, d.r. >98:2), $[\alpha]_D^{20}$ = -0.24 (c = 0.41, $CHCl_3$), >99% ee, and (-)-(3S*,5S*)-2,2-dimethyl-3-hydroxy-5-(4-nitro)-phenyltetrahydrofuran **380** a a white solid (58.00 mg, 39%, d.r. >98:2), $[\alpha]_D^{20}$ = -10.20 (c = 0.50, $CHCl_3$), >99% ee. Spectroscopic characteristics of both products correspond with those of the racemic compounds.

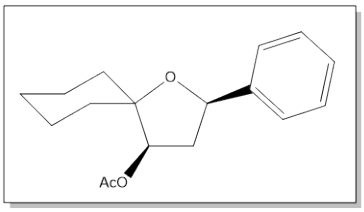
***Resolution of (±)-2,2-Dimethyl-3-hydroxy-5-tert-butyl-tetrahydrofuran* 381**

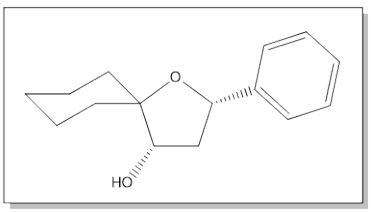




A racemic mixture of **381** (0.15 g, 0.87 mmmol), diisopropylether (20 mL), vinyl acetate (0.52 mg, 6.09 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 5% conversion after 20 days. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl acetate:hexane (5:95) was unsuccessful in yielding (+)-(3R*, 5R*)-2,2-dimethyl-3-acetoxy-5-phenyltetrahydrofuran **400**, and (3R*, 5R*)-2,2-dimethyl-3-hydroxy-5-phenyltetrahydrofuran **381** was isolated as an oil (54.00 mg, 36%, d.r. >98:2). Spectroscopic characteristics of the isolated product corresponded with that of the racemic compounds. Chiral analysis of this compound was not carried out owing to the poor conversion and the inability to isolate **400** for enantiomeric analysis.

***Resolution of (±)-2-Phenyl-1-oxaspiro[4.5]decan-4-ol* 382**

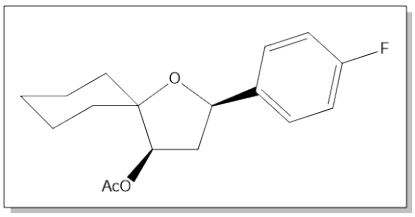


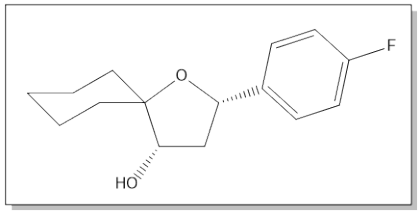


A racemic mixture of **382** (0.15 g, 0.64 mmmol), diisopropylether (20 mL), vinyl acetate (0.33 g, 3.84 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 48% conversion after 24 h. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl

acetate:hexane (5:95) yielded (-)-(3R*,5R*)-2-phenyl-1-oxaspiro[4.5]decan-4-ol **401** as a light gold oil (55.00 mg, 31%, d.r. >98:2), $[\alpha]_D^{20}$ = -1.29 (c = 0.50, $CHCl_3$), >99% ee, and (-)-(3S*,5S*)-2-phenyl-1-oxaspiro[4.5]decan-4-ol **382** as a light gold oil (60.00 mg, 40%, d.r. >98:2), $[\alpha]_D^{20}$ = -3.58 (c = 0.69, $CHCl_3$), 93% ee. Spectroscopic characteristics of both products correspond with those of the racemic compounds.

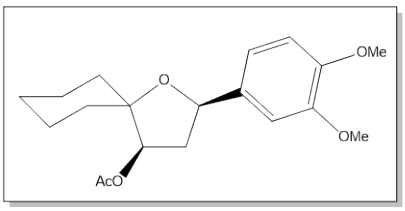
***Resolution of (±)-2-(4-Fluorophenyl)-1-oxaspiro[4.5]decan-4-ol* 383**

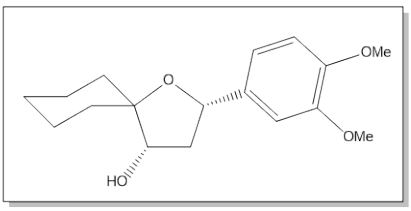




A racemic mixture of **383** (0.15 g, 0.59 mmmol), diisopropylether (20 mL), vinyl acetate (0.31 g, 3.54 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 50% conversion after 24 h. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl acetate:hexane (5:95) yielded (-)-(3R*,5R*)-2-(4-fluorophenyl)-1-oxaspiro[4.5]decan-4-ol **383** as a clear oil (61.00 mg, 35%, d.r. >98:2), $[\alpha]_D^{20}$ = -1.29 (c = 0.35, $CHCl_3$), >99% ee, and (-)-(3S*,5S*)-2-(4-fluorophenyl)-1-oxaspiro[4.5]decan-4-ol **383** as a white solid (51.00 mg, 34%, d.r. >98:2), $[\alpha]_D^{20}$ = -6.00 (c = 0.41, $CHCl_3$), >99% ee. Spectroscopic characteristics of both products correspond with those of the racemic compounds.

***Resolution of (±)-2-(3,4-Dimethoxyphenyl)-1-oxaspiro[4.5]decan-4-ol* 384**

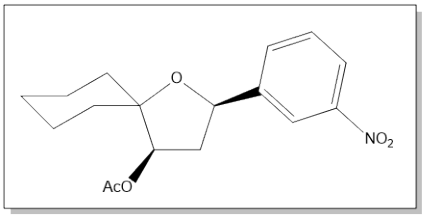


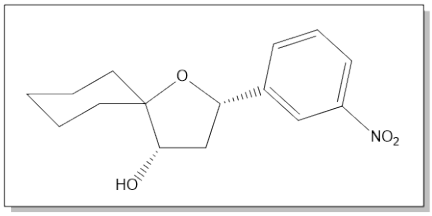


A racemic mixture of **384** (0.15 g, 0.59 mmmol), diisopropylether (20 mL), vinyl acetate (0.30 g, 3.54 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 50% conversion after 24 h. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash

chromatography with ethyl acetate:hexane (5:95) yielded (-)-(3R*, 5R*)-2-(3,4-dimethoxyphenyl)-1-oxaspiro[4.5]decan-4-ol **403** as a clear oil (49.00 mg, 25%, d.r. >98:2), $[\alpha]_D^{20}$ = -66.33 (c = 0.10, $CHCl_3$), >99% ee, and (-)-(3S*, 5S*)-2-(3,4-dimethoxyphenyl)-1-oxaspiro[4.5]decan-4-ol **384** as a clear oil (58.00 mg, 39%, d.r. >98:2), $[\alpha]_D^{20}$ = -0.48 (c = 0.83, $CHCl_3$), >99% ee. Spectroscopic characteristics of both products correspond with those of the racemic compounds.

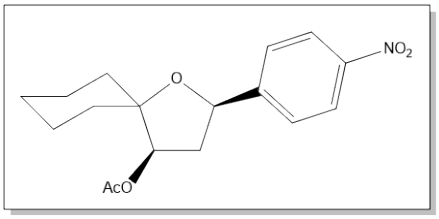
***Resolution of (±)-2-(3-Nitrophenyl)-1-oxaspiro[4.5]decan-4-ol* 385**

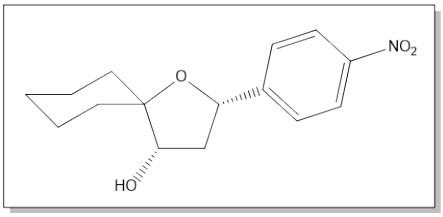




A racemic mixture of **385** (0.15 g, 0.54 mmmol), diisopropylether (20 mL), vinyl acetate (0.23 g, 2.70 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 50% conversion after 48 h. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl acetate:hexane (5:95) yielded (-)-(3R*,5R*)-2-(3-nitrophenyl)-1-oxaspiro[4.5]decan-4-ol **404** as oil (65.00 mg, 38%, d.r. >98:2), $[\alpha]_D^{20}$ = -2.12 (c = 0.45, $CHCl_3$), >99% ee, and (-)-(3S*, 5S*)-2-(3-nitrophenyl)-1-oxaspiro[4.5]decan-4-ol **385** as oil (53.00 mg, 35%, d.r. >98:2), $[\alpha]_D^{20}$ = -1.19 (c = 0.67, $CHCl_3$), >99% ee. Spectroscopic characteristics of both products correspond with those of the racemic compounds.

***Resolution of (±)-2-(4-Nitrophenyl)-1-oxaspiro[4.5]decan-4-ol* 386**

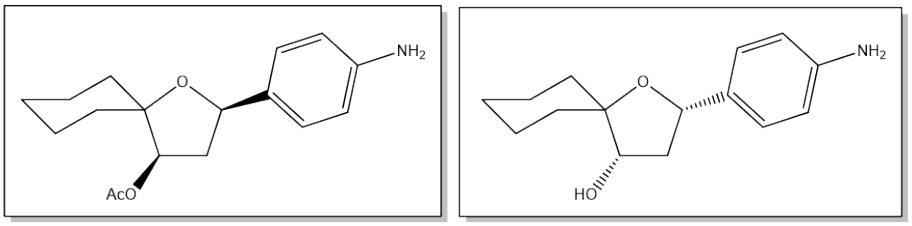




A racemic mixture of **386** (0.15 g, 0.54 mmmol), diisopropylether (20 mL), vinyl acetate (0.33 g, 3.78 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 49% conversion after 20 h. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined

washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl acetate:hexane (5:95) yielded (-)-(3R*,5R*)-2-(4-nitrophenyl)-1-oxaspiro[4.5]decan-4-ol **405** as oil (48.00 mg, 28%, d.r. >98:2), $[\alpha]_D^{20}$ = -16.68 (c = 0.62, $CHCl_3$), >99% ee, and (-)-(3S*,5S*)-2-(4-nitrophenyl)-1-oxaspiro[4.5]decan-4-ol **386** as oil (56.00 mg, 37%, d.r. >98:2), $[\alpha]_D^{20}$ = -20.68 (c = 0.51, $CHCl_3$), 95% ee. Spectroscopic characteristics of both products correspond with those of the racemic compounds.

***Attempted Resolution of (±)-2-(4-Aminophenyl)-1-oxaspiro[4.5]decan-4-ol* 388**



Racemic **388** was insoluble in the customary diisopropylether solvent. Table **3.2.4.3** shows the screen of solvents that took place.

Solvent	Solubility
Et_2O	No
MTBE	No
$CHCl_3$	Yes
EtOAc	Yes
Dioxane	Yes
DIPE/Dioxane	Yes
DIPE/DMSO	Yes (Biphasic)
DIPE/MeCN	Yes
DIPE/DMF	Yes
Neat Vinyl Acetate	Yes

Table 3.2.4.3

The successful solvents were then employed to attempt to resolve **390,** using *Pseudomonas stutzeri* and vinyl acetate as the respective enzyme and acyl donor. Table **3.2.4.4** shows the outcome of these reactions.

Solvent	Result
$CHCl_3$	Decomposition
EtOAc	Decomposition
Dioxane	Decomposition
DIPE/Dioxane	Decomposition
DIPE/DMSO	Starting Material Only
DIPE/MeCN	Decomposition
DIPE/DMF	Decomposition
Neat Vinyl Acetate	Decomposition

Table 3.2.4.4

As a mixture of diisopropylether and DMSO was the only successful solvent system to yield any result, conditions were attempted that would successfully resolve **390**, by varying the enzyme, acyl donor and reaction temperature.

Enzyme	Acyl Donor	Temp. (°C)	Result
Pseudomonas stutzeri	EtOAc	rt/30/40	Starting Material
Pseudomonas stutzeri	Isopropenyl Acetate	rt/30/40	Starting Material
Pseudomonas stutzeri	1-Acetoxybenzotriazole	rt/30/40	Starting Material

Table 3.2.4.5 *Pseudomonas stutzeri* as enzyme

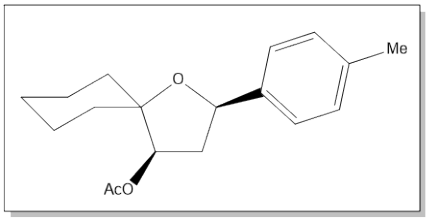
Enzyme	Acyl Donor	Temp. (°C)	Result
CAL A	EtOAc	rt/30/40	Starting Material
CAL A	Isopropenyl Acetate	rt/30/40	Starting Material
CAL A	1-Acetoxybenzotriazole	rt/30/40	Starting Material

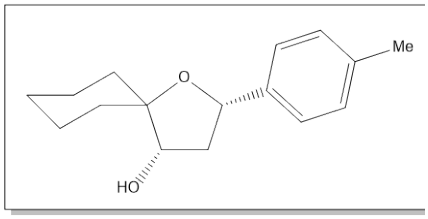
Table 3.2.4.6 *Candida Antarctica* Lipase A as enzyme

Enzyme	Acyl Donor	Temp. (°C)	Result
CCL	EtOAc	rt/30/40	Starting Material
CCL	Isopropenyl Acetate	rt/30/40	Starting Material
CCL	1-Acetoxybenzotriazole	rt/30/40	Starting Material

Table 3.2.4.7 *Candida Cylindracea* Lipase as enzyme

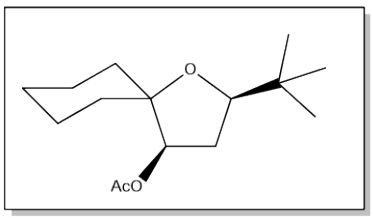
***Resolution of (±)-2-(4-Tolyl)-1-oxaspiro[4.5]decan-4-ol* 387**

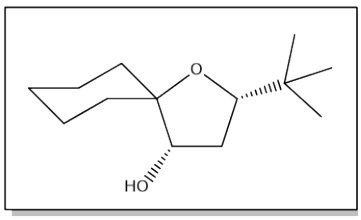




A racemic mixture of **387** (0.15 g, 0.60 mmol), diisopropylether (20 mL), vinyl acetate (0.05 g, 0.60 mmol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated 50% conversion after 24 h. The enzyme was filtered off, washed with ethyl acetate (10 mL), and the combined washings and filtrate concentrated under reduced pressure. Subsequent flash chromatography with ethyl acetate:hexane (5:95) yielded (-)-(3R*,5R*)-2-(4-tolyl)-1-oxaspiro[4.5]decan-4-ol **406** as oil (50.00 mg, 29%, d.r. >98:2), $[\alpha]_D^{20}$ = -2.60 (c = 0.69, $CHCl_3$), >99% ee, and (-)-(3S*,5S*)-2-(4-tolyl)-1-oxaspiro[4.5]decan-4-ol **387** as oil (47.00 mg, 31%, d.r. >98:2), $[\alpha]_D^{20}$ = -1.90 (c = 0.94, $CHCl_3$), >99% ee. Spectroscopic characteristics of both products correspond with those of the racemic compounds.

***Resolution of (±)-2-tert-butyl-1-oxaspiro[4.5]decan-4-ol* 391**





A racemic mixture of **391** (0.15 g, 0.70 mmol), diisopropylether (20 mL), vinyl acetate (0.06 g, 0.70

mol) and *Pseudomonas stutzeri* lipase (75.00 mg) were stirred at room temperature where ^{1}H NMR analysis indicated no conversion to the acetate up to a time of 3 weeks. The following table outlines the attempts made to attain the desired reaction products without any success.

Enzyme	Temp (C)	Time (h)
CCL[*]	37	168
CCL[#]	37	168
Pseudomonas stutzeri[*]	37	168
Pseudomonas stutzeri[*]	45	72
CAL A[*]	37	168
PLE[*]	37	168
Hog Pancreas Lipase[^]	45	168

* Lipases from ALMAC Sciences

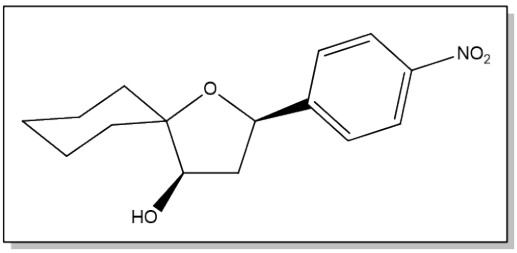
[#] Commercial lipase, Sigma-Aldrich

[^] Commerial lipase, Fluka

Table 3.2.4.8

3.2.5 Hydrolysis of Enantiomeric Acetate

***(-)-2-(4-Nitrophenyl)-1-oxaspiro[4.5]decan-4-ol* 386**

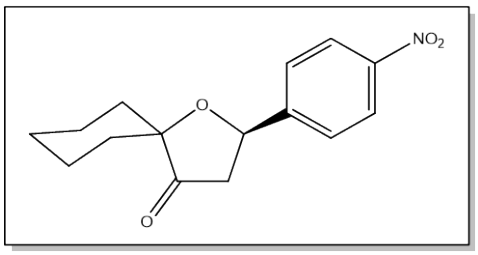


To a solution of (-)-2-(4-nitrophenyl)-1-oxaspiro[4.5]decan-4-yl acetate **405** (10.00 mg, 0.03 mmol, >99% ee) in methanol (1 mL) was added K_2CO_3 (6.00 mg, 0.04 mmol) in water (0.50 mL) and the mixture stirred overnight at room temperature. 10% HCl solution (1 mL) was added, the solution extracted with ethyl acetate (3 x 5mL) and the combined organic extracts were washed with water (5 mL), dried and concentrated *in vacuo*. The title compound was isolated as a gold oil (mg, 92 %, d.r. >98:2) by flash chromatography using ethyl acetate:hexane (20:80). $[\alpha]_D^{20}$= -4.55 (c

= 0.53, $CHCl_3$), >99% ee. Spectroscopic characteristics of the product correspond with those of the racemic compounds.

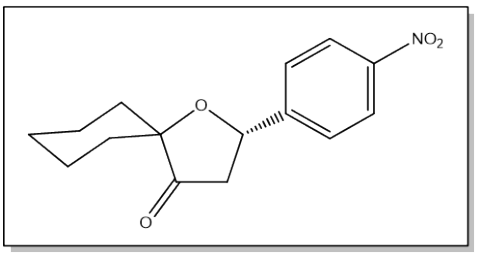
3.2.6 Synthesis of Asymmetric 4,5-Dihydro-3(*2H*)-Furanones

***(-)-2-(4-Nitrophenyl)-1-oxaspiro[4.5]decan-4-one* 346a**



To a solution of chromic acid (0.02 g, 0.18 mmol) at 0 °C was added (-)-2-(4-nitrophenyl)-1-oxaspiro[4.5]decan-4-ol **386a** (7.00 mg, 0.025 mmol, >99% ee), in ether (2 mL). The title furanone was isolated as pale yellow residue (5.20 mg, 76%) without further purification. $[\alpha]_D^{20}$= -2.46 (c = 0.89, $CHCl_3$), 99% ee. Spectroscopic characteristics of the product correspond with those of the racemic compound.

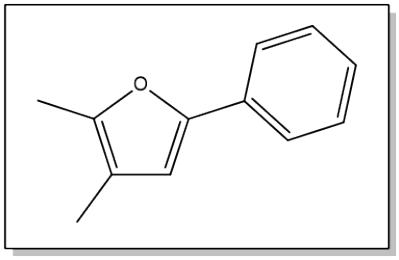
***(+)-2-(4-Nitrophenyl)-1-oxaspiro[4.5]decan-4-one* 346b**



This compound was prepared following the procedure for **346**a, from a solution of chromic acid (0.04 g, 0.35 mmol) at 0 °C was added (-)-2-(4-nitrophenyl)-1-oxaspiro[4.5]decan-4-ol **386b** (15.00 mg, 0.05 mmol, 95% e.e.), in ether (3 mL). The title furanone was isolated as pale yellow residue (10.20 mg, 74%) without further purification. $[\alpha]_D^{20}$= +1.86 (c = 0.65, $CHCl_3$), 95% ee. Spectroscopic characteristics of the product correspond with those of the racemic compound.

3.2.7 Acid Catalysed Cyclisation Reactions Forming 2,3,5-Trisubstituted Furans

***2,3-Dimethyl-5-phenylfuran* 411**

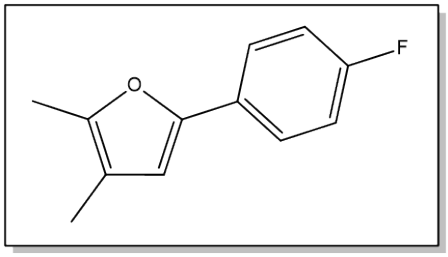


330 (0.20 g, 1.05 mmol) and PTSA (0.19 g, 1.05 mmol) in 1,2-dichlorobenzene (30 mL) was refluxed for 18 h. The reaction mixture was cooled, and then washed with 1M aqueous NaOH (2 x 20 mL), water (2 x 20 mL) and

brine (20 mL). The organic layer was subsequently dried and reduced to a dark brown oil by Kugelrohr distillation to ensure complete removal of the reaction solvent. The title compound was isolated as a dark gold oil (0.09 g, 50%) following flash chromatography using (20:80) ethyl acetate:hexane as eluant. ν_{max}/cm^{-1} (film): 1685, 1598, 1449, 1229; δ_H (300 MHz): 1.98 [3H, s, C(3)C**H**$_3$], 2.27 [3H, s, C(2)C**H**$_3$], 6.44 [1H, s, C(4)**H**], 7.20-7.50 (5H, m, Ar**H**); δ_C (75.5 MHz): 9.97 [C(3)**C**H$_3$], 11.51 [C(2)**C**H$_3$], 100.89 [**C**(4)H], 116.11 [**C**(3)], 123.17 (Ar**C**H), 126.54 (Ar**C**H), 127.72 (Ar**C**H), 128.56 (Ar**C**H), 130.55 (Ar**C**H), 131.25 (Ar**C**), 147.36 [**C**(5)], 150.88 [**C**(2)]; m/z: 173 (M+H), 104; HRMS (ES+): Found 173.0597, $C_{12}H_{12}O$ $(M+H)^+$ requires 173.0596. Spectroscopic characteristics were in agreement with reported data.[244]

411 was also synthesized in a closed vessel microwave reaction of **330** (0.10 g, 0.53 mmol), methanesulphonic acid (0.03 g, 0.30 mmol) and 1,2-dichlorobenzene (2.50 mL) at 300 W and 190 °C for 1 h. The crude reaction mixture was diluted with 1,2-dichloroethane (5 mL) and washed successively with 1M aqueous NaOH (2 x 5 mL), water (2 x 5 mL) and brine (5 mL). *Furan* **411** was isolated as a gold oil (53.00 mg, 58%) by flash chromatography using ethyl acetate:hexane (2:98) as eluant. Spectroscopic characteristics were in agreement with the previous synthesis of this compound.

***2,3-Dimethyl-5-(4-fluorophenyl)-furan* 412**

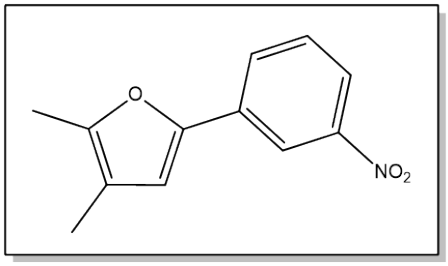


This compound was prepared following the procedure for **411**, from **331** (0.10 g, 0.48 mmol) and PTSA (0.05 g, 0.24 mmol) in 1,2-dichlorobenzene (20 mL) at reflux for 24 h. The *furan* was isolated as a light brown oil (0.06 g, 60%) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (film): 2924, 1600, 1509, 1231; δ_H (300 MHz): 1.97 [3H, s, C(3)C**H**$_3$], 2.27 [3H, s, C(2)C**H**$_3$], 6.36 [1H, s, C(4)**H**], 7.02 (1H, t, *J*=8.9, ArC(2)**H**), 7.55 (1H, dd, *J*=5.3, 8.9, ArC(3)**H**); δ_C (75.5 MHz): 8.94 [C(3)**C**H$_3$], 10.46 [C(2)**C**H$_3$], 106.97 [**C**(4)H], 114.34 [**C**(3)], 114.49 (d, $^2J_{CF}$=21.0, Ar**C**(3)H), 124.80 (d, $^3J_{CF}$=7.8, Ar**C**(2)H), 132.23 (d, $^4J_{CF}$=2.9, Ar**C**), 149.09 [**C**(5)], 156.36 [**C**(2)], 164.85 (d, $^1J_{CF}$=254.0, Ar**C**-F); δ_F: -104.36; m/z: 191 (M+H), 102, 74; HRMS (ES+): Found

191.0872, $C_{12}H_{12}FO$ $(M+H)^+$ requires 191.0524. Spectroscopic characteristics were in agreement with reported data.[244]

412 was prepared following the procedure for the microwave preparation of **411** from **331** (0.15 g, 0.72 mmol), methanesulphonic acid (0.20 g, 2.08 mmol) and 1,2-dichloroethane (3 mL) at 300 W and 175 °C for 10 min. *Furan* **412** (41.00 mg, 48%) was isolated as a brown semi-solid with *furanone* **350** (25.00 mg, 17%) by flash chromatography using ethyl acetate:hexane (2:98) as eluant. Spectroscopic characteristics were in agreement with the previous synthesis of this compound.

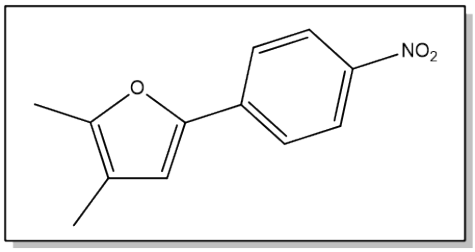
***2,3-Dimethyl-5-(4-nitrophenyl)-furan* 413**



This compound was prepared following the procedure for **413**, from **333** (0.15 g, 0.63 mmol) and PTSA (0.06 g, 0.30 mmol) in 1,2-dichlorobenzene (20 mL) at reflux for 26 h. The *furan* was isolated as a yellow solid (0.10 g, 71%) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. m.p.: 61-63 °C; Found C: 66.59, H: 5.34, N: 6.18, $C_{12}H_{11}NO_3$ requires C: 66.35, H: 5.10, N: 6.45; ν_{max}/cm^{-1} (KBr): 2924, 1640, 1524, 1348; δ_H (300 MHz): 2.00 [3H, s, C(3)C**H**$_3$], 2.30 [3H, s, C(2)C**H**$_3$], 6.60 [1H, s, C(4)**H**], 7.49 (1H, t, *J*=7.6, ArC(5)**H**), 7.85 (1H, d, *J*=7.6, ArC(6)**H**), 8.00 (1H, ddd, *J*=0.9, 2.0, 8.2, ArC(**4**)H, 8.41 (1H, t, *J*=2.0, ArC(2)**H**); δ_C (75.5 MHz): 9.91 [C(3)**C**H$_3$], 11.58 [C(2)**C**H$_3$], 110.71 [**C**(4)H], 116.79 [**C**(3)], 117.80 (Ar**C**(2)H), 120.82 (Ar**C**(4)H), 128.53 (Ar**C**(6)H). 129.53 (Ar**C**(5)H), 132.72 [Ar**C**-NO$_2$], 148.46 (Ar**C**), 148.74 [**C**(5)], 149.03 [**C**(2)]; m/z: 218 (M+H), 152, 123, 80, 64; HRMS (ES+): Found 218.0811, $C_{12}H_{12}NO_3$ $(M+H)^+$ requires 218.0817.

413 was prepared following the procedure for the microwave preparation of **411** from **333** (0.17 g, 0.72 mmol), PTSA (0.06 g, 0.36 mmol) and 1,2-dichloroethane (2.50 mL) at 300 W and 175 °C for 1 h. *Furan* **413** was isolated as an orange oil (0.08g, 51%) by flash chromatography using ethyl acetate:hexane (2:98) as eluant. Spectroscopic characteristics were in agreement with the previous synthesis of this compound.

***2,3-Dimethyl-5-(4-nitrophenyl)-furan* 409**

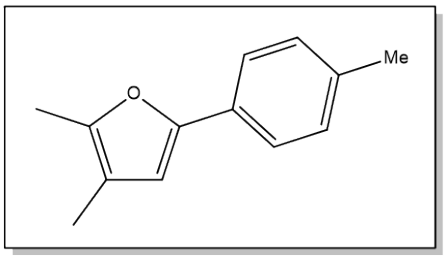


This compound was prepared following the procedure for **411**, from **334** (0.15 g, 0.60 mmol) and PTSA (0.01 g, 0.60 mmol) in 1,2-dichlorobenzene (20 mL) at reflux for 18 h. The *furan* was isolated as an orange solid (0.71 g, 51%) by flash chromatography, using ethyl acetate:hexane (15:85) as eluant. m.p.: 105-106 °C; Found C: 66.14, H: 5.30, N: 6.27, $C_{12}H_{11}NO_3$ requires C: 66.35, H: 5.10, N: 6.45; ν_{max}/cm^{-1} (KBr): 2926, 1595, 1549, 1510, 1349, 1109; δ_H (600 MHz): 2.01 [3H, s, C(3)C**H**$_3$], 2.31 [3H, s, C(2)C**H**$_3$], 6.67 [1H, s, C(4)**H**], 7.76 (2H, d, *J*=9.0, ArC(2)**H**), 8.30 (2H, d, *J*=9.0, ArC(3)**H**); δ_C (150 MHz): 9.88 [C(3)**C**H$_3$], 11.68 [C(2)**C**H$_3$], 117.4 [**C**(4)H], 117.45 [**C**(3)], 123.06 (Ar**C**(2)H), 124.34 (Ar**C**(3)H), 136.79 (Ar**C**-NO_2). 145.79 (Ar**C**), 148.77 [**C**(5)], 150.33 [**C**(2)]; m/z: 234 (M+H), 202, 151, 99; HRMS (ES+): Found 234.0762, $C_{12}H_{12}NO_4$ $(M+H)^+$ requires 234.0766.

409 was prepared following the procedure for the microwave preparation of **411** from **334** (0.17 g, 0.72 mmol), PTSA (0.06 g, 0.36 mmol) and 1,2-dichloroethane (2.5 mL) at 300 W and 175 °C for 1 h. *Furan* **409** was isolated as an orange solid (0.09 g, 58%) by flash chromatography using ethyl acetate:hexane (2:98) as eluant. Spectroscopic characteristics were in agreement with the previous synthesis of this compound.

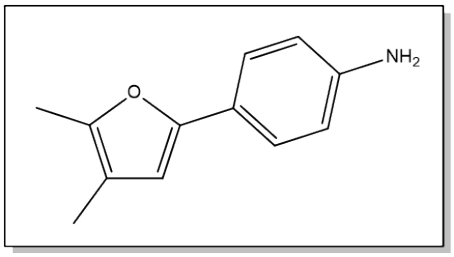
409 was prepared by reflux of **334** (4.50 g, 0.02 mol), methanesulphonic acid (0.96 g, 0.01 mol) and toluene (200 mL) in a 250 mL round-bottomed flask fitted with a Dean-Stark apparatus. The reaction was monitored by ^{1}H NMR, whereby a constant ratio of 62:38 **353**:**409** was observed after 96 h. The crude reaction mixture was washed with 1M aqueous NaOH (3 x 25 mL), water (2 x 50 mL) and brine (50 mL). The organic solution was dried and concentrated in vacuo to a brown oil. The desired *furan* was isolated as an orange solid (0.90 g, 21%) with *furanone* **353** (1.95g, 43%) by flash chromatography using ethyl acetate:hexane (5:95) as eluant. Spectroscopic characteristics were in agreement with previous syntheses of this compound.

***2,3-Dimethyl-5-(4-tolyl)-furan* 417**



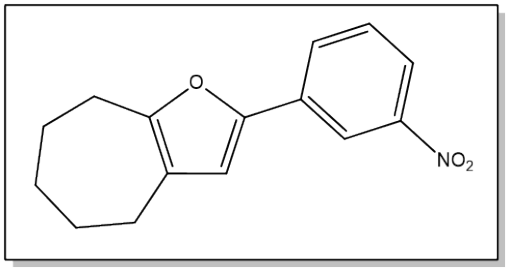
This compound was prepared following the procedure for **411** from **335** (0.15 g, 0.73 mmol), and methanesulphonic acid (0.09 g, 0.93 mmol) in 1,2-dichloroethane (2.50 mL) under microwave irradiation at 300 W and 175 °C for 10 min. The *furan* was isolated as a gold oil (58.00 mg, 43%) with furanone **354** (23.00 mg, 15%) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (film): 2930, 1605, 1512, 1240, 1159; δ_H (300 MHz): 1.70 [3H, s, C(3)C**H**$_3$], 2.26 [3H, s, C(2)C**H**$_3$], 6.37 [1H, s, C(4)**H**], 7.16 (2H, d, *J*=8.3, ArC(3)**H**), 7.48 (2H, d, *J*=8.3, ArC(2)**H**). Spectroscopic characteristics were in agreement with reported data.[244]

***2,3-Dimethyl-5-(4-aminophenyl)-furan* 410**



409 (0.20 g, 0.92 mmol) was dissolved in a mixture of 1,4-dioxane (5 mL) and acetic acid (0.14 mL) and brought to a gentle reflux. Iron powder (0.31 g) was added, immediately followed by iron (III) chloride hexahydrate (0.03 g) and refluxed for a further 3 h. The reaction mixture was cooled and filtered under vacuum. Ether (50 mL) and water (50 mL) were added to the filtrate and the layers separated. The aqueous layer was extracted with further portions of ether (3 x 25 mL). The organic layer was washed with 5% aqueous sodium bicarbonate (2 x 50 mL), water (2 x 50 mL), brine (50 mL), dried and concentrated *in vacuo* to yield an orange oil (0.12 g, 71%) without purification. ν_{max}/cm^{-1} (film): 3307, 2920, 2851, 1737, 1669, 1537, 1516, 1374; δ_H (300 MHz): 1.95 [3H, s, C(3)C**H**$_3$], 2.24 [3H, s, C(2)C**H**$_3$], 3.66 (2H, bs, N**H**$_2$), 6.23 [1H, s, C(4)**H**], 6.66 (2H, d, *J*=8.7, ArC(3)**H**), 7.40 (2H, d, *J*=8.7, ArC(2)**H**); δ_C (75.5 MHz): 10.02 [C(3)**C**H$_3$], 11.46 [C(2)**C**H$_3$], 105.87 [**C**(4)H], 115.20 (Ar**C**(3)H), 115.76 [**C**(3)], 122.50 (Ar**C**-NH$_2$), 124.62 (Ar**C**(2)H), 145.19 (Ar**C**), 145.97 [**C**(5)], 151.47 [**C**(2)]; m/z: 188 (M+H); HRMS (ES+): Found 188.1067, $C_{12}H_{14}NO$ $(M+H)^+$ requires 188.1075. STDEV: 4.30 ppm.

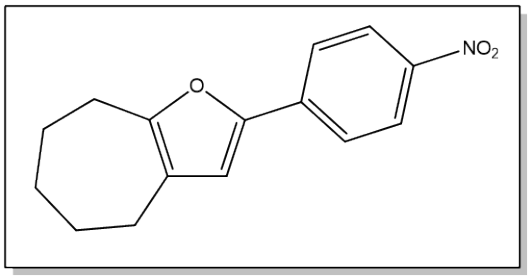
***2-(3-Nitrophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]furan* 414**



This compound was prepared following the procedure for **411**, from **339** (0.20 g, 0.73 mmol) and PTSA (0.06 g, 0.30 mmol) in 1,2-dichlorobenzene (20 mL) at reflux for 18 h. The *furan* was isolated as a yellow oil (0.14 g, 78%) by flash chromatography, using ethyl acetate:hexane (15:85) as eluant. ν_{max}/cm^{-1} (film): 2925, 2851, 1550, 1525, 1347; δ_H (300 MHz): 1.70-1.86 [6H, m, C(5)$\mathbf{H}_2$, C(6)$\mathbf{H}_2$, C(7)$\mathbf{H}_2$], 2.52 [2H, t, *J*=5.9, C(9)$\mathbf{H}_2$], 2.85 [2H, t, *J*=5.9, C(8)$\mathbf{H}_2$], 6.58 [1H, s, C(3)**H**], 7.49 (1H, t, *J*=8.0, ArC(5)**H**), 7.87 (1H, d, *J*=8.0, ArC(6)**H**), 8.01 (1H, ddd, *J*=0.9, 2.3, 8.0, ArC(4)**H**), 8.40 (1H, t, *J*=2.1, ArC(2)**H**); δ_C (75.5 MHz): 26.13 [**C**(5)H_2], 26.45 [**C**(8)H_2], 28.55 [**C**(6)H_2], 29.05 [**C**(9)H_2], 30.73 [**C**(7)H_2], 111.01 [**C**(3)H], 117.75 (Ar**C**(5)H), 120.70 (Ar**C**(6)H), 123.58 [**C**(4)], 128.50 (Ar**C**(4)H), 129.52 (Ar**C**(2)H), 132.79 (Ar**C**), 147.32 [Ar**C**-NO_2], 148.74 [**C**(2)], 155.01 [**C**(10)]; m/z: 258 (M+H), 203, 189, 105, 64; HRMS (ES+): Found 258.1130, $C_{15}H_{16}NO_3$ $(M+H)^+$ requires 258.1130.

414 was prepared following the procedure for the microwave preparation of **411** from **360** (0.25 g, 0.97 mmol), methanesulphonic acid (0.02 g, 0.19 mmol) and 1,2-dichloroethane (2.50 mL) at 300 W and 150 °C for 1 h. **414** was isolated as an orange oil (0.16 g, 64%) by flash chromatography using ethyl acetate:hexane (2:98) as eluant. Spectroscopic characteristics were in agreement with the previous synthesis of this compound.

***2-(4-Nitrophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]furan* 415**

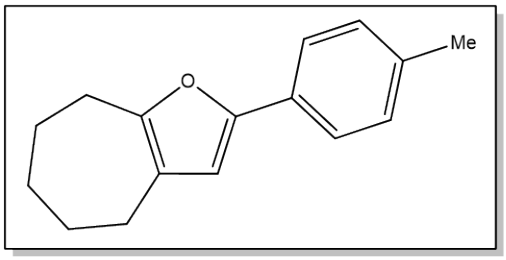


This compound was prepared following the procedure for **411**, from **340** (0.20 g, 0.73 mmol) and PTSA (0.06 g, 0.03 mmol) in 1,2-dichlorobenzene (20 mL) at reflux for 24 h. The *furan* was isolated as an orange oil (0.12 g, 67%) by flash chromatography, using ethyl acetate:hexane (15:85) as eluant. ν_{max}/cm^{-1} (film): 2926, 2852, 2360, 1593, 1547, 1509, 1446, 1337, 1107; δ_H (600 MHz): 1.70-1.77 [4H, m, C(5)$\mathbf{H}_2$ and C(7)$\mathbf{H}_2$], 1.79-1.86 [2H, m, C(6)$\mathbf{H}_2$], 2.54 [2H, t, *J*=6.0, C(9)$\mathbf{H}_2$], 2.85 [2H, t, *J*=6.0, C(8)**H**], 6.66 [1H, s, C(3)**H**], 7.70 (2H, d, *J*=9.1, ArC(2)**H**), 8.20 (2H,

d, *J*=9.1, ArC(3)**H**); δ_C (150 MHz): 26.11 [**C**(5)H_2], 26.36 [**C**(8)H_2], 28.47 [**C**(6)H_2], 29.15 [**C**(9)H_2], 30.71 [**C**(7)H_2], 112.96 [**C**(3)H], 123.00 (Ar**C**(2)H), 124.26 [**C**(4)], 124.35 (Ar**C**(3)H), 136.89 (Ar**C**), 145.64 [Ar**C**-NO_2], 147.65 [**C**(2)], 156.35 [**C**(10)]; m/z: 258 (M+H), 243, 203, 153, 105; HRMS (ES+): Found 258.1130, $C_{15}H_{16}NO_3$ $(M+H)^+$ requires 258.1130.

415 was prepared following the procedure for the microwave preparation of **411** from **340** (0.15 g, 0.54 mmol), PTSA (0.03 g, 0.14 mmol) and 1,2-dichloroethane (2.50 mL) at 300 W and 150 °C for 1 h.. **415** was isolated as an orange oil (34.00 mg, 24%) by flash chromatography using ethyl acetate:hexane (2:98) as eluant. Spectroscopic characteristics were in agreement with the previous synthesis of this compound.

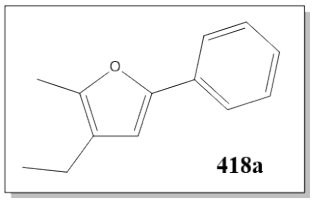
***2-(4-Tolyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]furan* 416**

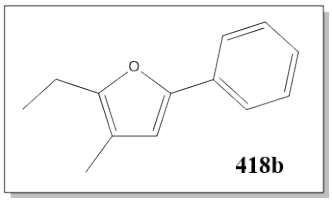


This compound was prepared following the procedure for **411**, from **341** (0.10 g, 0.41 mmol) and PTSA (0.04 g, 0.20 mmol) in 1,2-dichlorobenzene (20 mL) at reflux for 18 h. The *furan* was isolated as an orange oil (0.05 g, 52%) by flash chromatography, using ethyl acetate:hexane (15:85) as eluant. ν_{max}/cm^{-1} (film): 2934, 1688, 1589, 1505, 1367, 1261; δ_H (300 MHz): 1.30-1.90 [10H, m, -(C**H**$_2$)$_5$-], 2.44 [3H, s, ArC**H**$_3$], 5.94 [1H, s, C(4)**H**], 7.29 (2H, d, *J*=8.1, Ar**H**), 7.75 (2H, d, *J*=8.3, Ar**H**); δ_C (75.5 MHz): 21.76 [Ar-**C**H$_3$], 21.95 [**C**H$_2$], 24.56 [**C**H$_2$], 31.91 [**C**H$_2$], 90.75 [**C**(4)], 98.58 [**C**(3)H], 126.59 (Ar**C**-CH$_3$), 127.19 (Ar**C**(2)H), 129.18 (Ar**C**(3)H), 143.39 (Ar**C**), 183.79 [**C**(2)], 207.10 [**C**(10)]; m/z: 225 (M−H), 171, 137, 121, 62; HRMS (ES-): Found 225.1230, $C_{16}H_{19}O$ $(M-H)^-$ requires 225.1235.

416 was prepared following the procedure for the microwave preparation of **411** from **341** (0.20 g, 0.82 mmol), PTSA (0.03 g, 0.16 mmol) and 1,2-dichloroethane (2.50 mL) at 300 W and 150 °C for 1 h. **416** was isolated as an orange oil (0.09 g, 48%) by flash chromatography using ethyl acetate:hexane (2:98) as eluant. Spectroscopic characteristics were in agreement with the previous synthesis of this compound.

***2-Methyl-3-ethyl-5-phenylfuran* 418a/*2-Ethyl-3-methyl-5-phenylfuran* 418b**





This compound was prepared following the procedure for **411**, from **345** (5.00 g, 24.00 mmol) and PTSA (0.95 g, 5.00 mmol) in 1,2-dichloroethane (100 mL) at reflux for 18 h. The *furan* was isolated as a light brown oil and an inseparable mixture of isomers in a 91:9 (**418a**: **418b**) ratio (0.45 g, 10%) by flash chromatography, using ethyl acetate:hexane (5:95) as eluant. ν_{max}/cm^{-1} (NaCl): 2966, 2931. 2874, 1602, 1554, 1449, 1276; δ_H (600 MHz): 1.16 [2.73H, t, *J*=7.6, -$CH_2C\mathbf{H}_3$, isomer **a**], 1.24 [0.27H, t, *J*=7.6, -$CH_2C\mathbf{H}_3$, isomer **b**], 1.97 [0.27H, s, C(3)$C\mathbf{H}_3$, isomer **b**], 2.27 [2.73H, s, C(2)$C\mathbf{H}_3$, isomer **a**], 2.36 [1.82H, q, *J*=7.6, -$C\mathbf{H}_2CH_3$, isomer **a**], 2.63 [0.18H, q, *J*=7.6, -$C\mathbf{H}_2CH_3$, isomer **b**], 6.42 [0.09H, s, C(4)**H**, isomer **b**] 6.49 [0.91H, s, C(4)**H**, isomer **a**], 7.16 (1H, t, *J*=7.4, ArC(4)**H**, both isomers), 7.31 (2H, t, *J*=7.4, ArC(3)**H**, both isomers), 8.30 (2H, d, *J*=7.4, ArC(2)**H**, both isomers); δ_C (150 MHz): 9.85 [C(3)$\mathbf{C}H_3$, isomer **b**], 11.58 [C(2)$\mathbf{C}H_3$, isomer **a**], 13.09 [-$CH_2\mathbf{C}H_3$, isomer **b**], 14.94 [-$CH_2\mathbf{C}H_3$, isomer **a**], 18.17 [-$\mathbf{C}H_2CH_3$, isomer **a**], 19.55 [-$\mathbf{C}H_2CH_3$, isomer **b**], 106.81 [**C**(4)H, isomer **a**], 108.55 [**C**(4)H, isomer **b**], 115.26 [**C**(3), isomer **b**], 122.94 [**C**(3), isomer **a**], 123.21 (Ar**C**(2)H, both isomers), 126.55 (Ar**C**(4)H, both isomers), 129.57 (Ar**C**(3)H, both isomers), 131.35 (Ar**C**, isomer **a**), 132.82 (Ar**C**, isomer **b**), 146.64 [**C**(2), isomer **a**], 150.85 [**C**(5), isomer **b**], 151.08 [**C**(5), isomer **a**], 152.53 [**C**(2), isomer **b**]; m/z: 187 (M+H), 105; HRMS (ES+): Found 187.1123, $C_{13}H_{15}O$ $(M+H)^+$ requires 187.1116.

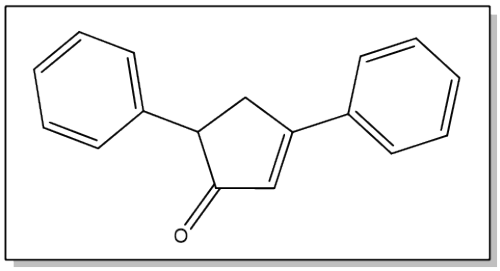
418 was prepared following the procedure for the microwave preparation of **411** from **345** (0.10 g, 0.49 mmol), PTSA (0.02 g, 0.10 mmol) and 1,2-dichloroethane (2.50 mL) at 300 W and 150 °C for 1 h. **418** was isolated as an orange oil and an inseparable mixture of isomers in a 91:9 (**418a**: **418b**) ratio (35.00 mg, 39%) with *furanone* **364** (22.00 mg, 12%), by flash chromatography using ethyl acetate:hexane (2:98) as eluant. Spectroscopic characteristics were in agreement with the previous synthesis of this compound.

418 was also prepared following the procedure for the microwave preparation of **411** from **364** (0.10 g, 0.49 mmol), PTSA (0.02 g, 0.10 mmol) and 1,2-dichloroethane (2.50

mL) at 300 W and 150 °C for 40 min. **418** was isolated as an orange oil and an inseparable mixture of isomers in a 91:9 (**418a**: **418b**) ratio (61.00 mg, 67%) and *furanone* **364** (12.00 mg, 12%), by flash chromatography using ethyl acetate:hexane (2:98) as eluant. Spectroscopic characteristics were in agreement with the previous synthesis of this compound.

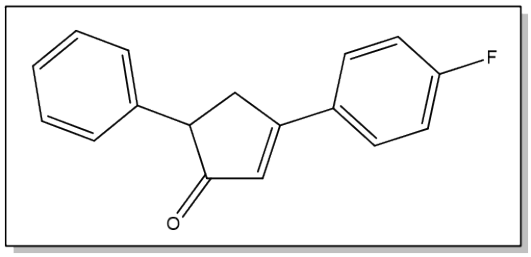
3.2.8 Synthesis of Cyclopentenones

***3,5-Diphenylcyclopent-2-en-1-one* 419**



This was prepared following the procedure described for **349,** from **342** (0.50 g, 1.98 mmol) and PTSA (0.19 g, 1.00 mol) in 1,2-dichloroethane (25 mL). The title compound was isolated as a light brown solid (0.39 g, 84%) by recrystallisation from ethyl acetate/hexane. m.p.: 89-91°C; Found C: 86.95, H: 6.09, $C_{17}H_{14}O$ requires C: 87.15, H: 6.02; ν_{max}/cm^{-1} (film): 3061, 3029, 1695, 1599, 1448, 1177; δ_H (600 MHz): 3.13 [1H, ddd, *J*=1.8, 2.8. 18.2, one of C(4)$\mathbf{H}_2$], 3.58 [1H, ddd, *J*=1.8, 7.4, 18.2, one of C(4)$\mathbf{H}_2$], 3.80 [1H, dd, *J*=2.8, 7.4, C(5)**H**], 6.60 [1H, t, *J*=1.8, C(2)**H**], 7.21 (2H, d, *J*=7.5, Ar**H**), 7.26 (1H, d, *J*=13.8, Ar**H**), 7.34 (2H, t, *J*=7.5, Ar**H**), 7.71 (2H, dd, *J*=1.5, 7.5, Ar**H**); δ_C (150 MHz): 38.48 [**C**(4)H_2], 52.44 [**C**(5)H], 126.37 [**C**(2)H], 126.97 (Ar**C**H), 127.05 (Ar**C**H), 127.67 (Ar**C**H), 128.90 (Ar**C**H), 129.04 (Ar**C**H), 131.55 (Ar**C**H), 133.73 (Ar**C**), 139.81 (Ar**C**), 172.94 [**C**(3)], 208.42 [**C**(1)O]; m/z: 235 (M+H), 182, 130, 64; HRMS (ES+): Found 235.1123, $C_{17}H_{15}O$ $(M+H)^+$ requires 235.1110. Spectroscopic characteristics were in agreement with reported data.[233]

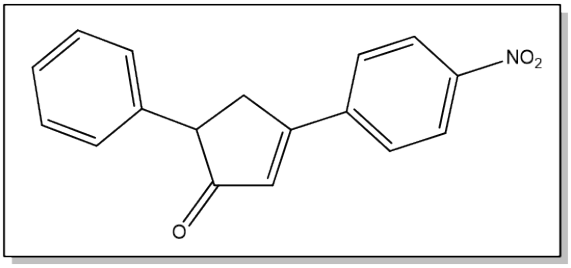
***3-(4-Fluorophenyl)-5-phenyl-cyclopent-2-en-1-one* 420**



This was prepared following the procedure described for **349,** from **343** (0.15 g, 0.55 mmol) and PTSA (0.10 g, 0.50 mol) in 1,2-dichloroethane (15 mL). The title compound was isolated as a gold oil (0.09 g, 69%) by flash

chromatography using ethyl acetate:hexane (15:85) as eluant. ν_{max}/cm^{-1} (film): 1671, 1599, 1454, 1328, 1160; δ_H (300 MHz): 3.17 [1H, ddd, *J*=1.8, 2.6. 18.3, one of C(4)**H**$_2$], 3.61 [1H, ddd, *J*=1.8, 7.3, 18.2, one of C(4)**H**$_2$], 3.81 [1H, dd, *J*=2.6, 7.3, C(5)**H**], 6.67 [1H, t, *J*=1.8, C(2)**H**], 7.21 (2H, d, *J*=7.1, ArC**H**), 7.26 (1H, d, *J*=13.9, ArC**H**), 7.34 (2H, t, *J*=7.4, ArC**H**), 7.47-7.52 (3H, m, ArC**H**), 7.72 (2H, dd, *J*=1.9, 7.9, ArC**H**); δ_C (75.5 MHz): 38.56 [**C**(4)H$_2$], 52.26 [**C**(5)H], 116.24 (d, $^2J_{CF}$=21.8, Ar**C**H), 126.13 [**C**(2)H], 127.10 (Ar**C**H), 127.68 (Ar**C**H), 128.92 (Ar**C**H), 129.11 (d, $^3J_{CF}$=8.8, Ar**C**H), 130.09 (d, $^4J_{CF}$=3.3, Ar**C**), 139.71 (Ar**C**), 164.65 (d, $^1J_{CF}$=253.4, Ar**C**-F) 171.48 [**C**(3)], 208.10 [**C**(1)O]; m/z: 253 (M+H), 113, 83, 42; δ_F (470 MHz): -107.50; HRMS (ES+): Found 253.1029, $C_{17}H_{14}FO$ $(M+H)^+$ requires 253.1018.

***3-(4-Nitrophenyl)-5-phenyl-cyclopent-2-en-1-one* 421**



This was prepared following the procedure described for **349,** from **344** (0.50 g, 1.68 mmol) and PTSA (0.19 g, 1.00 mol) in 1,2-dichloroethane (25 mL). The title compound was isolated as a brown oil (0.38 g, 81%) by flash chromatography using ethyl acetate:hexane (20:80) as eluant. ν_{max}/cm^{-1} (film): 1699, 1587, 1519, 1347; δ_H (300 MHz): 3.19 [1H, ddd, *J*=1.9, 2.9, 18.5, one of C(4)**H**$_2$], 3.64 [1H, ddd, *J*=1.9, 7.4, 18.5, one of C(4)**H**$_2$], 3.86 [1H, dd, *J*=2.9, 7.4, C(5)**H**], 6.77 [1H, t, *J*=1.9, C(2)**H**], 7.18-7.50 (5H, m, Ar**H**), 7.86 (1H, d, *J*=8.9, ArC(2)**H**-NO_2), 8.34 (2H, d, *J*=8.9, ArC(3)**H**-NO_2); δ_C (75.5 MHz): 38.47 [**C**(4)H$_2$], 52.36 [**C**(5)H], 124.24 (Ar**C**(3)H), 127.32 [**C**(2)H], 127.67 (Ar**C**H), 127.83 (Ar**C**(2)H), 129.03 (Ar**C**H), 129.55 (Ar**C**H), 139.09 (Ar**C**), 139.61 (Ar**C**), 149.15 (Ar**C**-NO_2) 169.54 [**C**(3)], 207.73 [**C**(1)O]; m/z: 280 (M+H), 115, 105, 64; HRMS (ES+): Found 280.1020, $C_{17}H_{14}NO_3$ $(M+H)^+$ requires 280.0974.

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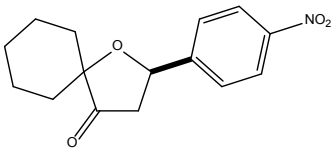
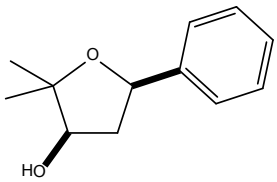
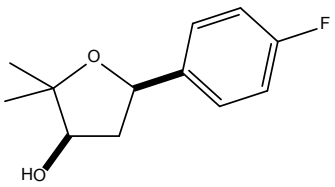
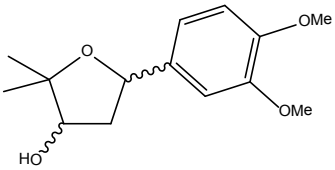
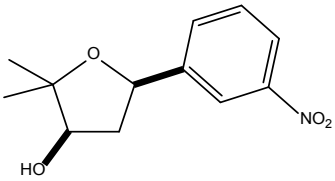
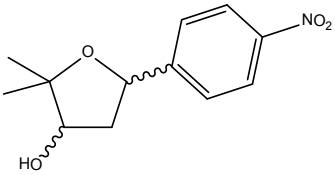
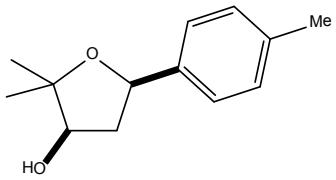
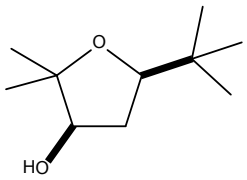
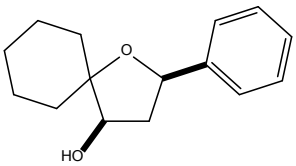
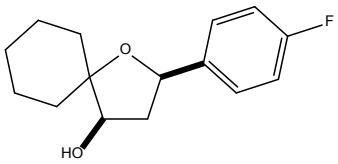
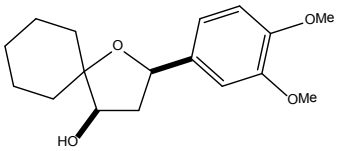
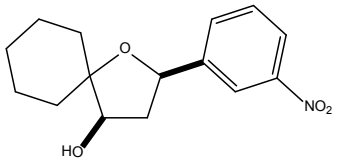
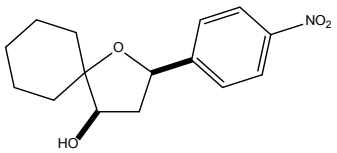
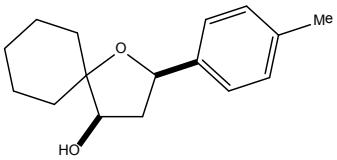
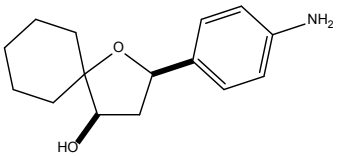
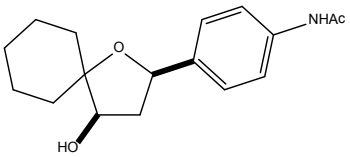
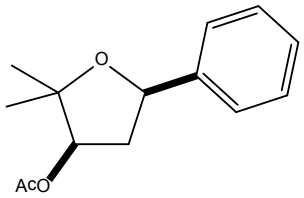
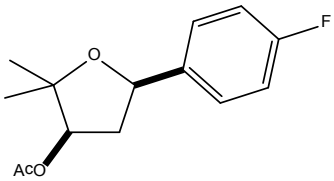
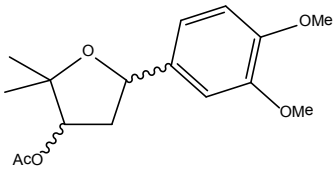
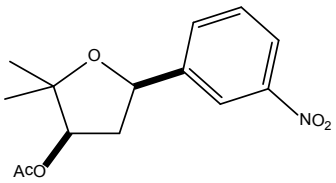
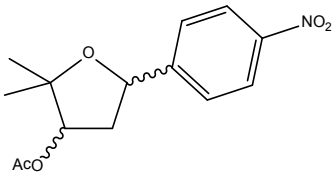
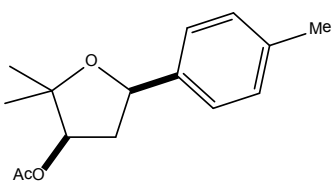
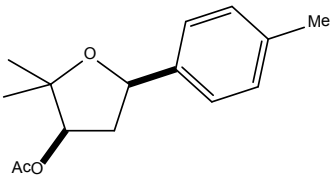
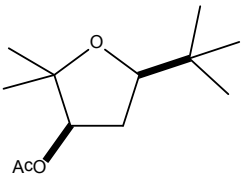
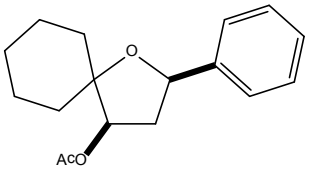
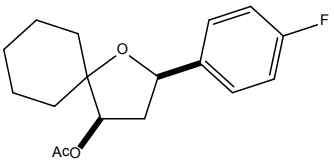
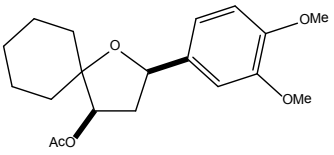
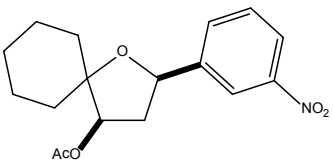
Appendix A: HPLC Conditions

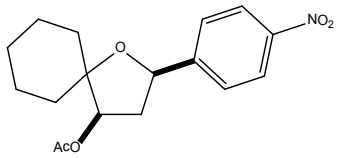
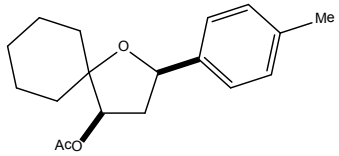
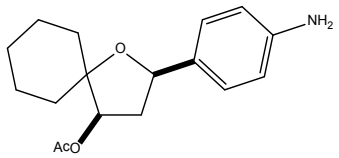
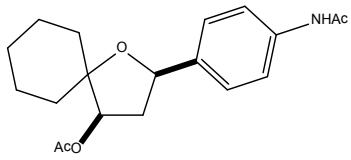
Compound	Column	Temp. (°C)	Eluant (Hex:IPA)	Retention Time (min.)
	AS-H	17	98:2 (*1.00 mL/min*)	41.57 (5*S*) 47.19 (5*R*)
	AS-H	17	99:1 *(1.00 mL/min)*	25.78 (3*R*, 5*R*) 36.99 (3*S*, 5*S*)
	AS-H	17	99:1 *(1.00 mL/min)*	37.95 (3*R*, 5*R*) 69.19 (3*S*, 5*S*)
	OD-H	0	90:10 *(0.20 mL/min)*	88.32 (3*R*, 5*S*) 83.65 (3*S*, 5*R*) 104.20 (3*S*, 5*S*) 116.53 (3*R*, 5*R*)
	AS-H	17	90:10 *(1.00 mL/min)*	11.52 (3*R*, 5*R*) 13.37 (3*S*, 5*S*)
	AS-H	17	90:10 *(1.00 mL/min)*	17.69 (3*R*, 5*S*) 25.93 (3*S*, 5*R*) 37.78 (3*S*, 5*S*) 46.49 (3*R*, 5*R*)

Compound	Column	Temp. (°C)	Eluant (Hex:IPA)	Retention Time (min.)
	AS-H	17	99:1 *(1.00 mL/min)*	20.91 (3*R*, 5*R*) 31.70 (3*S*, 5*S*)
	AS-H	17	Chiral Shift ^{1}H NMR	
	AS-H	17	99:1 *(1.00 mL/min)*	21.83 (3*R*, 5*R*) 24.71 (3*S*, 5*S*)
	Cell-4	17	99:1 *(1.00 mL/min)*	21.07 (3*R*, 5*R*) 23.50 (3*S*, 5*S*)
	AS-H	17	95:5 *(0.25 mL/min)*	74.89 (3*R*, 5*R*) 80.63 (3*S*, 5*S*)
	AS-H	17	99:1 *(1.00 mL/min)*	98.45 (3*R*, 5*R*) 108.79 (3*S*, 5*S*)

Compound	Column	Temp. (°C)	Eluant (Hex:IPA)	Retention Time (min.)
	AS-H	17	95:5 *(1.00 mL/min)*	43.40 (3*R*, 5*R*) 50.57 (3*S*, 5*S*)
	AS-H	17	99:1 *(0.10 mL/min)*	52.85 (3*R*, 5*R*) 60.26 (3*S*, 5*S*)
	OD-H	17	80:20 *(0.5 mL/min)*	33.59 (3*R*, 5*S*) 37.74 (3*S*, 5*R*) 67.16 (3*S*, 5*S*) 75.37 (3*R*, 5*R*)
	OJ-H	17	90:10 (Hexane:EtOH) *(0.5 mL/min)*	44.95, 60.27 47.97, 72.77

Compound	Column	Temp. (°C)	Eluant (Hex:IPA)	Retention Time (min.)
	AS-H	17	99:1 *(1.00 mL/min)*	8.12 (3*S*, 5*S*) 10.00 (3*R*, 5*R*)
	AS-H	17	99:1 *(1.00 mL/min)*	10.19 (3*S*, 5*S*) 26.29 (3*R*, 5*R*)
	AS-H	0	98:2 (Hexane:EtOH) (0.20 mL/min)	45.10 (3*R*, 5*S*) 47.29 (3*S*, 5*R*) 52.74 (3*S*, 5*S*) 81.19 (3*R*, 5*R*)
	AS-H	17	90:10 *(1.00 mL/min)*	11.43 (3*S*, 5*S*) 13.31 (3*R*, 5*R*)
	OJ-H	17	98:2 (Hexane:EtOH) (1.00 mL/min)	30.24 (3*R*, 5*S*) 34.03 (3*S*, 5*R*) 48.83 (3*S*, 5*S*) 45.60 (3*R*, 5*R*)
	AS-H	17	95:5 *(0.50 mL/min)*	28.63 (3*S*, 5*S*) 30.25 (3*R*, 5*R*)

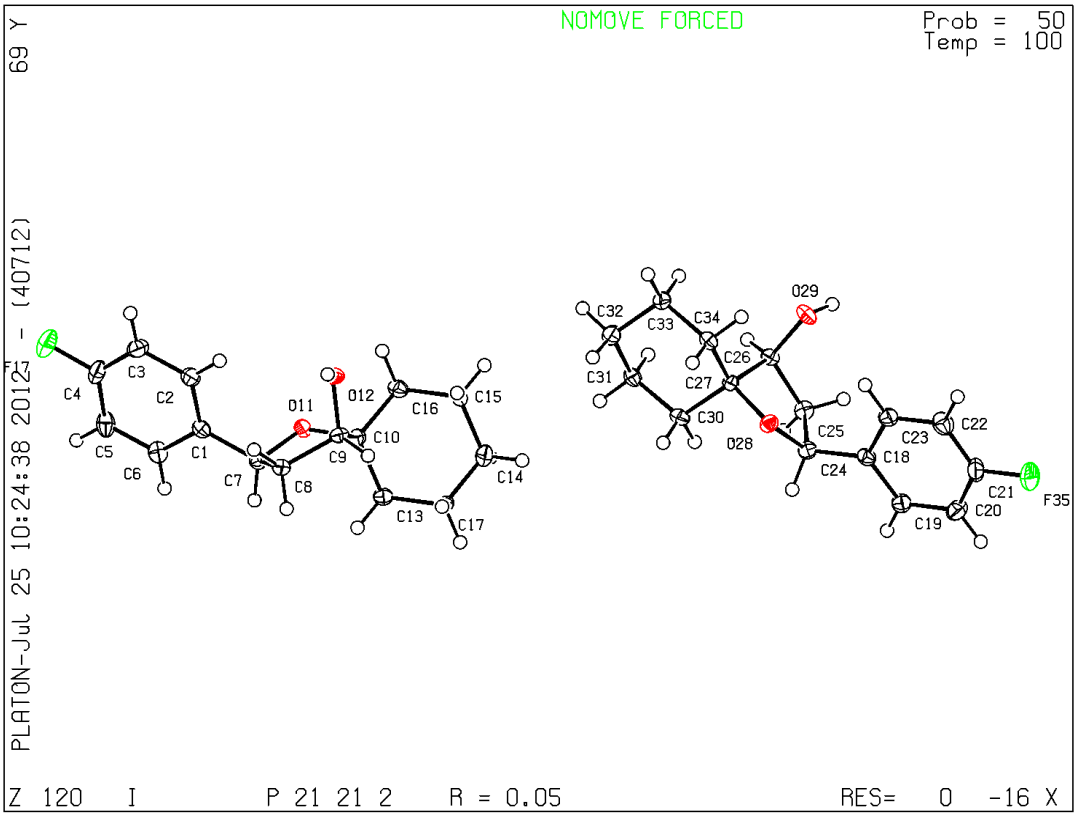
Compound	Column	Temp. (°C)	Eluant (Hex:IPA)	Retention Time (min.)
	AS-H	17	95:5 *(0.50 mL/min)*	28.63 (3*S*, 5*S*) 30.25 (3*R*, 5*R*)
	AS-H	17	Chiral Shift ^{1}H NMR	
	AS-H	17	99:1 *(1.00 mL/min)*	8.12 (3*S*, 5*S*) 10.01 (3*R*, 5*R*)
	Cell-4	17	99:1 (1.00 mL/min)	6.04 (3*S*, 5*S*) 6.58 (3*R*, 5*R*)
	AS-H	17	8:15 *(1.00 mL/min)*	6.91 (3*S*, 5*S*) 10.51 (3*R*, 5*R*)
	AS-H	17	95:5 *(1.00 mL/min)*	14.01 (3*S*, 5*S*) 18.13 (3*R*, 5*R*)

Compound	Column	Temp. (°C)	Eluant (Hex:IPA)	Retention Time (min.)
	AS-H	17	95:5 *(0.50 mL/min)*	20.03 (3*S*, 5*S*) 25.24 (3*R*, 5*R*)
	AS-H	17	98:2 *(1.00 mL/min)*	6.06 (3*S*, 5*S*) 8.53 (3*R*, 5*R*)
	AS-H	17	95:5 (Hex:EtOH) *(1.00 mL/min)*	17.58, 22.73 20.06, 36.19
	Unable to separate diastereomers under various conditions			

Appendix B: Crystallographic Data

Determination of Absolute Stereochemistry of Compund 383

Single crystal X-ray data for **383** was collected at University College Cork on a Bruker APEX II DUO diffractometer at temperature 100 K using graphite monochromatic Mo Kα (λ = 0.7107 Å) radiation fitted with an Oxford Cryosystems Cobra low-temperature device. The structures were solved using direct methods and refined on F^2 using SHELXL-97. Analysis was undertaken with the SHELX1 suite of programs[1] and diagrams prepared with Mercury 2.3.[2] All non-hydrogen atoms were located and refined with anisotropic thermal parameters. Hydrogen atoms were included in calculated positions or they were located and refined with isotropic thermal parameters.

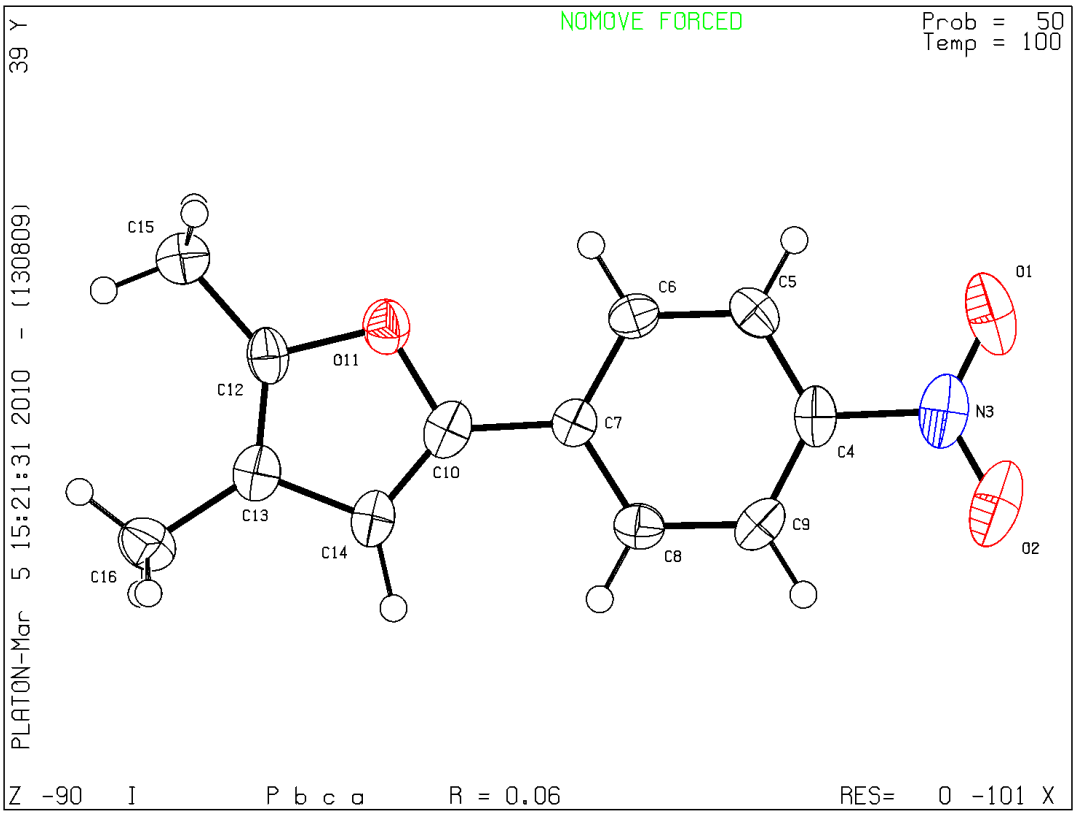


Single crystals of compound **383** were grown from hexane / ethyl acetate.

Crystal data: $C_{30}H_{38}F_2O_4$, MW = 500.60, orthorhombic, $P2_12_12$, a = 17.793(3) Å, b = 23.960(3) Å, c = 6.0798(8) Å, α = 90°, β = 90°, γ = 90°, V = 2591.9(6) Å^3, Z = 4, Dc = 1.283 g cm^{-3}, F_{000} = 1072, Mo Kα radiation, λ = 0.71073 Å, T = 100.(2) K, $2\theta_{max}$ = 26.38°, μ = 0.093 mm^{-1}, 14797 reflections collected, 5256 unique (R_{int} = 0.0550), final GooF = 0.969, R_1 = 0.0451, wR_2 = 0.0932 (4086 obs. data: $I > 2\sigma(I)$); R_1 = 0.0682, wR_2 = 0.1041 (all data).

Structure Determination of Compund 409

Single crystal X-ray data for **409** was collected at University College Cork on a Bruker APEX II DUO diffractometer at temperature 100 K using graphite monochromatic Mo Kα (λ = 0.7107 Å) radiation fitted with an Oxford Cryosystems Cobra low-temperature device. The structures were solved using direct methods and refined on F^2 using SHELXL-97. Analysis was undertaken with the SHELX1 suite of programs[1] and diagrams prepared with Mercury 2.3.[2] All non-hydrogen atoms were located and refined with anisotropic thermal parameters. Hydrogen atoms were included in calculated positions or they were located and refined with isotropic thermal parameters.

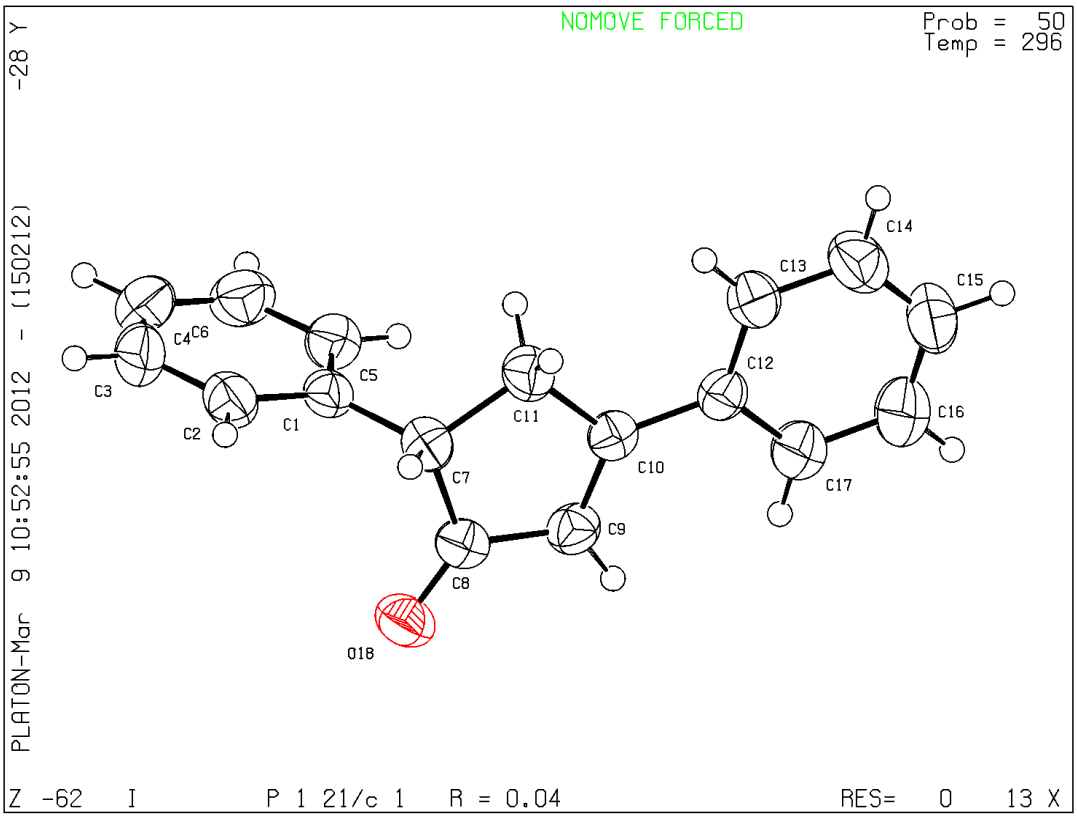


Single crystals of compound **409** were grown from hexane/ethyl acetate.

Crystal data: $C_{12}H_{11}NO_3$, MW = 217.22, orthorhombic, $Pbca$, a = 10.690(7) Å, b = 7.808(5) Å, c = 25.210(17) Å, α = 90°, β = 90°, γ = 90°, V = 2104.(2) Å^3, Z = 8, Dc = 1.371 g cm^{-3}, F_{000} = 912, Mo Kα radiation, λ = 0.71073 Å, T = 100.(2) K, $2\theta_{max}$ = 28.44°, μ = 0.100 mm^{-1}, 12113 reflections collected, 2603 unique (R_{int} = 0.0585), final GooF = 1.043, R_1 = 0.0610, wR_2 = 0.1540 (1595 obs. data: $I > 2\sigma(I)$); R_1 = 0.1102, wR_2 = 0.1824 (all data).

Structure Determination of Compund 419

Single crystal X-ray data for **419** was collected at University College Cork on a Bruker APEX II DUO diffractometer at temperature 296 K using graphite monochromatic Mo Kα (λ = 0.7107 Å) radiation fitted with an Oxford Cryosystems Cobra low-temperature device. The structures were solved using direct methods and refined on F^2 using SHELXL-97. Analysis was undertaken with the SHELX1 suite of programs[1] and diagrams prepared with Mercury 2.3.[2] All non-hydrogen atoms were located and refined with anisotropic thermal parameters. Hydrogen atoms were included in calculated positions or they were located and refined with isotropic thermal parameters.



Single crystals of compound **419** were grown from hexane/ethyl acetate.

Crystal data: $C_{17}H_{14}O$, MW = 234.28, monoclinic, $P2_1/c$, a = 5.3475(5) Å, b = 23.148(2) Å, c = 10.1504(10) Å, α = 90°, β = 92.550(4)°, γ = 90°, V = 1255.2(2) Å^3, Z = 4, Dc = 1.240 g cm^{-3}, F_{000} = 496, Mo Kα radiation, λ = 0.71073 Å, T = 296.(2) K, $2\theta_{max}$ = 25.72°, μ = 0.075 mm^{-1}, 7266 reflections collected, 2399 unique (R_{int} = 0.0392), final GooF = 1.083, R_1 = 0.0426, wR_2 = 0.0916 (1504 obs. data: $I > 2\sigma(I)$); R_1 = 0.0842, wR_2 = 0.1058 (all data).

References:

1. Sheldrick, G. M.; *Acta Crystallographica*, 2008*,* **A64**, 112–122.

2. Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Rodriguez Monge, L.; Taylor, R.; van de Streek, J.; Wood, P. A.; *Journal of Applied. Crystallography*, 2008, **41**, 466–470.