UNIVERSITY
of
GLASGOW

Diastereoselective Conjugate additions of Grignard reagents to homochiral fumarates derived from Oppolzer's sultam

A thesis presented in part fulfilment of the requirements for the Degree of

Doctor of Philosophy

by

Gary Patrick Reid

Department of Chemistry,
University of Glasgow

March 2004

Acknowledgements

Firstly I would like to thank Professor David Robins for all his help and advice throughout the three years of work that has went into this thesis, and his assistance in the compilation of this thesis.

The members of the technical staff deserve a mention for their support and advice: Dr. D. Rycroft and Mr. J. Gall for their help in obtaining and interpreting the NMR spectra; Mr. A. Ritchie and Mr J. Tweedie for their work in obtaining mass spectra; and Mrs. K. Wilson for elemental analyses.

Thanks should also go to Isabel Freer for her endless assistance around the lab and for her work in the enzyme extractions and assays.

Special thanks should go to all the members of the synthetic section who through their help and encouragement have made the time spent on this project both enjoyable and entertaining at times. The members of the Henderson Lab over the past three years especially Jill, Sam, Laurie, Chris, Stuart, Christine, Neil, Kathryn and Stephen created an atmosphere that was never gloom.

I would like to thank the University of Glasgow for funding this project.

I would like to say a special thanks to Jill. Through her support she has kept me motivated during the composition of this thesis.

Finally I would like to dedicate this thesis to my late mother Patricia, who unfortunately succumbed to cancer in the second year of my research. Without her help, motivation and hard work I know I would not be where I am today. To which I am forever grateful.

Abbreviations

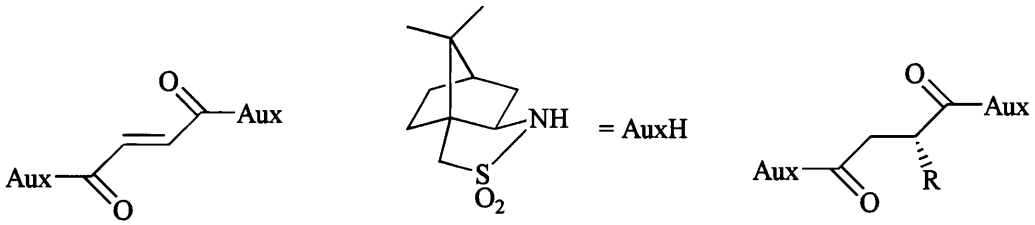
CC	Cyanuric chloride
DAO	Diamine oxidase
DBU	(1,8-Diazabicyclo[5.4.0]undec-7-ene)
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DFMO	α-Difluoromethylornithine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DNA	Deoxyribonucleic acid
De	Diastereomeric excess
Dr	Diastereomeric ratio
EDCI	[1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride]
E	Enzyme
Ee	Enantiomeric excess
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
HFIP	Hexafluoro-2-propanol
HOBt	1-Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
K_M	Michaelis Menten constant
LAD	Liver alcohol dehydrogenase
LDA	Lithium diisopropylamide
LSAO	Lentil seedling amine oxidase
LUMO	Lowest occupied molecular orbital
MNNG	*N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine
MTPA	α-Methoxy-α-(trifluoromethyl)phenylacetic acid
NDMBA	*N*-Dimethylbarbituric acid
NHS	*N*-Hydroxysuccinamide
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance

ODC	Ornithine decarboxylase
PKAO	Pig kidney amine oxidase
PSAO	Pea seedling amine oxidase
R_f	Retention factor
RNA	Ribonucleic acid
S	Substrate
THF	Tetrahydrofuran
tlc	Thin layer chromatography
V	Reaction rate
V_{max}	Maximum rate

Table of Contents

Summary

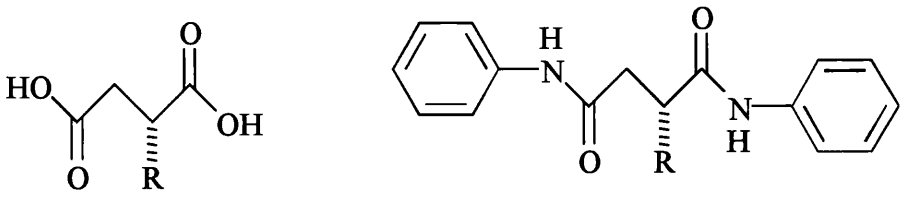
Asymmetric conjugate addition to α,β-unsaturated organic compounds is one of the most useful methods for producing β-substituted products in a stereoselective manner. It was shown that Grignard reagents add in a conjugate manner to *N,N'*-fumaroylbis[(2*R*)-bornane-10,2-sultam] **i**, readily available from Oppolzer's (2*R*)-bornane-10,2-sultam **ii**.



i **ii** **iii**

The fumaramide system **i** was treated with a series of Grignard reagents to produce diastereomers **iii** in excess for a range of different Grignard reagents incorporating alkyl and aromatic groups. This selectivity results from attack on the *re* face of **i**.

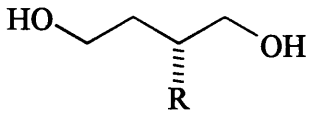
The mixtures of diastereomers were hydrolysed to the corresponding (2*R*)-substituted succinic acids **iv**. Enantiomeric excesses were determined by conversion of the diacids into dianilides **v** and analysis using chiral HPLC. Substituted succinic acids are important intermediates in organic synthesis. They are building blocks for the synthesis of enantiomerically pure β-substituted, β-amino acids. They also have a role as structural components in natural products. Using our methodology (2*R*)-benzylsuccinic acid was obtained in high 92% ee. (2*R*)-Benzylsuccinic acid has previously been shown to be an inhibitor of carboxypeptidase A.



iv **v**

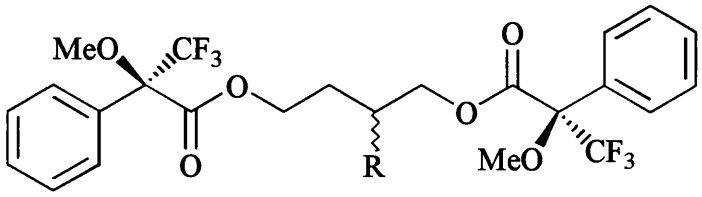
The extent of diastereofacial differentiation of the conjugate addition was also determined by analysis of the ^{1}H NMR spectra of the diastereomeric mixtures. The ABX system of the succinamide protons resonated at different frequency for each pair of diastereomers.

The mixture of diastereomers were also reduced producing the (2*R*)-substituted butane-1,4-diols **vi**.



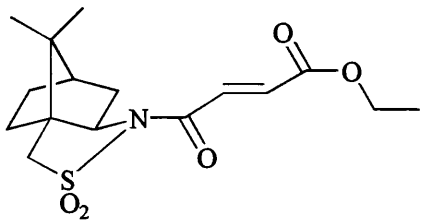
vi

The enantiomeric excesses of the diols were estimated from ^{19}F NMR spectra of the corresponding Mosher's esters **vii**.

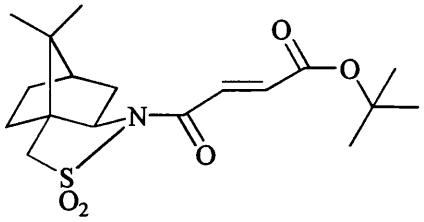


vii

The addition of Grignard reagents to two differentially protected fumarates **viii** and **ix** was carried out.



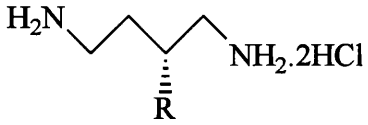
viii



ix

The Grignard reagent did not add exclusively in a 1,4 manner to **viii** and a mixture of 1,2-addition and 1,4-addition products was observed. The reaction of fumarate **ix** with Grignard reagents gave only conjugate addition products. Diastereomeric excesses could not be determined from the proton NMR spectra of the reaction mixtures. Therefore the diastereomeric excess was determined from the bis-Mosher ester of each diol. The stereoselectivity obtained with fumarates **viii** and **ix** was not as good as that observed using fumaramide **i**.

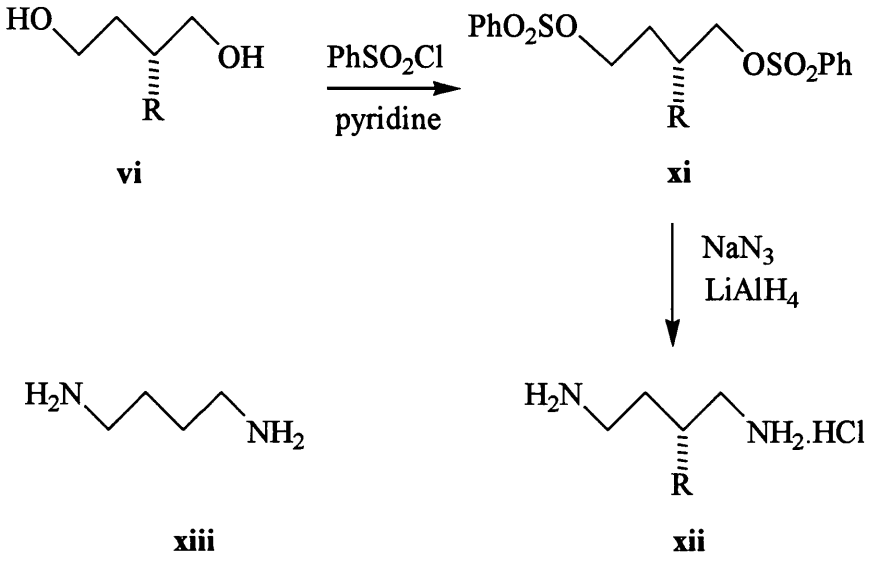
The diastereomers **iii** were used to synthesise enantiomerically pure 2-substituted putrescines **x**.



x

Removal of the chiral auxiliaries from **iii** using lithium aluminium hydride produced the corresponding enantiomerically enriched 2-substituted butane-1,4-diols **vi**. The enantiomeric excess of these diols was improved to >95% by separation of the diastereomers of **iii** using column chromatography or by recrystallisation. The diols **vi**

were converted into the disulfonate esters **xi**, followed by substitution by sodium azide. The diazides were directly reduced to the diamines using lithium aluminium hydride and isolated as the dihydrochloride salts **xii**. Racemic 2-substituted putrescines were also prepared.



vi **xi**

xiii **xii**

Diamine oxidase (DAO) enzymes are involved in the terminal catabolism of polyamines, and putrescine **xiii** is a natural substrate for DAO. DAO catalyses the oxidation of diamines to aminoaldehydes. Some of the 2-substituted putrescines produced were shown to be substrates for pea seedling DAO. Part of this work has been published (G. P. Reid, K. W. Brear and D. J. Robins, *Tetrahedron: Asymmetry*, 2004, **15**, 793).

1. Asymmetric synthesis

1.1 Introduction

Asymmetric synthesis is a term that can be used to describe a wide variety of transformations. The original definition of asymmetric synthesis by Marckwald in 1904 stated that it is a process that produces an optically active compound from the reaction of an achiral substrate with a chiral reagent.[1] This definition has now evolved to describe asymmetric synthesis as a reaction where an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in order to produce stereoisomeric products in unequal amounts. Nature provides the best examples of chiral compounds where proteins, carbohydrates, and nucleotides all have chiral monomers present. The requirement to prepare chiral compounds in enantiomerically pure form has increased recently as a result of several factors, mainly driven by the stereodiscrimination of chiral compounds by most biological systems and therefore the pressure on the pharmaceutical industry to develop nonracemic drugs.

1.2 Various Methods of Asymmetric Synthesis

As mentioned before in order to achieve an enantioselective synthesis, at least one of the reagents in the system must be homochiral. There are essentially two major methods to produce a chiral compound: resolution or asymmetric synthesis. These methods involve the use of chiral starting materials, chiral auxiliaries or chiral reagents.

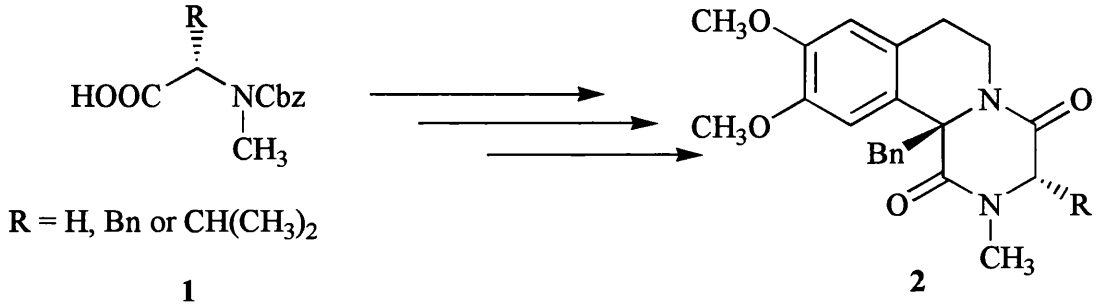
1.2.1 Why does asymmetric induction occur?

Asymmetric synthesis is a kinetic phenomenon. The interaction of a chiral substrate or reagent with a prochiral substrate gives rise to two diastereomeric transition states. The difference in energy between the transition states of the two diastereomers determines the ratio of diastereomers. The major diastereomer will be formed from the transition state with the lower energy pathway. If the free energy of the reaction can be manipulated then the stereoinduction can be tuned. The most popular way to achieve this is to carry out

reactions at low temperature thus reducing the contribution from the higher energy pathway.

1.2.2 Chiral Substrates

This term refers to the use of homochiral starting material in order to control the stereoselective outcome of the reaction. At the start of a synthetic route there are limited sources of chirality and most come from nature providing the chiral pool. This approach can be extremely limited by means of source and price. Another drawback to this method can be the chemical reactions involved in transforming the natural product to a useful starting material. However with all these difficulties addressed it is by far the best method as it avoids resolution and enantiospecific reactions in the synthetic route. It is also a methodology that is increasingly used as more natural products are identified. Naturally occurring amino acids **1** [e.g. L-(-)-phenylalanine, L-(+)-valine and L-(-)-proline)] have been used in the synthesis of enantiomerically pure heterocycles (Scheme 1.1).[2]



Scheme 1.1

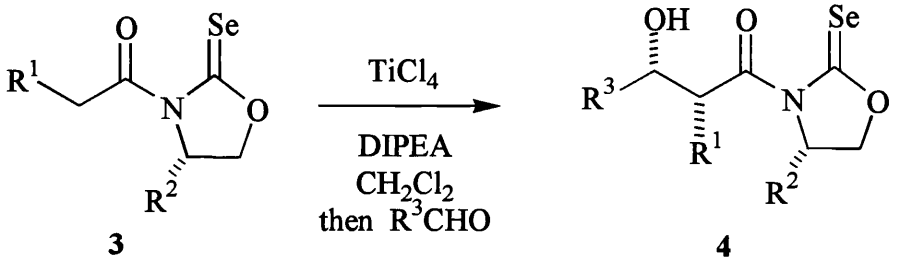
The amino acids were used as chiral inducers in the diastereoselective synthesis of 1-benzyltetrahydroisoquinoline derivatives **2**.

1.2.3 Chiral Auxiliaries

Chiral auxiliaries are a source of chirality that arises from the attachment of a chiral compound to an achiral molecule. These groups then produce stereoselectivity via a chemical reaction and subsequent removal of the auxiliary to produce a product enriched in one enantiomer. The drawback to this method is the two extra steps involved in the addition and removal of the auxiliary, which must be high yielding and should provide a means of auxiliary recycling.

A number of different auxiliaries are available mainly derived from camphor, amino acids, and oxazolidinones. In some instances the auxiliary does not need to be chiral but just requires the absence of symmetry in the form of mirror or inversion symmetry. It is highly recommended to use auxiliaries with a C_2 symmetry axis as this cuts down the number of possible competing diastereomeric transition states.

The use of chiral auxiliaries in asymmetric aldol reactions has proved highly successful (Scheme 1.2).[3] The titanium(IV) enolates of **3** gave predominately *syn*-aldol products **4** with the selone having a role in determining the stereoselectivity.



3 **4**

d e >99:1

Scheme 1.2

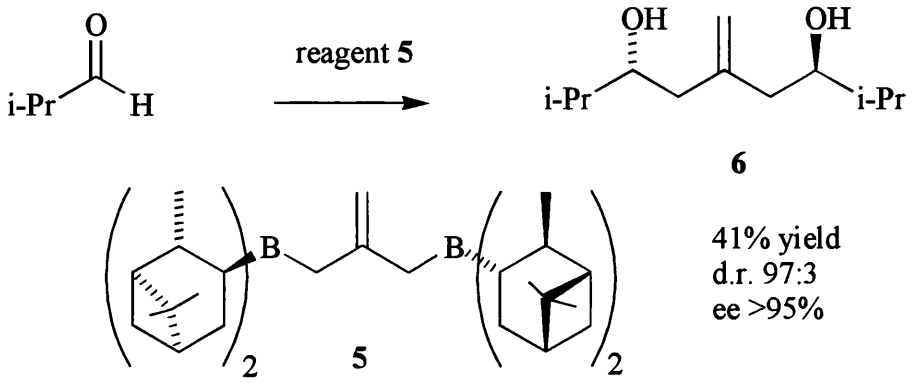
1.2.4 Regeneration of Stereocentres

This involves the transfer of a chiral centre within a molecule to another part of the molecule. This creates a new chiral centre which provides control for a stereoselective reaction, where a new centre of asymmetry can be created or the original chirality of the starting material can be re-established.[4]

1.2.5 Chiral Reagents

This method can involve many different sources of chiral reagents arising from nature as in enzymes, or prepared synthetically and used stoichiometrically, or as chiral catalysts. The reagent that is used must be selective for the substrate it reacts with in terms of induction of chirality and also specificity for the functional group. The use of a chiral reagent must justify the expense and the means of recycling or the turnover rate must be carefully considered and this is where chiral catalysts lead the field. However in order to develop a chiral catalyst the catalytic cycle must be well understood. An example of a

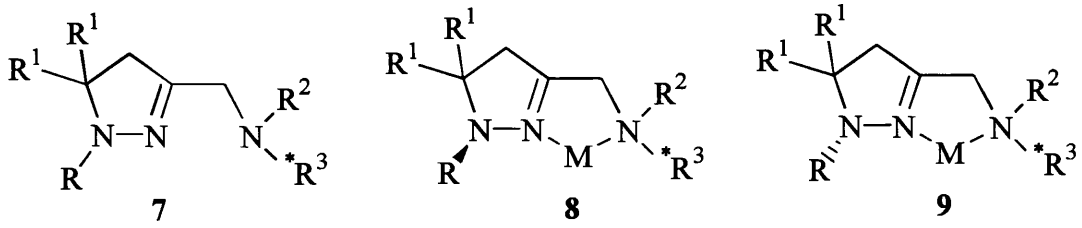
chiral reagent is the use of an asymmetric bidirectional allylboration reagent **5** to prepare C_2 symmetric 1,5-diols **6** (Scheme 1.3).[5]



Scheme 1.3

1.2.6 Chiral Environments

The environment of a chemical reaction can be made chiral by introducing a chiral solvent or chiral additives. Chiral solvents have not been very successful, but the use of chiral ligands can produce good levels of stereoselectivity. A new class of ligands **7** has been developed incorporating a fluxional group which controls the stereochemical induction.[6]

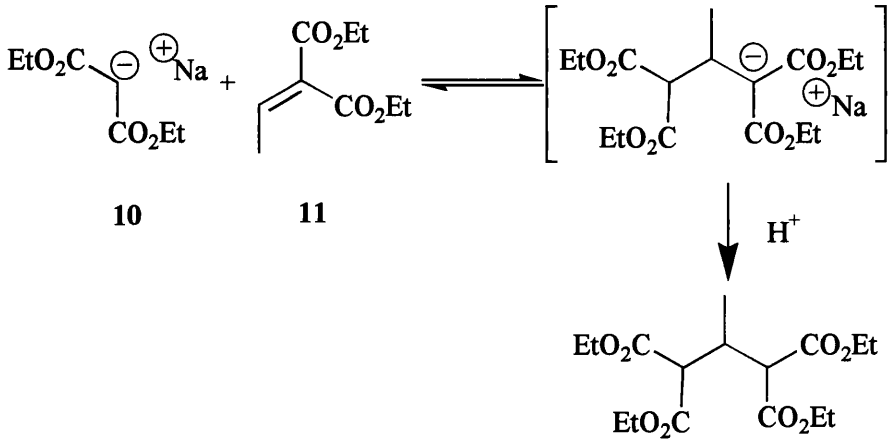


The ligand contains a dihydropyrazole core with two nitrogen atoms that can form a five-membered chelate **8** with Lewis acids. The chiral source arises from R^3 (examples include chiral amines) and this dictates the orientation of the fluxional group R in **8** or **9**. The fluxional group R can be varied by a simple alkylation reaction. These ligands have been used successfully to induce face selectivity in Diels-Alder reactions.

2. Conjugate Addition Reactions

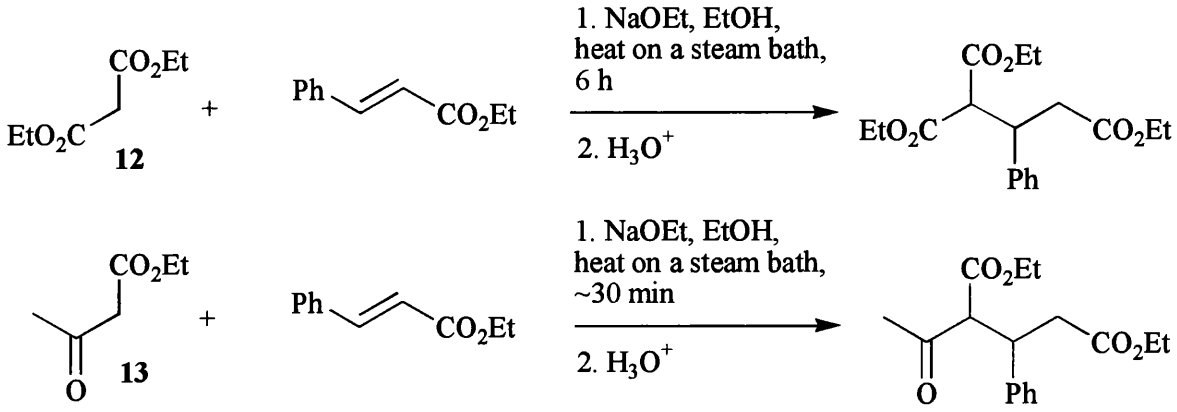
2.1 Introduction

Conjugate additions were first reported over a century ago when Komnenos described the conjugate addition of diethyl sodiomalonate **10** to diethyl ethylidenemalonate **11** in 1883 (Scheme 2.1).[7,8]



Scheme 2.1

The real significance of this reaction was first realised by an American chemist called Arthur Michael. In 1887 he reported the base-promoted additions of sodium salts of malonates **12** and β-ketoesters **13** to ethyl cinnamate (Scheme 2.2).[9] When we refer to a Michael addition or a Michael reaction the terminology has emerged from this original study.



Scheme 2.2

The conjugate addition is sometimes referred to as 1,4-addition but throughout this thesis the term conjugate addition will be used. "Conjugate addition refers to the addition of any class of nucleophile to an unsaturated system in conjugation with an activating group, usually an electron-withdrawing group."[10]

2.2 Mechanism

The reason why nucleophiles add to the β-carbon of an α,β-unsaturated system is to do with the activation from the carbonyl group. The carbonyl group is responsible for polarizing the C=C double bond which is shown by the resonance structures (Figure 2.1).

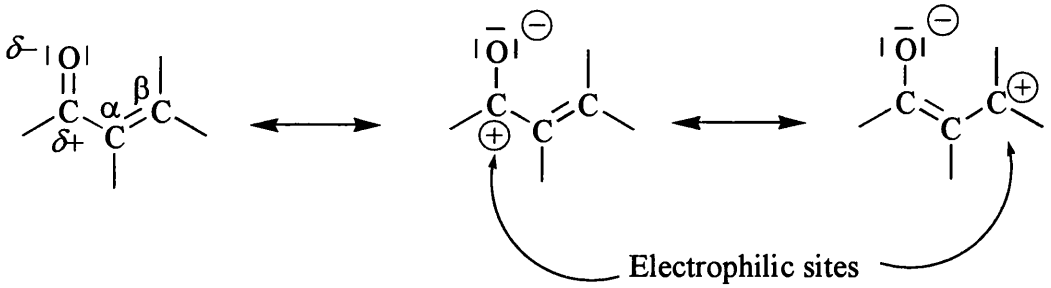
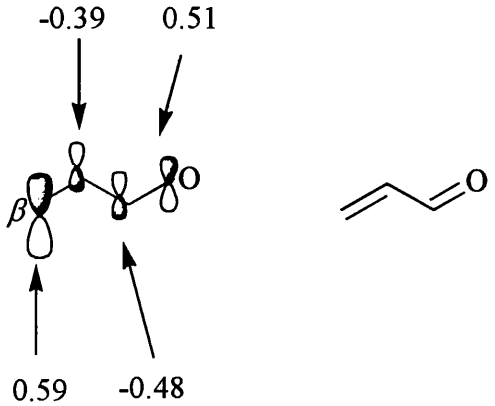


Figure 2.1

The configuration of the C=C double bond with the C=O group makes the β-carbon electrophilic and hence susceptible to attack from nucleophiles.

We can also use the frontier molecular orbital approach to help explain why the β-carbon is the preferred site of attack. For successful addition of nucleophile electrons must move from the HOMO of the nucleophile to the LUMO of the α,β-unsaturated system. The orbital coefficients for acrolein have been calculated and the largest coefficient is on the β-carbon which is where the nucleophile attacks (Figure 2.2).[11]



Orbital coefficients for the LUMO of acrolein

Figure 2.2

We have explained orbital overlap to account for why conjugate addition takes place and we can also introduce the terms 'hard' and 'soft' to refer to the reagents being added. Hard nucleophiles have a high charge density and react by electrostatic attractions whereas soft nucleophiles are either uncharged or have more diffuse orbitals. The α,β-unsaturated system can also be classified in terms of hard and soft electrophiles. The carbon atom of the carbonyl group carries a partial positive charge due to polarization of the C=O bond thus classing it as a hard electrophile. On the other hand the β carbon is a soft electrophile as it does not have a high partial charge and as shown in figure 2.2 it is the site of the largest coefficient in the LUMO. A hard nucleophile will always react with a hard electrophile and likewise a soft nucleophile will react with a soft electrophile. The conjugate addition to an α,β-unsaturated system can be tuned by the careful selection of the nucleophile. For example hard nucleophiles are NH_3, RMgX and RLi whereas soft nucleophiles are RSH, R_2CuLi and R_3P.

Something that has not been mentioned yet is the possibility of producing the direct addition product resulting from addition of the nucleophile to the carbon of the carbonyl group. There are three main factors that have to be considered in an attempt to minimise this side reaction:

- the conditions of the reaction;
- the reactivity of the carbonyl carbon;
- the nature of the nucleophile;

It is widely accepted that the reaction conditions should allow the reaction to reach an equilibrium. At this equilibrium the conjugate product is favoured over the direct product as it is more stable because the C=O π bond is stronger than the C=C π bond. The direct product will form faster but this reaction is reversible. The conjugate product can also form and this reaction is irreversible allowing an accumulation of the conjugate product over time (Figure 2.3). If the reaction temperature is increased this also increases the rate of reaction so favouring the conjugate product.

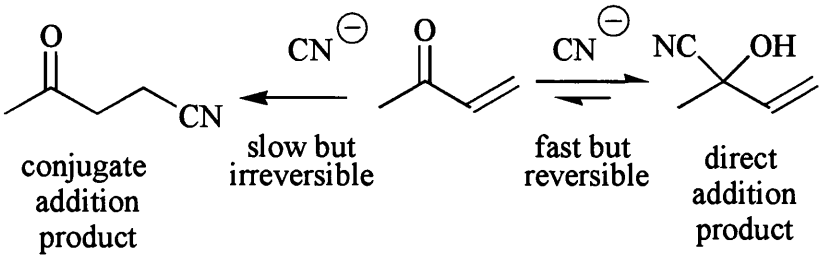


Figure 2.3

However the direct addition of organometallic reagents to α,β-unsaturated systems is not reversible and the proportion of direct addition versus conjugate addition depends on the reactivity of the carbonyl group. The more reactive the carbonyl group the more susceptible it is to attack. For the α,β-unsaturated system the order is:

$$COCl > CHO > COR > CO_2R > CONR_2$$

Another structural factor that has shown some effect in the proportion of products formed relates to the substituents attached to the β-carbon. This produces steric hindrance that can block the incoming nucleophile.

There is a large array of conjugate acceptors which are composed of the activating group (carbonyl derivative) and the part containing the C=C double bond. There are many carbonyl activating groups such as RCHO, RCOR, RCOCOR, RCOCOOR, RCOCN, RCOOH and RCOOR. Other conjugate acceptors are sulfone derivatives, phosphonate derivatives, nitriles, enamines, nitroso compounds and aromatic compounds. The nature of the nucleophile is very wide with reactions being carried out using cyanides, amines, alcohols, thiols, halides and organometallic reagents. The most popular of these nucleophiles used in conjugate additions are probably organometallic reagents due to the variety of substituents that can be prepared in this way.

2.3 Asymmetric Conjugate Additions

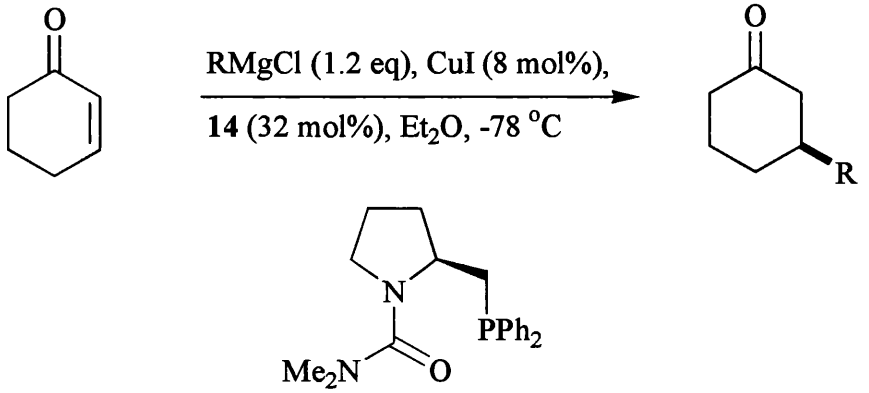
In attempts to induce stereoselectivity in the product of a conjugate addition reaction the reaction can be carried out in the presence of chiral catalysts, with chiral reagents, or using substrates that have chiral moieties attached. The use of chiral catalysts

and chiral reagents will be discussed briefly and the use of chiral moieties attached to the electrophile will be discussed in greater detail.

2.3.1 Chiral Catalysts

The research carried out on the catalysis of asymmetric conjugate additions has mainly focused on cyclic α,β-unsaturated systems. The catalytic aspect comes from the use of a chiral ligand and usually catalytic amounts of Cu(I) salts together with stoichiometric amounts of organomagnesium or organozinc reagents.

Tomioka *et al.* reported the addition of Grignard reagents to cyclohexenone in the presence of a catalytic amount of Cu(I) salts together with a chiral bidentate amidophosphine **14** (Scheme 2.3).[12]

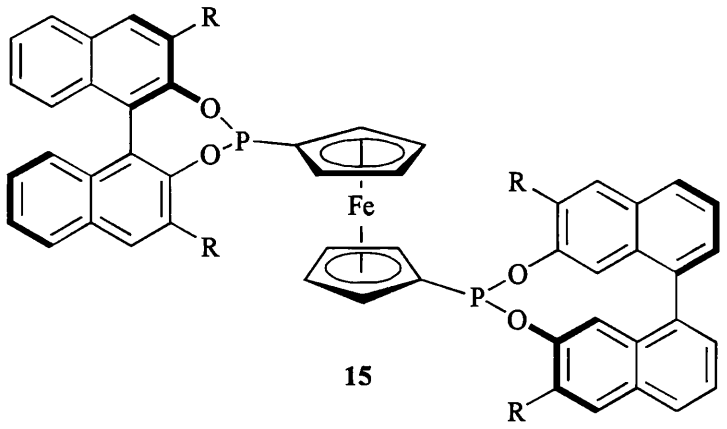


14

Scheme 2.3

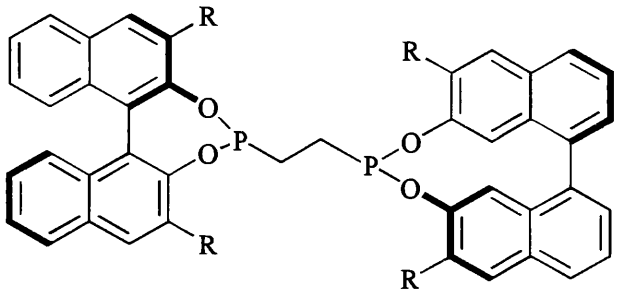
The amidophosphine ligand **14** has a diphenylphosphino group which coordinates to copper and an amide group which coordinates to the magnesium. The chiral bidentate amidophosphine was prepared easily from commercially available L-proline. It was found that good levels of stereoselectivity were obtained when $n > 2$ for $R(CH_2)_nMgCl$. The chiral phosphine would be recovered for reuse without any loss of optical purity.

Diphosphonites have been used as chiral ligands for the copper catalysed asymmetric conjugate addition of diethylzinc to cyclic α,β-unsaturated systems. The ligands **15** and **16** are BINOL-based and have been previously used to induce excellent enantioselectivity in rhodium catalysed hydrogenations of alkenes (97-99% ee).[13]



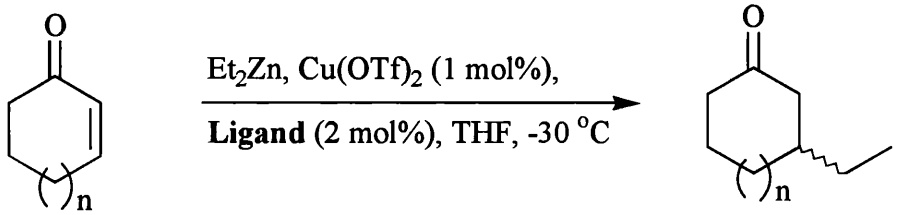
15

R = H
R = CH_3
R = C_6H_5



16

Ligand **15** displays good levels of stereoselectivity (87-99% ee) and conversion at temperatures of –30 °C (Scheme 2.4). However ligand **16** shows low levels of stereoselectivity suggesting that the nature of the achiral backbone is important in achieving asymmetric induction.[14]

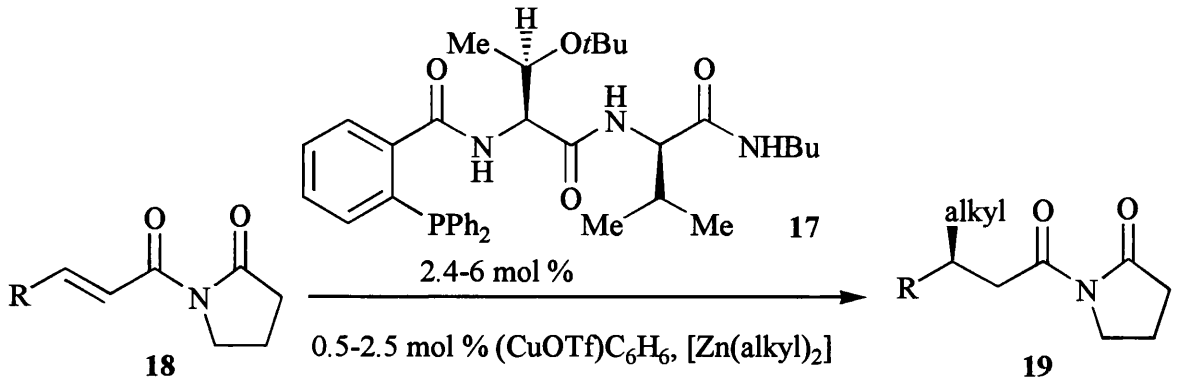


n = 1
n = 2

n = 1
n = 2

Scheme 2.4

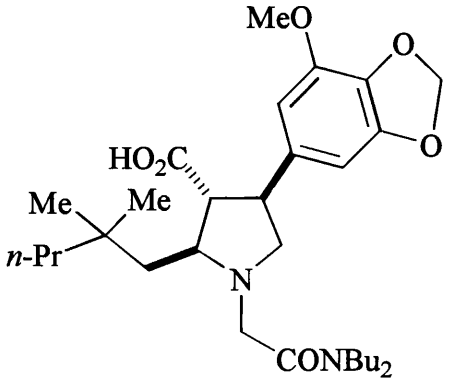
Hird and Hoveyda have reported the use of a novel amino acid based phosphine amide **17** as an effective chiral ligand for asymmetric conjugate addition.[15] Catalytic asymmetric conjugate addition of alkyl zinc reagents to unsaturated *N*-acyloxazolidinones **18** was achieved with excellent levels of stereoselectivity (76->98% ee) (Scheme 2.5).



Scheme 2.5

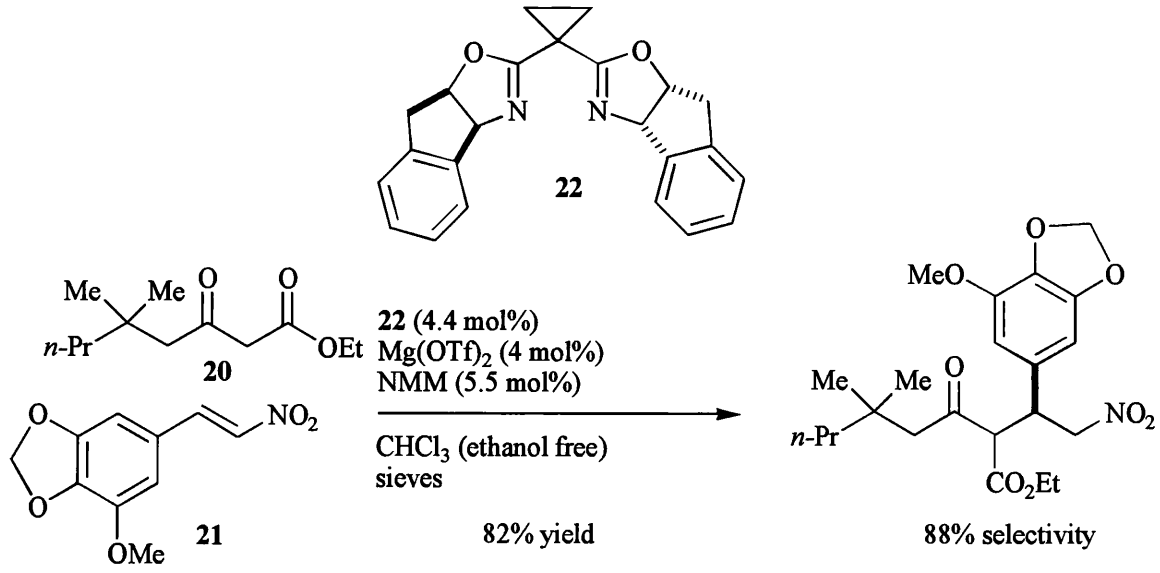
Ligand **17** is a triamide containing an L- and D-amino acid dipeptide. The amino acids in this ligand **17** are D-threonine and L-valine. This showed better results than the corresponding L,L-dipeptide. This methodology allows the use of a range of alkyl zinc reagents not just diethyl zinc, and the optically enriched *β*-alkyl *N*-acyloxazolidinones **19** can be converted into other carbonyl derivatives that have not previously been accessible by catalytic asymmetric conjugate addition reactions.

In an attempt to develop an enantioselective synthesis of an enodothelin-A antagonist **ABT-546** a highly selective catalytic asymmetric conjugate addition was discovered.[16]



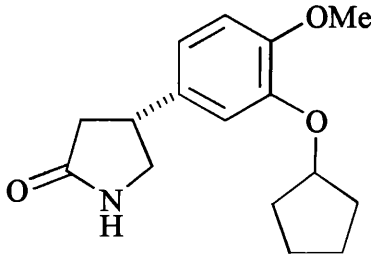
ABT-546

The conjugate addition of ketoester **20** to nitrostyrene derivative **21** is catalysed by the complex bis(oxazoline) **22** together with $Mg(OTf)_2$ and an amine cocatalyst *N*-methylmorpholine (NMM) (Scheme 2.6).



Scheme 2.6

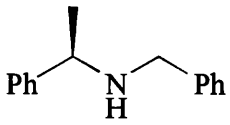
A range of dicarbonyl substrates and nitroalkenes have been used in this reaction. This methodology has been applied to the multikilogram synthesis of **ABT-546** and also the antidepressant rolipram **23**.



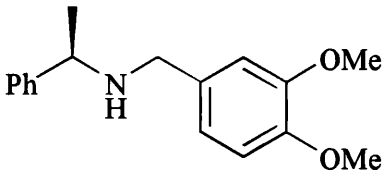
(*R*)-rolipram (**23**)

2.3.2 Chiral Reagents

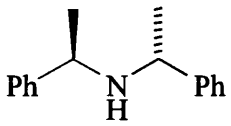
Lithium amides derived from enantiomerically pure amines have been shown to add to α,β-unsaturated systems in an conjugate fashion with excellent levels of stereoselectivity. The research group of Davies has made extensive progress in this field by developing useful asymmetric methodology for the synthesis of homochiral β-amino acids. It was first shown that when amines **24**, **25** and **26** were converted into their corresponding lithium amides they added to methyl crotonate **27** in high yield and high diastereoselectivity (95 - >99%) (Scheme 2.7).[17]



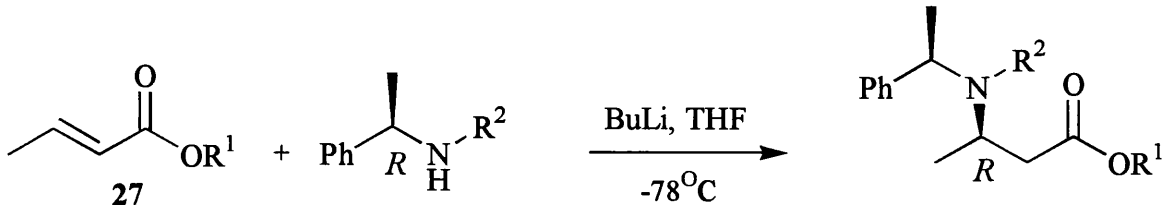
24



25



26



27

R^1 = Me, CH_2Ph, ^tBu

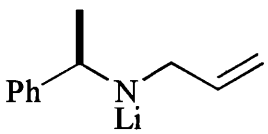
R^2 = see above

BuLi, THF, -78°C

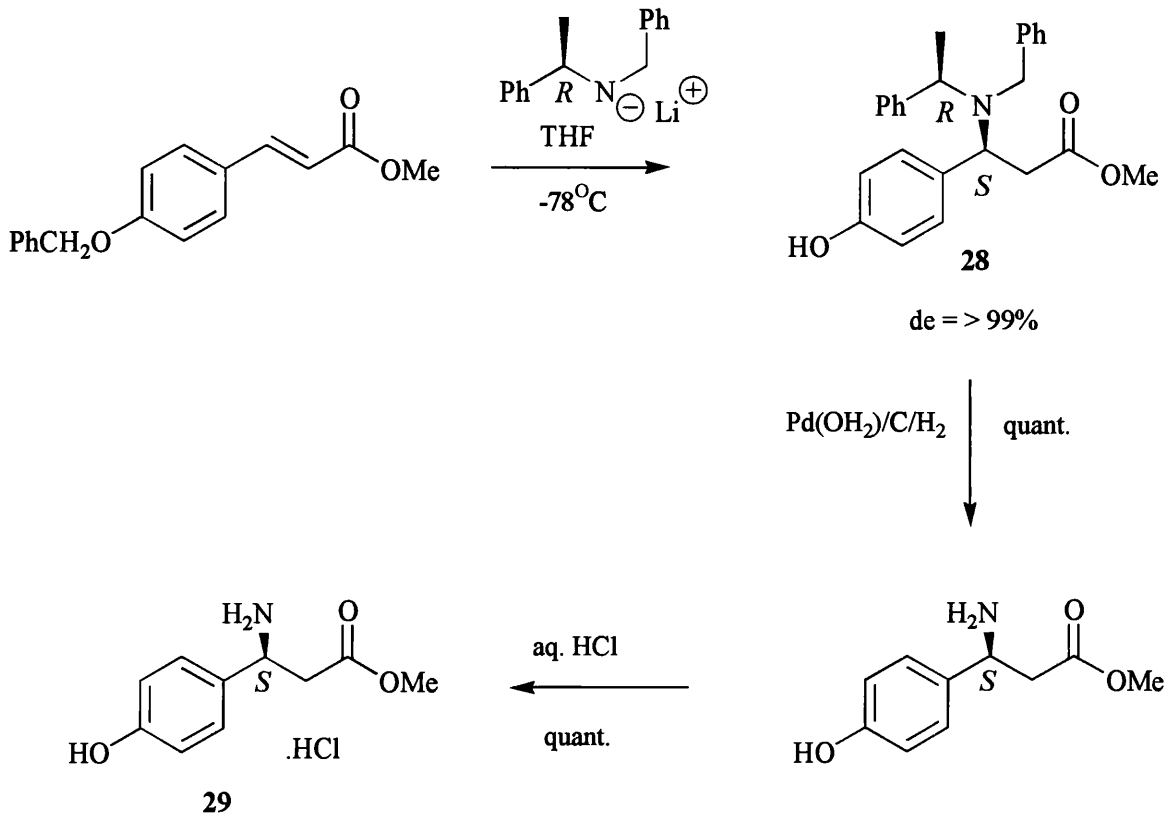
Scheme 2.7

The adducts **28** can be converted into homochiral β-amino acids by debenzylation and subsequent hydrolysis as shown for (*S*)-β-tyrosine.HCl **29** (Scheme 2.8).

The lithium (α-methylbenzyl)benzylamide **24** was shown to be a very good homochiral ammonia equivalent in the synthesis of homochiral β-amino acids. The use of this lithium amide is limited by the deprotection carried out by hydrogenolysis. Selective removal of one of the *N*-benzyl groups can be achieved; however it is somewhat problematic.[18] In an attempt to solve this problem Davies et al. have developed a differentially protected homochiral ammonia equivalent **30**.

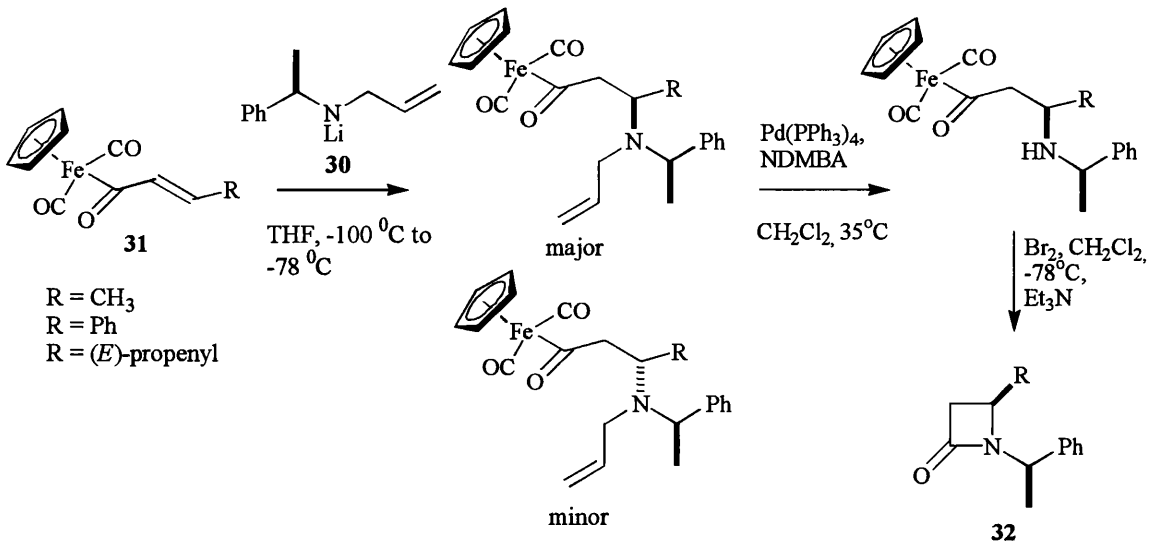


30



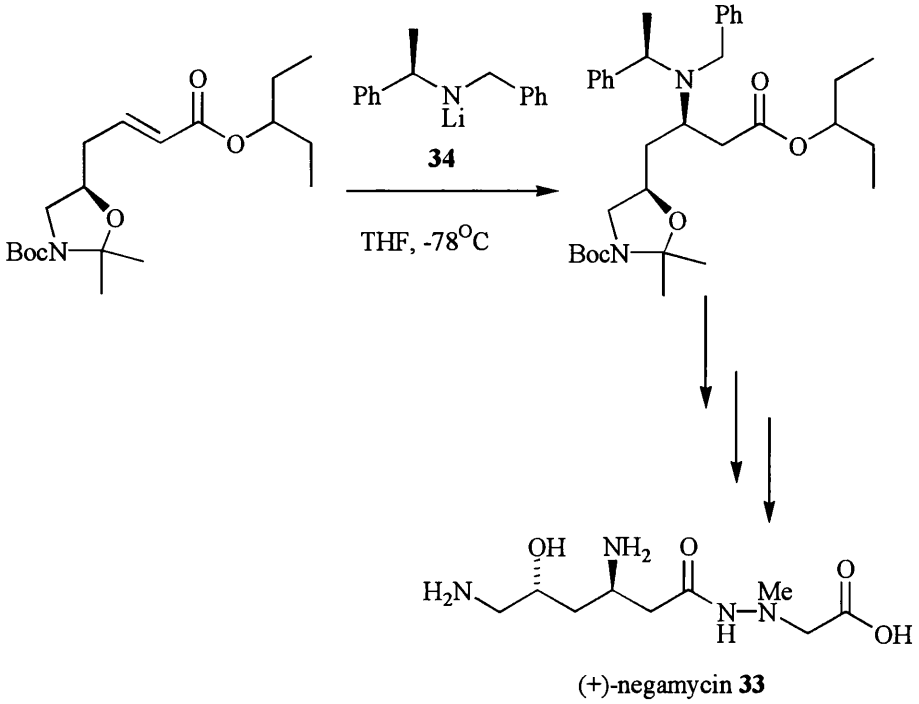
Scheme 2.8

The advantage of this lithium amide **30** is that the *N*-allyl group can be selectively deprotected to yield the secondary amine which can then be utilised in further transformations. The lithium amide **30** has been used in the stereoselective conjugate addition to (*E*)-α,β-unsaturated acyl(cyclopentadienyl)-dicarbonyliron complexes **31** and applied to the synthesis of β-lactams **32** (Scheme 2.9).[19] The conjugate additions proceeded with good diastereoselectivities (82:18-95:5) and moderate yields. However one limitation was that conjugate additions had to be carried out at a temperature of –100 °C and then warmed to –78 °C due to instability of the intermediate ferra-enolate adduct. If the lithium amide is replaced by the equivalent magnesium amide, conjugate addition occurs with greater diastereoselectivity (>95% when R = CH_3); however the reactivity of the amide is compromised.



Scheme 2.9

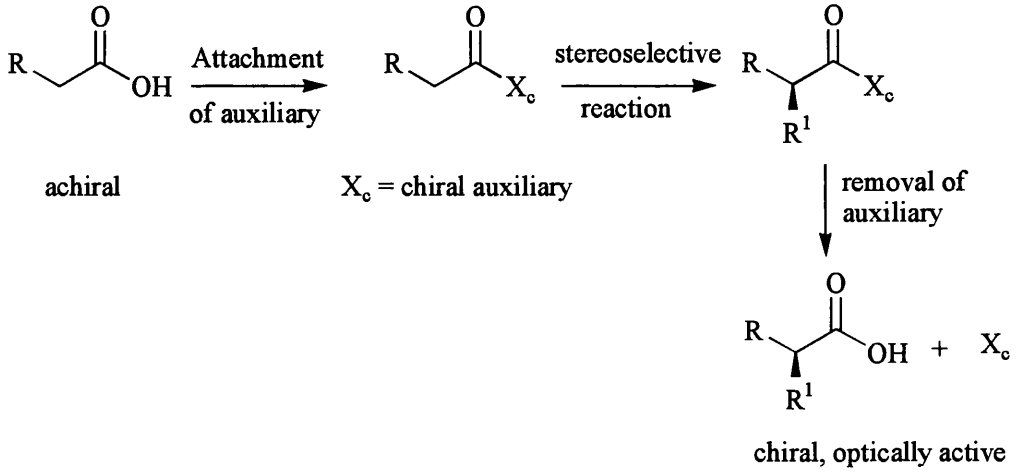
These lithium amides can be a very good source for introducing stereoselectively at an amine group at the β-carbon of an α,β-unsaturated system. Just to show the versatility in organic synthesis of these amides the key step in the asymmetric total synthesis of (+)-negamycin **33** utilised the asymmetric conjugate addition of lithium (*R*)-(α-methylbenzyl)benzylamide **34** (Scheme 2.10).[20] Negamycin **33** was discovered in 1970 by Hamada *et al.*[21] and was found to be a pseudopeptide antibiotic possessing strong inhibitory activity against Gram-negative bacteria together with very low acute toxicity.



Scheme 2.10

2.3.3 Chiral moieties attached to the electrophile

This section will focus on α,β-unsaturated systems which contain chiral moieties attached by a covalent bond. The chiral moieties mainly consist of chiral auxiliaries. The use of chiral auxiliaries to control stereochemistry is a valuable tool for an organic chemist. The strategy of using an auxiliary is very simple (Scheme 2.11).

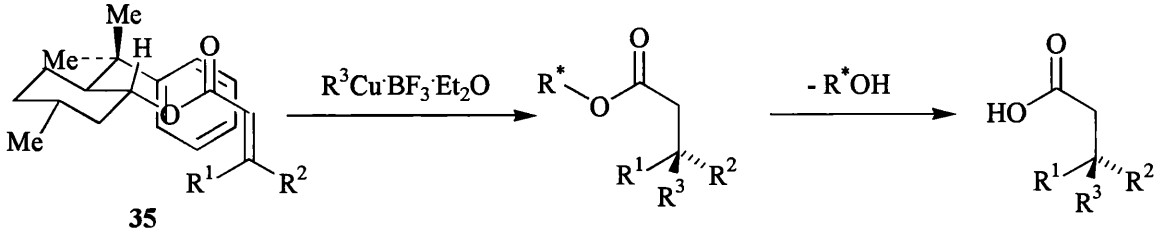


Scheme 2.11

The optically active chiral auxiliary is attached to the achiral substrate by a covalent bond. It is then used to control the stereochemistry in a bond forming reaction (in the above example an alkylation reaction). The chiral auxiliary can be removed unchanged to be used again.

2.3.3.1 α,β-Unsaturated esters

Chiral enoates **35** derived from (-)-8-phenylmenthol were shown to direct the conjugate addition of boron trifluoride-mediated organocopper reagents (Scheme 2.12).[22]



35

$R^1 = H, R^2 = Me$
$R^1 = Me, R^2 = H$
$R^1 = H, R^2 = n\text{-}C_4H_9$

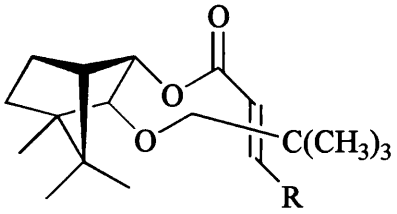
36

$R^3 = C_6H_5, n\text{-}C_4H_9, Me$

Scheme 2.12

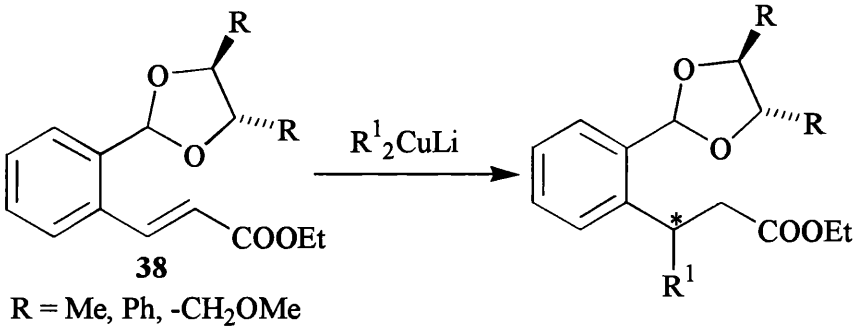
It was proposed that the boron trifluoride coordinates to the oxygen of the C=O group producing a transition state where the C=O is antiperiplanar to the C=C bond. The aromatic ring can shield one enantiotopic face of the enoate. The results were shown to support this and when R^1 = H, R^2 = Me and R^3 = C_6H_5 or *n*- C_4H_9 the stereoselectivity was greater than 99%. The advantage of this methodology is that a rigid substrate conformation can be achieved without the need for chelation with a metal. The chiral auxiliary can be removed easily by saponification to yield the corresponding enantiomerically enriched β-substituted alkanoic acids **36** together with the recovered auxiliary in 98% yield.

A modification to the above methodology was to introduce a camphor based auxiliary and see if this produced good levels of π-face differentiation for BF_3-promoted conjugate additions of alkyl copper reagents. The chiral enaote **37** was synthesised and the conjugate adducts showed high levels of stereoselectivity (94-99%) when reacted with alkenylcopper reagents.[23]



37

The use of chiral auxiliaries with a C_2 axis of symmetry is thought to be beneficial in directing stereochemical control. Alexakis *et al.* reported the use of chiral acetals which possess a C_2 axis of symmetry to direct the diastereoselective conjugate addition of cuprates to α,β-ethylenic esters **38** containing a chiral acetal (Scheme 2.13).[24]

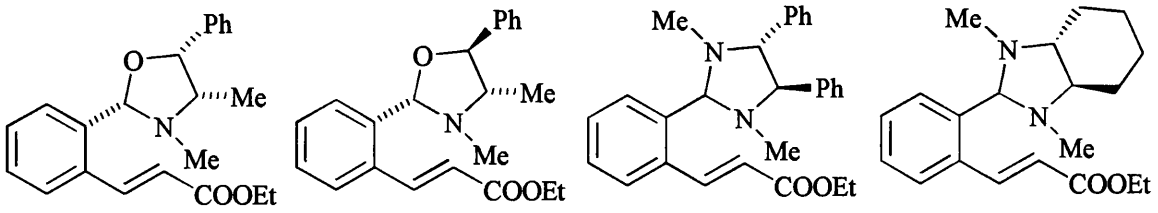


38

R = Me, Ph, -CH_2OMe

Scheme 2.13

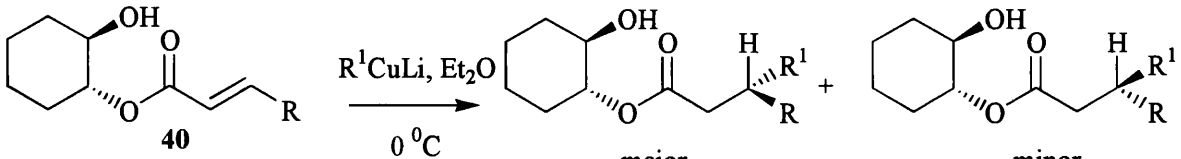
This reaction produced low levels of diastereomeric excesses (15-20%). The chiral acetal moiety was modified by replacing one or both of the oxygen atoms with nitrogen in order to promote better stereochemical control (Figure 2.4). It was thought that the nitrogen would act as a better σ donor than oxygen or create a more sterically crowded centre. Compound **39** was shown to be the most effective at asymmetric induction (90-96% de) and also overall yield of reaction (84-90%). The chiral moiety of compound **39** consists of an imidazolidine ring synthesised from (*R*,*R*)-(-)-1,2-bis(methylamino)cyclohexane. Therefore cinnamates that have a chiral oxazolidine or imidazolidine ring attached undergo conjugate additions of organocopper reagents with high levels of stereoselectivity.



39

Figure 2.4

The use of a chiral cyclic diol as a chiral auxiliary has been used to induce stereoselectivity of the conjugate addition of organocuprates to α,β-unsaturated esters **40** giving diastereomeric excesses of 88% (Scheme 2.14).[25]



40

R = Me, Et and Ph

major

minor

R^1 = Ph, Bu and Me

Scheme 2.14

This example contains the chiral moiety derived from an α,β-unsaturated carboxylic acid and the corresponding chiral diol. The proposed stereochemical outcome was rationalised by the proposed transition state which shows that a free hydroxy and the ester carbonyl chelate with the diakylcuprate which is believed to have a square planar dimeric structure (Figure 2.5).[26] This leads to the formation of a copper(I)-alkene π-complex allowing the R group to attack from the *re*-face in a stereocontrolled manner.

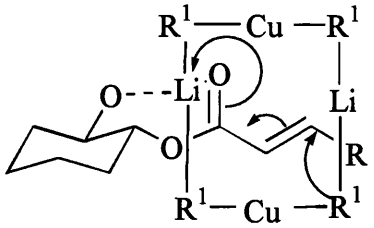
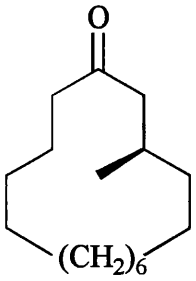


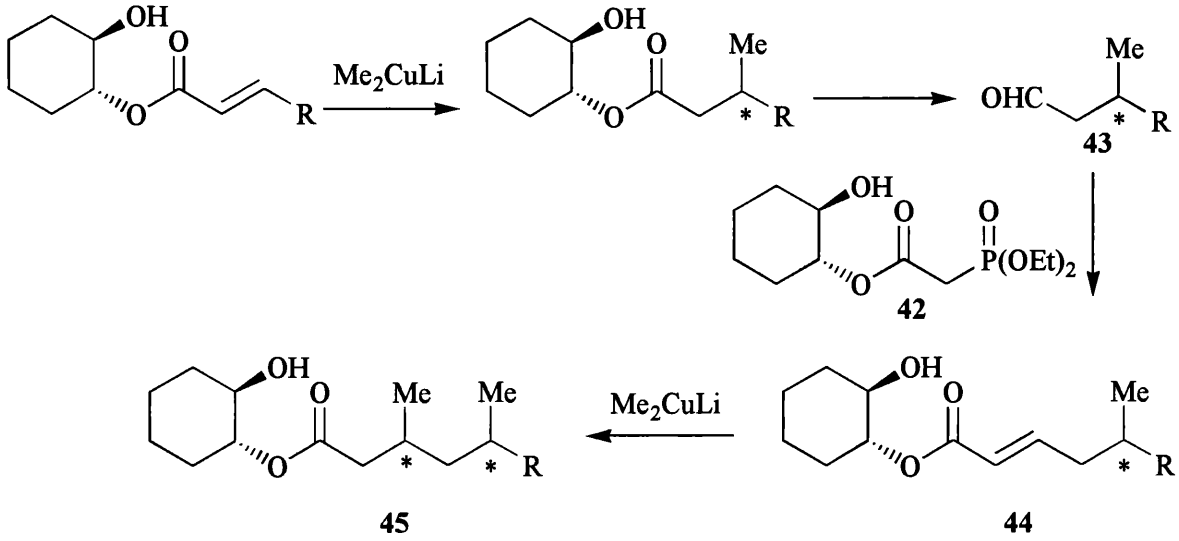
Figure 2.5

This chiral cyclic diol has also been used in the asymmetric synthesis of (*R*)-(-)-muscone **41** based on diastereoselective conjugate addition previously described.[27]



41

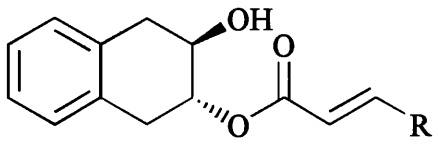
Ogawa *et al.* have extended the use of cyclohexane diols to incorporate their stereoinduction effect in the synthesis of 1,3-polymethyl functions which have been observed in the structures of antibiotic macrolides and insect pheromones.[28] Synthesis of the optically active phosphonate **42** followed by a Horner-Emmons reaction with aldehyde **43** produced **44** which underwent another diastereoselective conjugate addition of dimethylcopper lithium to produce a 1,3-methyl function in **45** (Scheme 2.15). This synthetic route can be repeated in order to produce 1,3-polymethyl functions.



Scheme 2.15

The selectivity produced by this method was 77 : 23 to favour attack from the *re*-face.

A derivative of the above auxiliary has been used for the diastereoselective conjugate addition of organocuprates to α,β-unsaturated esters **46** displaying similar diastereomeric excesses.[29]

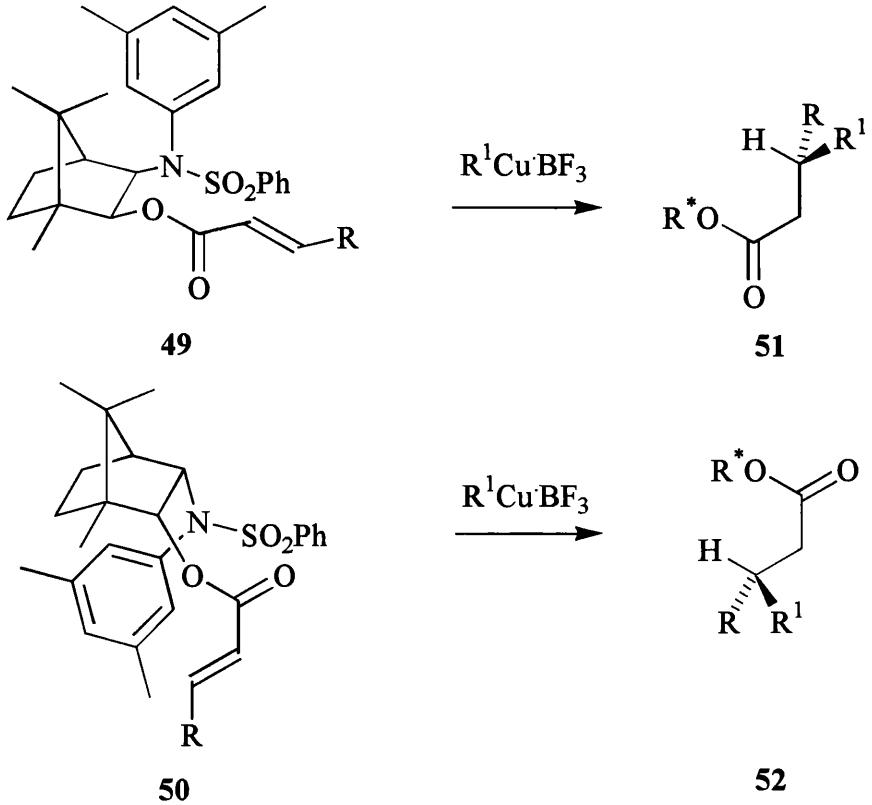


R = Me and Ph

46

The chiral auxiliary (2*R*,3*R*)-dihydroxytetrahydronaphthalene is readily prepared in an enantiomerically pure form by an efficient chemoenzymatic procedure from naphthalene using a modified strain of *Pseudomonas fluorescens*.[30]

Camphor-derived concave alcohols **47** and **48** have been used as chiral auxiliaries for the diastereoselective addition of organocopper reagents to enoates **49** and **50** to give β-branched esters with stereoselectivity of 96->98% (Scheme 2.16).[31]

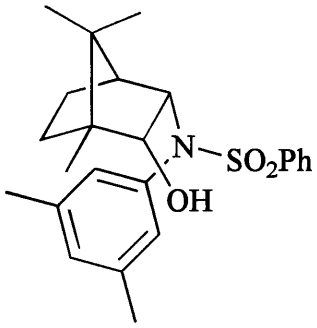


49 **51**

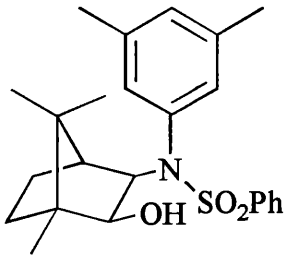
50 **52**

Scheme 2.16

The conjugate adducts **51** and **52** are crystalline and the diastereomers are separable by HPLC allowing the determination of the diastereoselectivity.

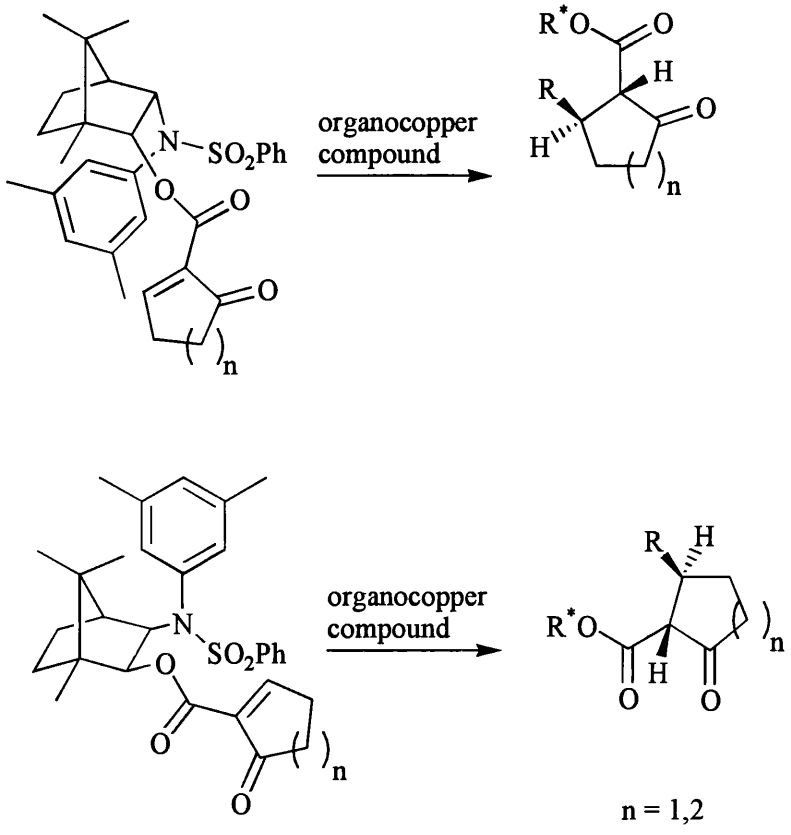


47



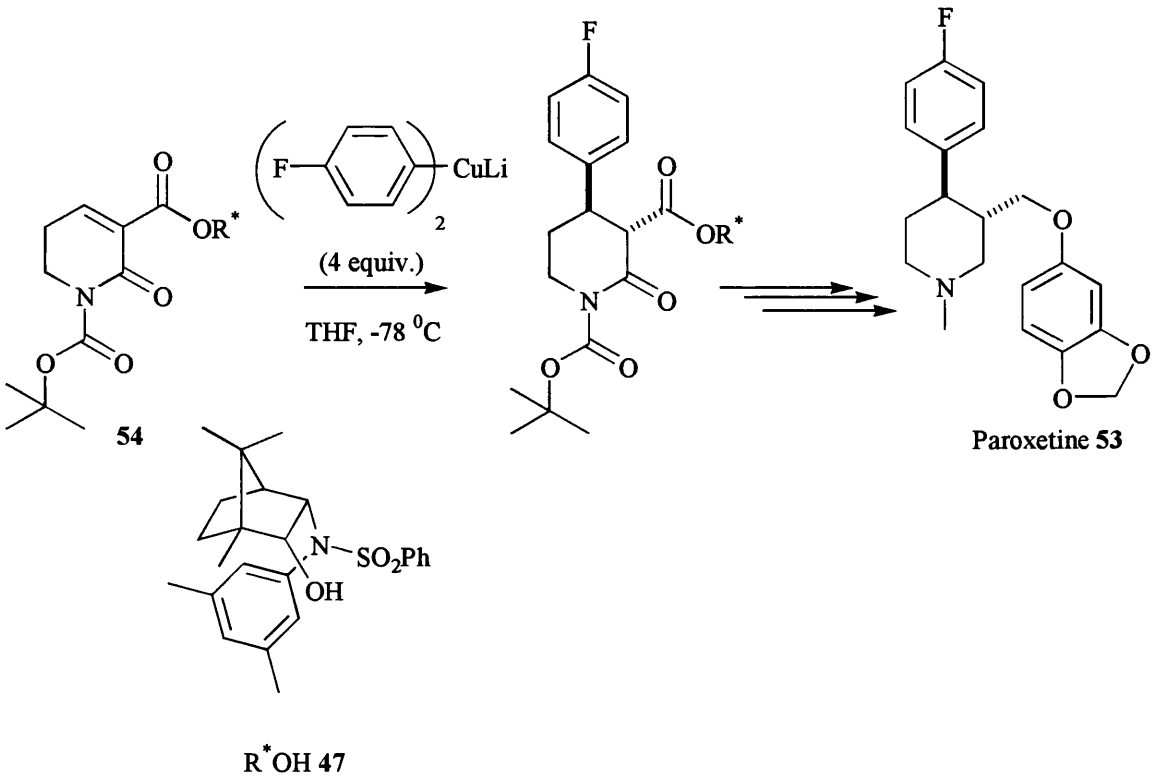
48

The chiral auxiliaries **47** and **48** have been shown to induce addition of organocuprates diastereoselectively to 2-oxo-cyclopentanecarboxylates and 2-oxo-cyclohexanecarboxylates to give enantiomerically pure 5-substituted 2-oxo-cyclopentanecarboxylates and the corresponding 6-substituted cyclohexanecarboxylates (Scheme 2.17). [32,33]



Scheme 2.17

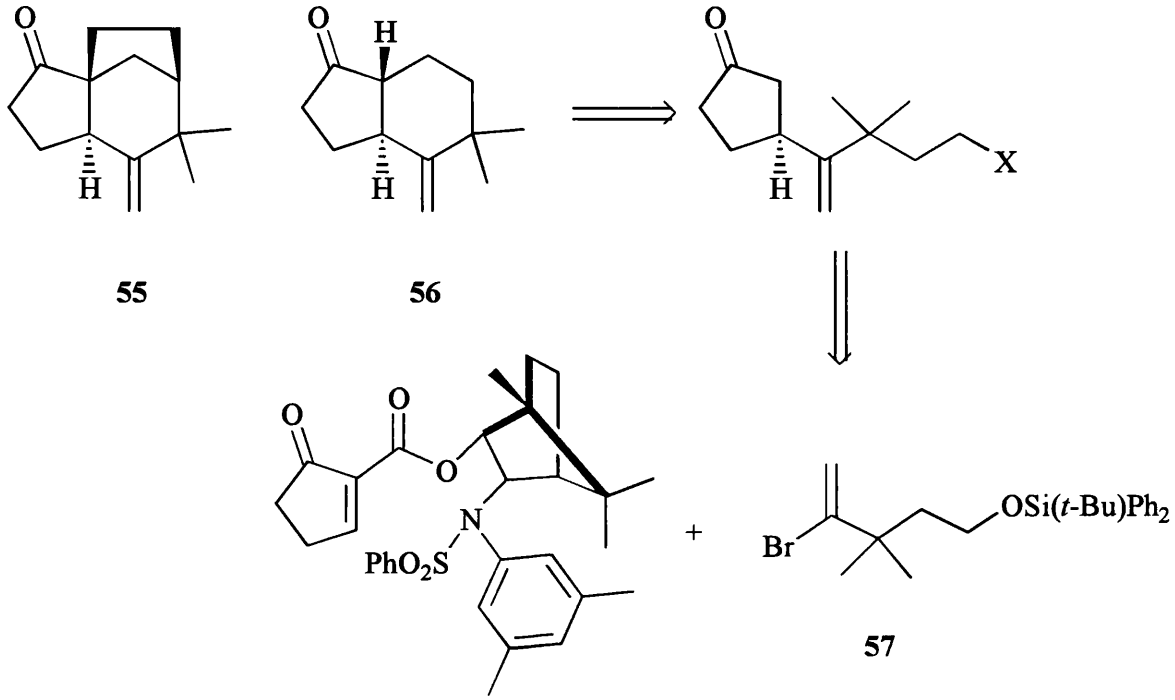
The camphor-derived chiral auxiliary **47** has been utilized in the formal synthesis of Paroxetine **53**. Paroxetine is a disubstituted piperidine used in the treatment of depression, obsessive compulsive disorder and panic disorder. The key step to a formal synthesis of paroxetine involved the conjugate addition of an organocopper reagent to a chiral unsaturated ester **54** with diastereoselectivity of >98% (Scheme 2.18).[34] The organocopper reagent adds to the less hindered face of the s-*trans* enoate double bond.



Scheme 2.18

Vetiver oil is used in the manufacture of expensive perfumery compositions and soap perfumes due to its strong woody aroma. In order to determine the structure/odour relationship of khusimone **55**, one of the main odour-donating compounds of vetiver oil, an analogue of it was synthesised. In an attempt to identify if the ethano bridge was essential for the odour component the ethano bridge was removed to produce a bicyclic system **56** (Scheme 2.19).[35] The key step in the synthesis of **56** involved a diastereoselective conjugate addition of an appropriate nucleophile **57** to a chiral olefinic keto ester **58** which incorporates the previously discussed camphor-derived concave alcohol. The presence of the geminal dimethyl group next to the exocyclic alkene bond decreased the reactivity of the conjugate addition. The use of the highly reactive diorganocuprates, known as

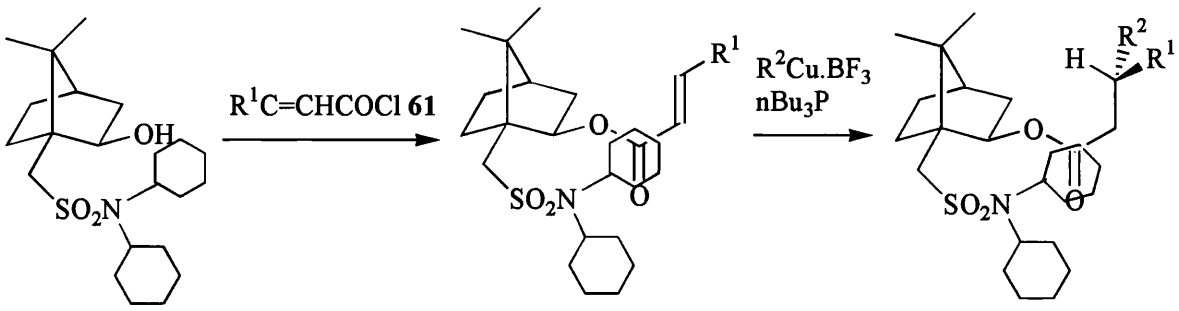
Gilman's reagents (R_2CuLi), proved unsuccessful. However using the method of Piers *et al.*[36] successful addition was observed to produce diastereomerically pure product. The organolithium reagent is produced by reaction of the halide with two equivalents of *t*-BuLi, followed by $MgBr_2 \cdot Et_2O$ and $CuBr \cdot Me_2S$, $BF_3 \cdot Et_2O$. Unlike the Gilman's reagent this method consumes only one equivalent of **57**. The diastereomeric excess was high with no diastereomeric impurities detected by ^1H and ^{13}C NMR spectrometry.



55 **56** **57** **58**

Scheme 2.19

The availability of both enantiomers of camphor-10-sulfonic acid allowed access to another camphor-based chiral auxiliary **59** synthesised by amidation and carbonyl reduction of the corresponding sulfonic acid.[37] This auxiliary has been used to provide excellent π-face differentiation for the conjugate addition of organocopper reagents to enoates **60** (Scheme 2.20).[38]

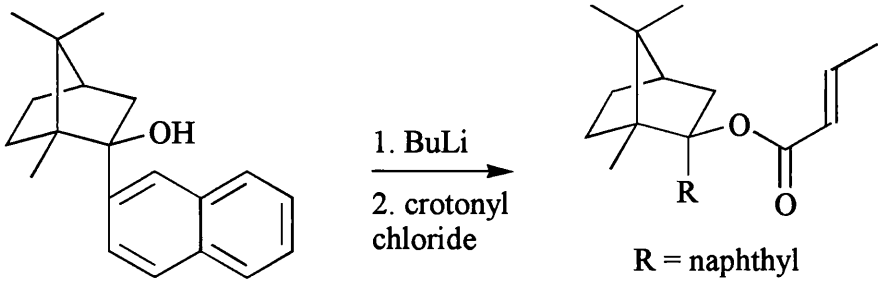


59 60

Scheme 2.20

The homochiral α,β-unsaturated system **60** was synthesised by acylating the auxiliary **59** with the corresponding acid chloride **61**. The conjugate addition of the organocopper reagent occurred with high levels of stereoselectivity (>94%) and this was accounted for by the steric bulk of the sulfonamide group blocking one face of the α,β-unsaturated system.

Another simple but useful chiral auxiliary **62** is generated from the reaction of 1-naphthylmagnesium bromide with camphor. This auxiliary has shown good levels of stereoselection (95%) for the conjugate addition of organocopper reagents to crotonate esters **63** (Scheme 2.21).[39] A number of different groups (R = H, Me, phenyl and benzyl) were investigated with the naphthyl substituent being the best at inducing stereoselectivity.

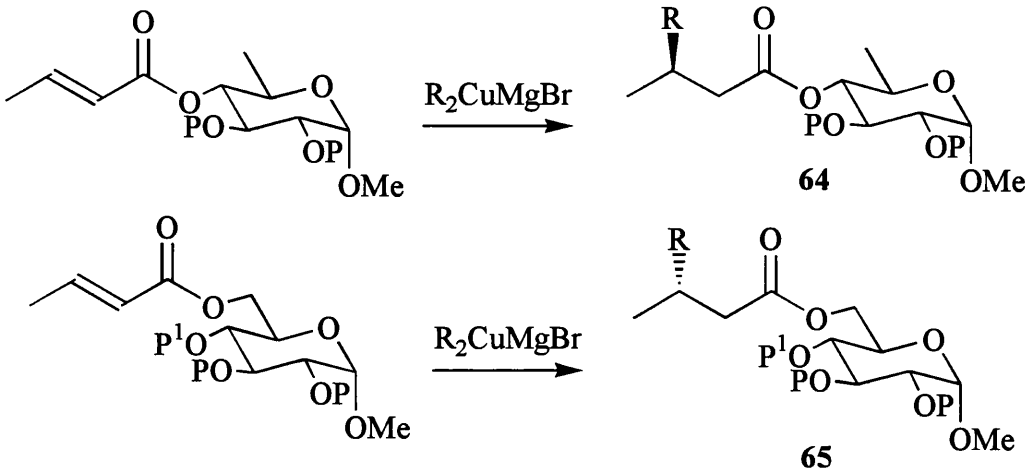


62 63

Scheme 2.21

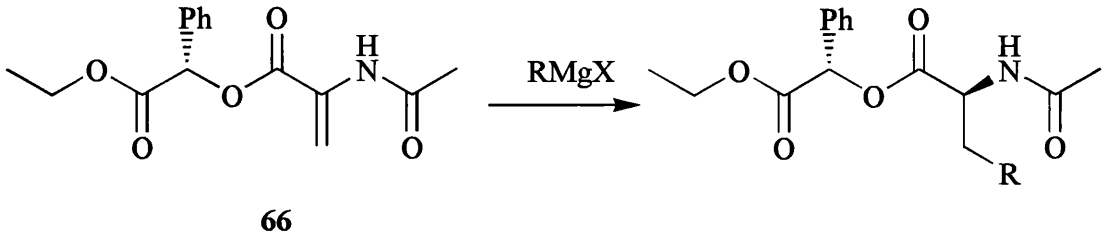
The use of carbohydrate based templates as chiral auxiliaries was reported by Totani *et al.*[40] The derivatives of methyl α-D-glucopyranoside act as chiral auxiliaries for the diastereoselective conjugate additions of organocopper reagents to α,β-unsaturated esters (Scheme 2.22). A noteworthy observation was that the configuration obtained for the 6-*O*-crotonyl derivative **65** was the opposite to that of the 4-*O*-crotonyl derivative **64**. It is

still unclear what leads to this stereochemical change but it is believed that the pivaloyloxy group at C-4 is essential, because when this is substituted for a benzyloxy group the diastereoselectivity is lowered considerably.



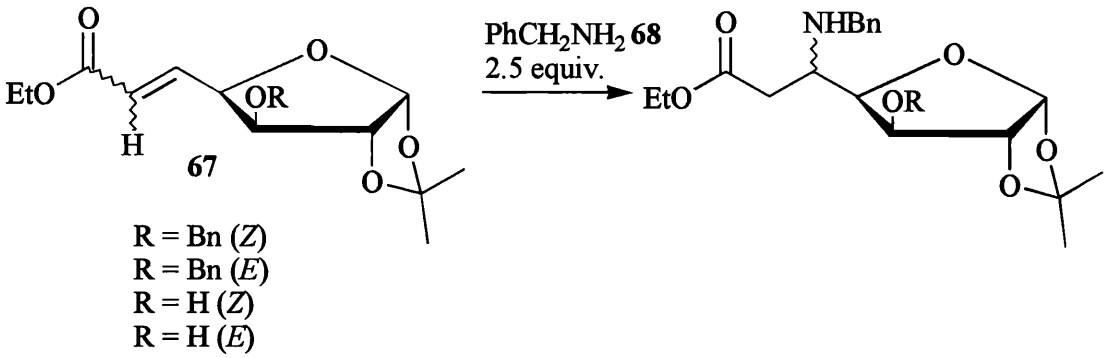
Scheme 2.22

The incorporation of ethyl(*R*)-mandelate as a chiral auxiliary has been utilised in the synthesis of α-amino acids.[41] The conjugate addition of Grignard reagents to the (*S*)-isomer **66** followed by selective protonation occurs with moderate selectivity of 70% de (Scheme 2.23).



Scheme 2.23

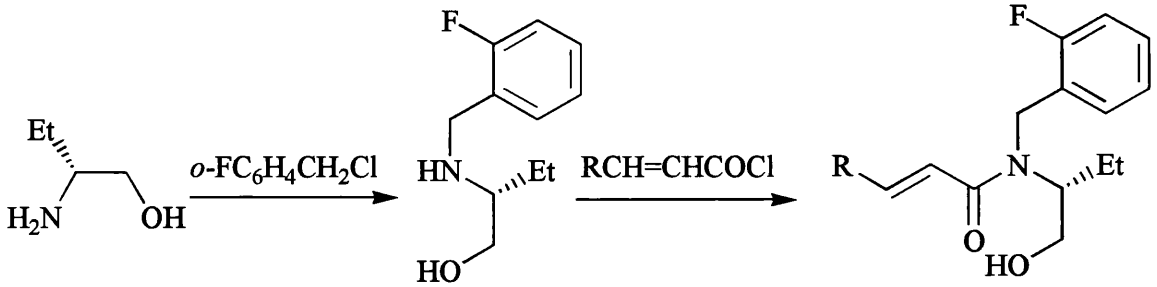
The synthesis of an α,β-unsaturated ester derived from D-glucose **67** has been the subject of a study showing that the diastereoselective conjugate addition of substituted amines **68** occurs with moderate stereoselectivity (40-52%) (Scheme 2.24).[42] However changing the Michael donor to the more nucleophilic lithium *N*-benzylamide resulted in the production of only one diastereomer under kinetically controlled conditions.



Scheme 2.24

2.3.3.2 α,β-Unsaturated amides

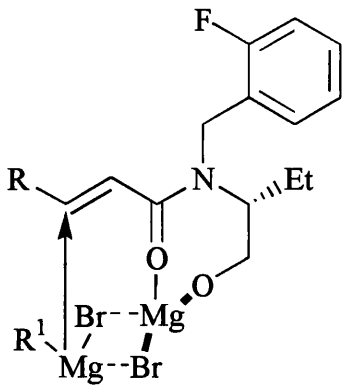
In an attempt to produce a chiral auxiliary that is relatively cheap, and also capable of inducing another new asymmetric centre with high levels of stereoselectivity, a chiral auxiliary derived from (2*R*)-aminobutan-1-ol **69** and 2-fluorobenzyl chloride was synthesised. The auxiliary **70** was attached to cinnamoyl or crotonoyl chloride to synthesise the corresponding amides **71** (Scheme 2.25). These systems underwent conjugate additions with various Grignard reagents to give adducts with high diastereomeric excesses of 92-97%.[43,44]



69 **70** **71**

Scheme 2.25

The mechanism of addition of the Grignard reagent is postulated to occur by a pseudocyclic structure produced by the binding of the magnesium to the amide oxygen and also to the alkoxy group. This allows another equivalent to add to the double bond (Figure 2.5). It was observed that when the primary hydroxy group was protected as a benzyl ether this led to a decrease in the diastereomeric excess.

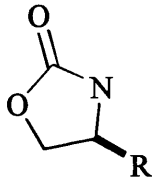


R = Ph or Me

Figure 2.5

The benefit of introducing the fluorobenzyl group into the chiral auxiliary is that it increases the stereoselectivity induced by the chiral auxiliary. There is also an added benefit in that it allows the proportion of the conjugate adducts to be determined by ^{19}F NMR spectrometry due to the presence of the fluorine atom on the aromatic ring.

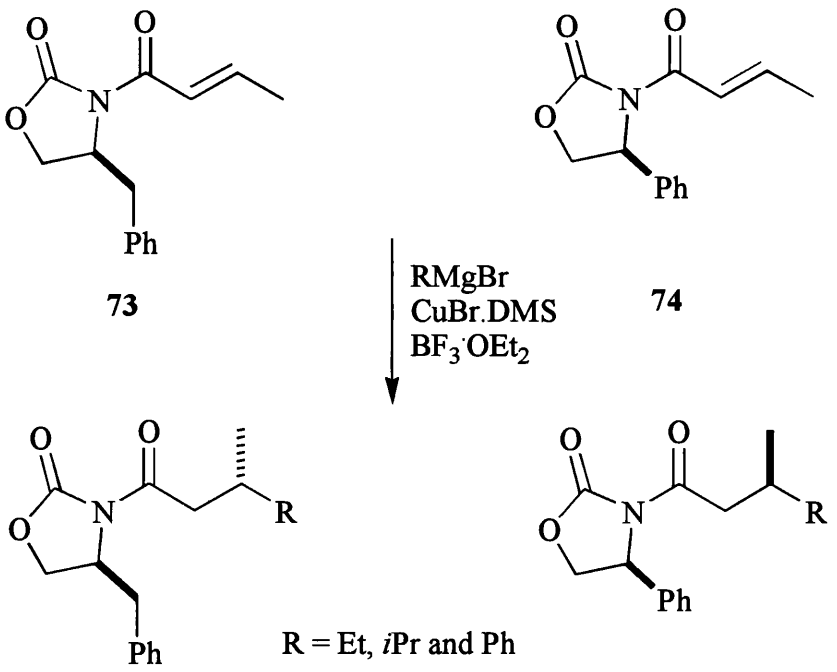
Optically pure oxazolidinones, known as "Evans auxiliaries", with the general structure **72** are commercially available. Because of their ease of removal and recovery they are of potential interest in asymmetric synthesis.[45]



72

R = Ph, Bn and ^{i}Pr

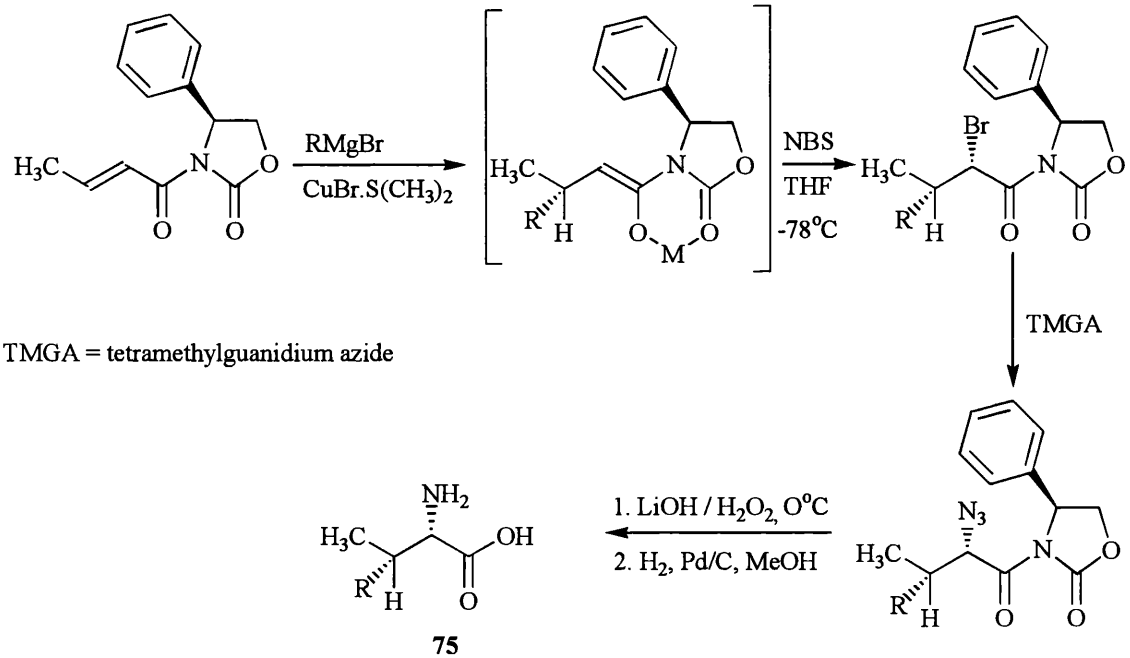
Oxazolidinones similar to **72** have been used to synthesise *N*-enoyloxazolidinones **73** and **74**.[46] These underwent conjugate additions of organocopper reagents to give opposite stereoselectivity for alkyl and phenyl cuprates (Scheme 2.26). The conjugate reactions were carried out by generating the cuprate using the Grignard reagent and copper(I) bromide dimethylsulfide together with boron trifluoride diethyl etherate as the Lewis acid. It is not fully understood why there is a divergence of stereoselectivity with these two *N*-enoyloxazolidinones; however it is postulated that it arises from the complexation of the Lewis acid to both carbonyl oxygens or just to the carbonyl oxygen of the crotonoyl moiety.



73 **74**

Scheme 2.26

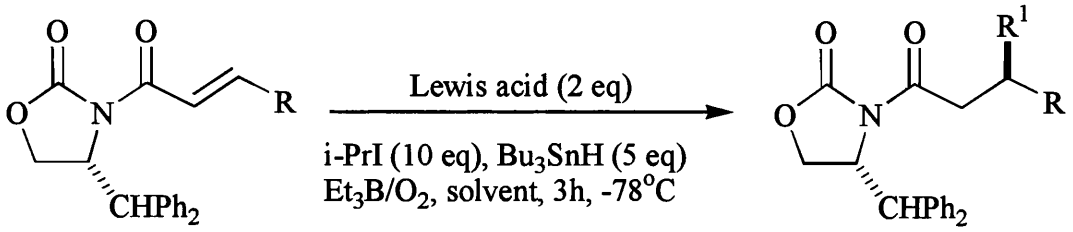
The levels of diastereoselectivity are moderate to high (53-97%). The diastereoselectivity increases as the steric bulk of the nucleophile increases (Ph > ^{i}Pr > Et). Nicholàs *et al.* reported the addition of aryl-organocopper reagents to oxazolidinones **73** and **74**. Oxazolidinones **74** were superior in terms of inducing stereoselectivity.[47] This has been applied to the asymmetric synthesis of precursors of unusual amino acids **75** to be used in the rational design of peptide ligands (Scheme 2.27).[48]



75

Scheme 2.27

Oxazolidinone auxiliaries have also been applied successfully to radical reactions. Conjugate addition of carbon radicals takes place with high diastereoselectivity to chiral α,β-unsaturated *N*-enoyloxazolidinones (Scheme 2.28).[49]



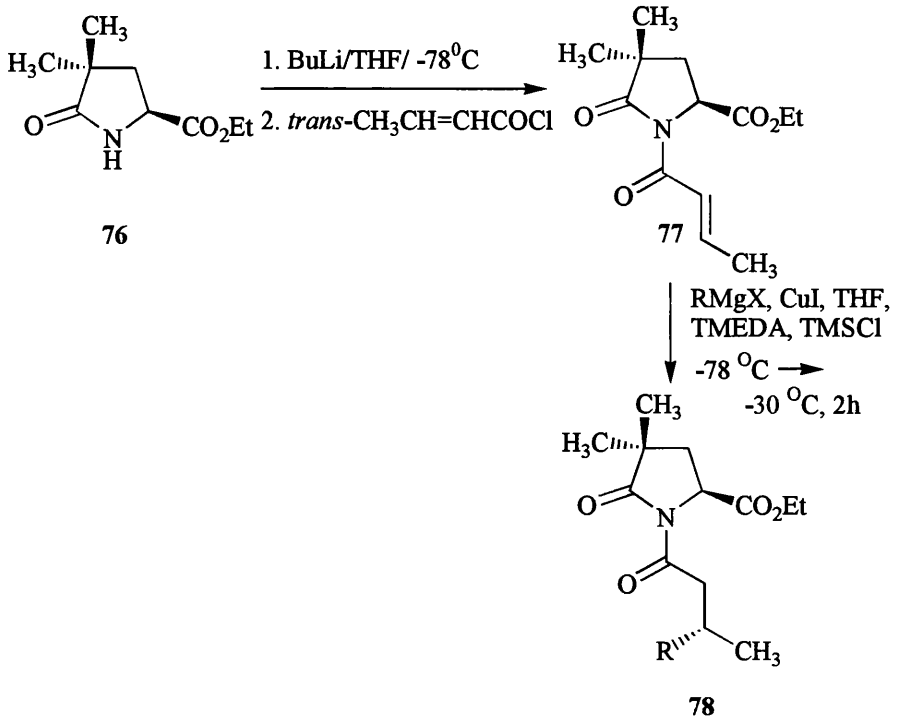
R = Me
R = Ph

R = Me, R[1] = i-Pr
R = Ph, R[1] = i-Pr
R = Me, R[1] = Et

Scheme 2.28

This methodology involves the use of a novel diphenylmethyl-substituted oxazolidinone auxiliary which is superior to previous oxazolidinones in terms of inducing stereoselectivity. A series of Lewis acids were screened and ytterbium triflate $Yb(OTf)_3$ was the best in terms of chemical yield and diastereoselectivity. It was shown to be important to have a chelating Lewis acid that could bind both substrate carbonyls thus fixing the orientation of the system. This then allows radical addition to take place from the opposite face to the bulky diphenylmethyl substituent on the oxazolidinone ring. One practical advantage to using $Yb(OTf)_3$ is that it does not require handling under inert conditions and reactions can be carried out without the need for predried solvents. Tributyl tin hydride was used as the radical chain carrier and triethylborane/oxygen as the radical initiator. A number of carbon radicals added successfully; however electrophilic radicals were not successful. The reaction temperature must be maintained at –78 °C for successful addition displaying diastereoselectivity ratios of 46:1.

In attempts to synthesise optically pure β-branched carboxylic acids a new "quat" chiral auxiliary, ethyl 4,4-dimethylpyroglutamate **76**, has been utilised (Scheme 2.29).[50]

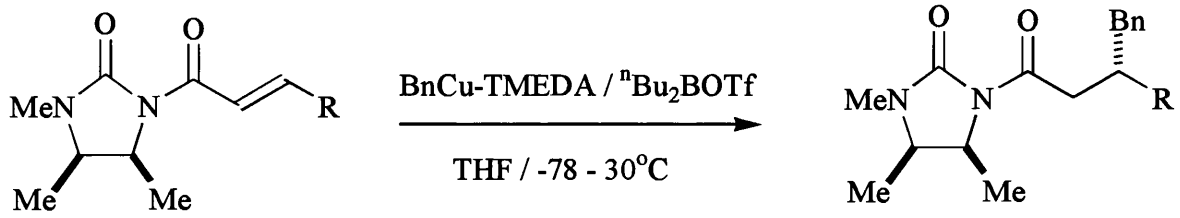


76 77 78

Scheme 2.29

The α,β-unsaturated system **77** was obtained by treating **76** with butyllithium followed by addition of crotonyl chloride. The conjugate addition was then carried out using the organocopper-Lewis acid reagent RCu-TMEDA-TMSCl. This produced excellent diastereomeric excesses (75->95%) and the corresponding enantiomerically enriched β-branched carboxylic acids could be synthesised by base hydrolysis of **78**.

Chiral auxiliaries have been developed from optically pure substituted imidazolidinones and have been employed in diastereoselective conjugate additions. They have been shown to be excellent auxiliaries for stereocontrol at the β-position of an α,β-unsaturated system using organocopper reagents (Scheme 2.30).[51]



R = Me and Ph

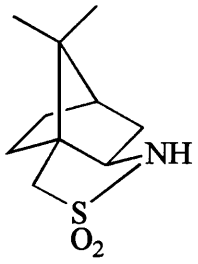
Scheme 2.30

In this example a new organocopper-Lewis acid system was applied to transfer the highly reactive benzyl ligand. Previous Lewis acids like BF_3 were unsuccessful in achieving this and the organocuprate-trimethylsilyl chloride reagent, BnCu-TMEDA-TMSCl, achieved

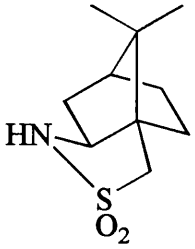
successful transfer but was compromised by excessive reaction times. The use of Bu_2BOTf as the Lewis acid dramatically reduced reaction times with no loss of stereoselectivity (>94%). It is presumed that boron is a much stronger chelating agent than TMSCl therefore lowering the LUMO energy of the substrate and favouring 1,4-addition.

2.3.3.3 *N*-Enoyl-sultams

By far the most well known class of *N*-enoyl-sultams are the examples that incorporate Oppolzer's camphorsultam (Figure 2.6). They were first prepared by Oppolzer and coworkers in 1984 for use as chiral auxiliaries in asymmetric Diels Alder reactions.[52] The main advantage of Oppolzer's sultams are that they are easy to prepare from both enantiomers of camphorsulfonic acid. The auxiliary can be easily removed and recycled. It has been found to induce stereoselectivity in numerous different reactions.[53]



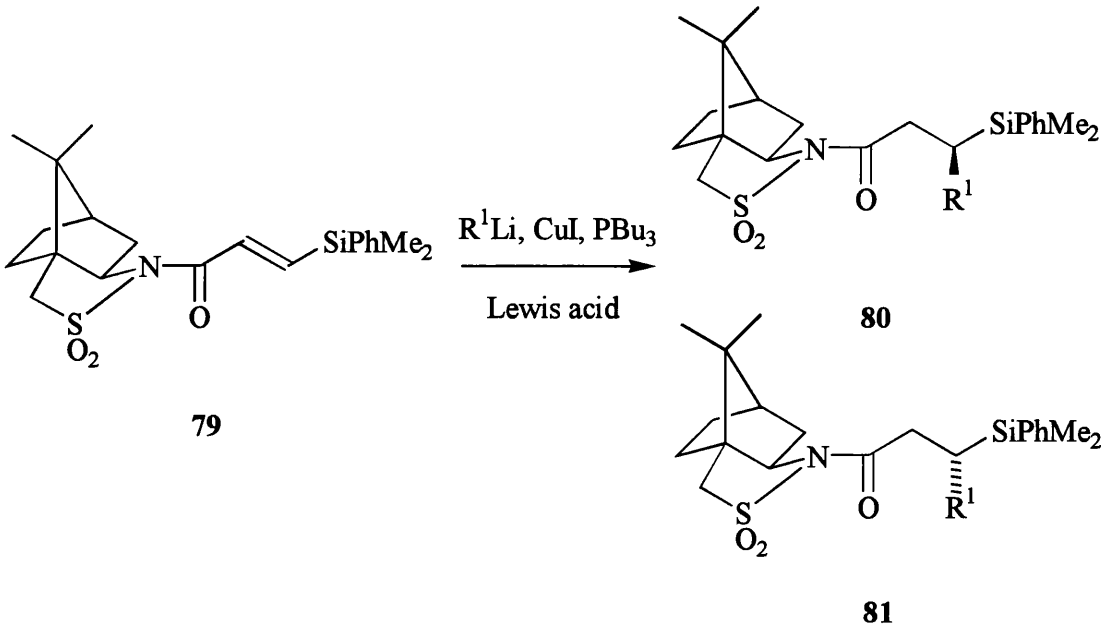
(-)-D-camphorsultam



(-)-L-camphorsultam

Figure 2.6

In particular conjugate additions of organometallic reagents have taken place diastereoselectively with substrates containing Oppolzer's sultam. Oppolzer and co-workers published a paper outlining the synthesis of enantiomerically pure β-silylcarboxyl derivatives by the asymmetric conjugate addition to *N*-enoyl-sultams.[54] Tributylphosphine-stabilized organocopper reagents R^2Cu added smoothly to *N*-[β-(silyl)enoyl]sultam **79** in the presence of a Lewis acid to give a mixture of diastereomers **80** and **81** (Scheme 2.31).



Scheme 2.31

It was reported that when $BF_3.OEt_2$ was used as the Lewis acid promoter as opposed to $EtAlCl_2$ the opposite stereoselectivity was observed. This was attributed to the different transition states formed when the Lewis acid coordinates to the α,β-unsaturated system (Figure 2.7).

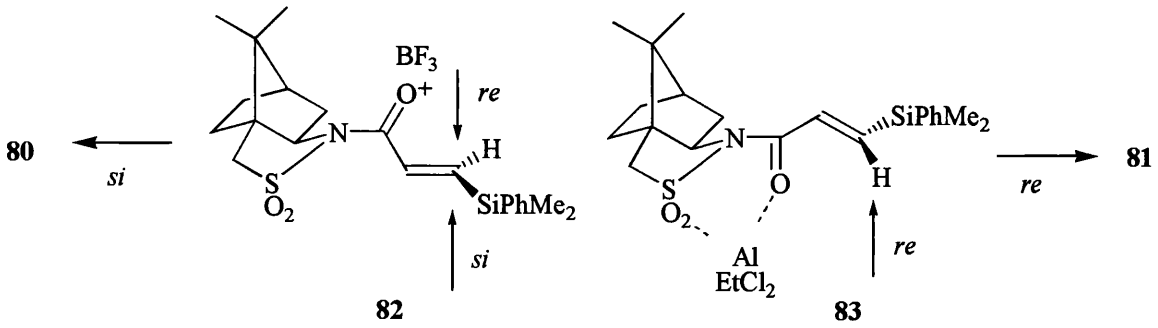
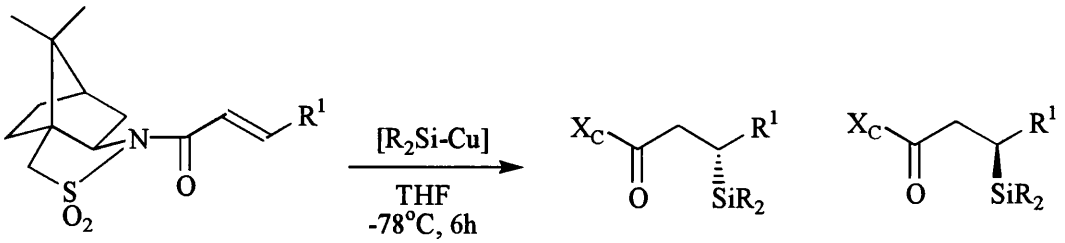


Figure 2.7

The $BF_3.OEt_2$ forms a monocoordinated transition state **82** forcing the SO_2/C=O groups *anti* whereas the $EtAlCl_2$ coordinates to the SO_2 and C=O groups producing a *cis*-arrangement **83** forcing attack of the organocopper reagents from the *re*-face. Using $EtAlCl_2$ as the Lewis acid together with various alkenyl- and alkylcopper reagents the conjugate adducts produced displayed stereoselectivity favouring the C(β)-*re*-face attack (86-96%).

The conjugate addition of silylcuprates to Oppolzer *N*-enoylsultams demonstrated that the nature of the silylcuprate affects the stereoselectivity of the reaction (Scheme 2.32).[55] The benefit of the dimethylphenylsilyl substituent is two fold in that it can be removed after the stereochemical reaction has taken place or converted into a hydroxyl group with retention of configuration. This was the first report that focused on the chemical nature of the silylcuprate used [e.g. monocuprate R_2SiCu, lower order cuprate $(R_2Si)_2CuLi$, or higher order cuprate $(R_2Si)_2Cu(CN)Li_2$] (Scheme 2.32).



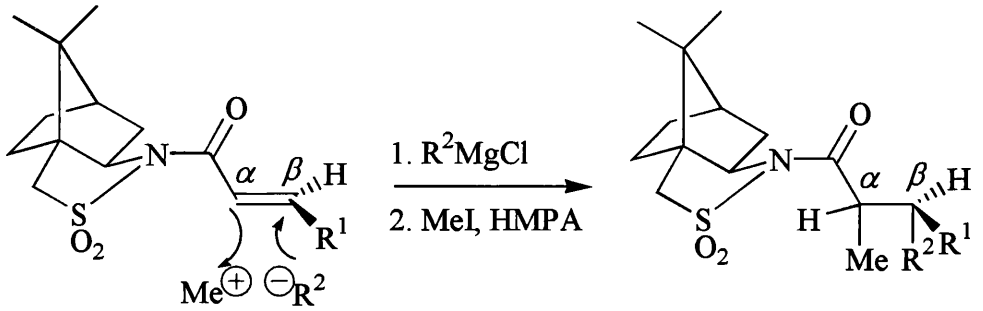
X_C: chiral auxiliary
R^1 = Me, Ph, 4-MePh, 4-MeOPh, 4-ClPh and 2-Furyl

[R_2Si-Cu] :
R_2SiCu : R_2SiLi, CuI, PBu_3 (1:1:1)
$(R_2Si)_2Cu$: R_2SiLi, CuI, PBu_3 (2:1:1)
$(R_2Si)_2Cu(CN)Li_2$: R_2SiLi, CuCN (2:1)

Scheme 2.32

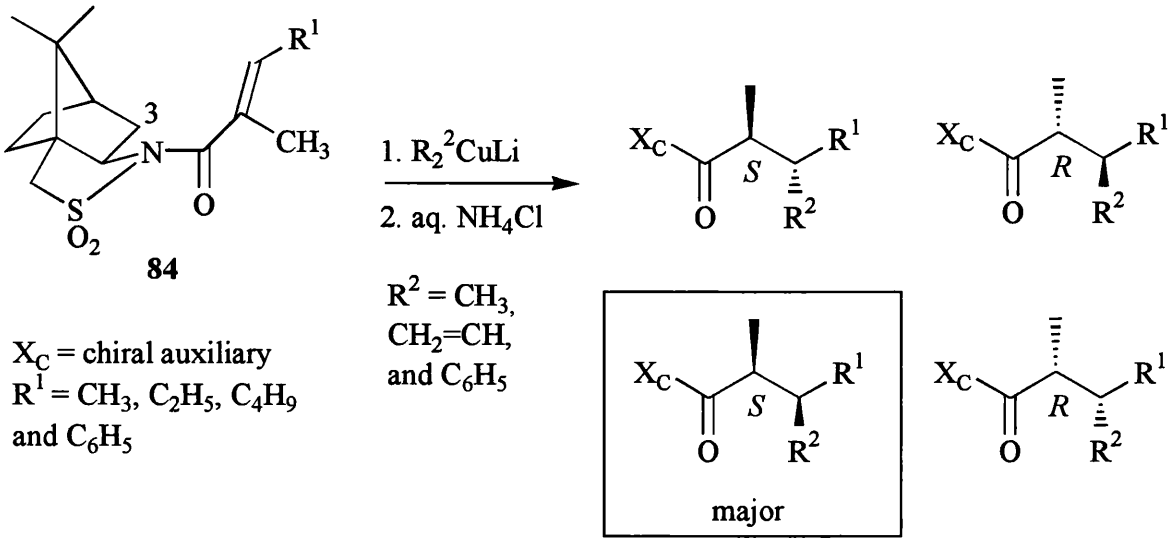
Cuprates generally showed high reaction yields; however the stereoselectivity increased when higher order cuprates were used. The stereochemical outcome can be explained as previously discussed in which the SO_2/C=O *syn* conformation together with *s-cis* C=O/C=C conformation invokes attack of the silylcuprate from the *re*-face.[54]

The conjugate addition of Grignard reagents to *N*-enoylsultams takes place with moderate to high levels of stereoselectivity (72-90%). The β-substituted adducts can then undergo enolate trapping with MeI to produce enantiomerically pure C(α,β)-substituted carbonyl compounds (Scheme 2.33).[56]



Scheme 2.33

N-Enoyl-sultams were prepared from (*E*)-Cα, Cβ-disubstituted enoyl chlorides **84** with Gilman reagents and on protonation generated two new stereogenic centres at Cα and Cβ (Scheme 2.34).[57]



84

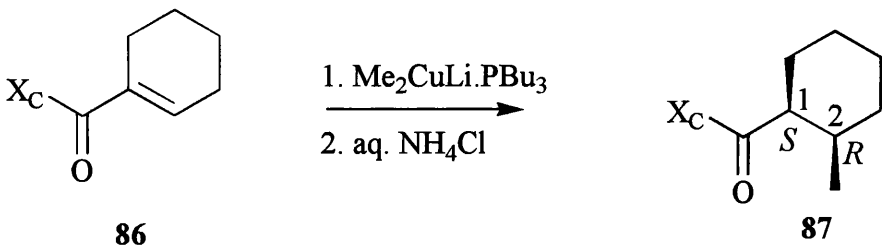
X_C = chiral auxiliary
R^1 = CH_3, C_2H_5, C_4H_9 and C_6H_5

R^2 = CH_3, CH_2=CH, and C_6H_5

85

Scheme 2.34

This tandem reaction does not require the use of a Lewis acid as for previously mentioned organocopper conjugate additions. In all cases the isomer **85** predominated in good excess. The stereochemical control stems from the carbonyl group being *s-trans* to the C=C bond avoiding the steric repulsion of the Cα methyl substituent with the camphor 3-H_2 group. Attack of the Gilman reagent takes place from the *re*-face generating an *E*-enolate. Protonation of the enolate therefore occurs from the *re*-face forcing the methyl group up. An example of this stereoselection was observed when 1-cyclohexenoyl-sultam **86** was reacted with the methyl Gilman reagent and C*α*-protonation produced the (1*S*, 2*R*)–isomer **87** as the sole product (Scheme 2.35).



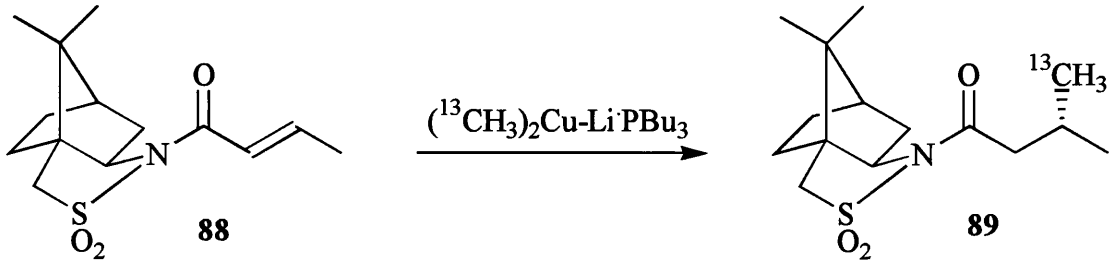
86

X_C = chiral auxiliary

87

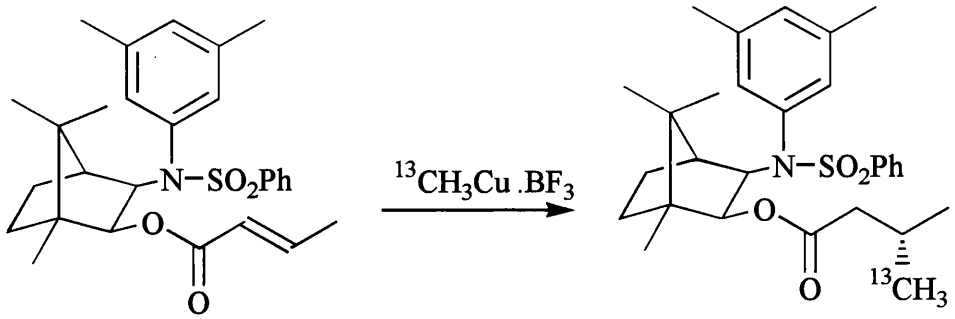
Scheme 2.35

In an attempt to synthesise carbon-13 labelled L-leucine a labelled Gilman reagent was added to a crotonyl unit attached to Oppolzer's auxiliary **88** and a de of 82% was achieved (Scheme 2.36).[58]



Scheme 2.36

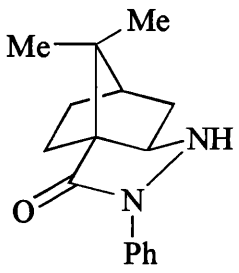
It was very important that the synthesis of **89** was accomplished with maximum diastereoselectivity and minimum isotopic label wastage. The labelled Gilman reagent was prepared from [^{13}C]iodomethane, lithium metal and copper(I) iodide-tri-*n*-butylphosphine complex. The moderate stereoselectivity produced compromised this approach and another method was sought which involved a different camphor-based auxiliary producing the desired carbon-13 labelled adduct in 98% diastereomeric excess (Scheme 2.37).



Scheme 2.37

This approach utilises the Yamamoto reagent, $^{13}CH_3Cu{\cdot}BF_3$, in an excess of 7 equivalents. The commercial availability of the chiral auxiliary in both enantiomeric forms allows access to both diastereomers in high diastereomeric purity and isotope yield.

The conjugate addition of thiols to α,β-unsaturated amides derived from a novel camphor-based chiral auxiliary pyrazolidinone **90** has produced diastereoselectivities of 90% in the presence of Lewis acids.[59] The synthesis of both diastereomers can be achieved by changing the Lewis acid. The use of $SnCl_4$ as the Lewis acid produced the opposite diastereomer to that produced when $TiCl_4$ was used.



90

The role that the Lewis acid plays in changing the configuration can be accounted for by the steric bulk of the Lewis acid together with the chelating ability to the carbonyl group (Figure 2.8). When $SnCl_4$ is used, the metal atom monocoordinates to the carbonyl oxygen of the amide forming the complex **A** resulting in attack from the Cβ *si*-face. However $TiCl_4$ is a bulkier Lewis acid due to the shorter bond length of Ti-O compared with the Sn-O bond. As shown in the complex **B** the CO-C(α) bond twists to prevent steric repulsion between the metal and Cβ hydrogen resulting in addition of the thiol from the Cβ *re*-face.

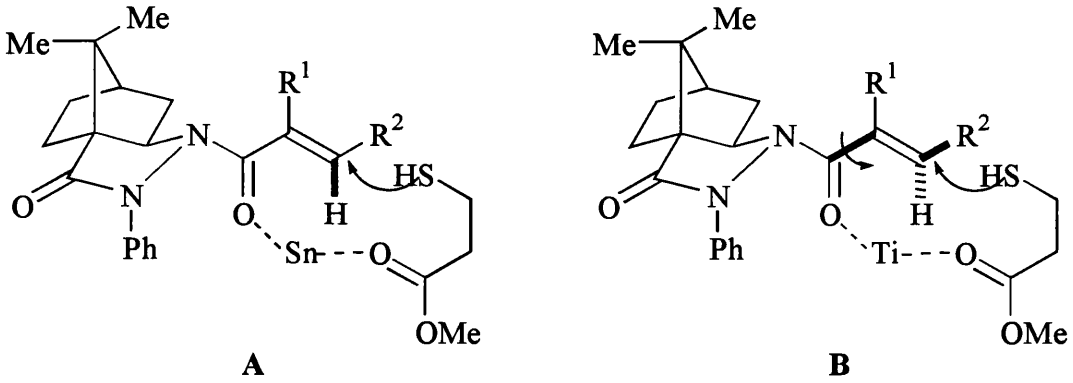


Figure 2.8

In the field of organic synthesis the development of stereoselective conjugate additions to prepare optically active chiral compounds has been achieved using various methodologies. The use of chiral auxiliaries still remains the most popular approach and the development of highly stereoselective conjugate additions using chiral auxiliaries is still an extensively researched area. Our group has made progress in the development of a homochiral fumaramide derived from Oppolzer's sultam. Conjugate addition of Grignard reagents to this fumaramide occurred with moderate to high levels of diastereoselectivity.

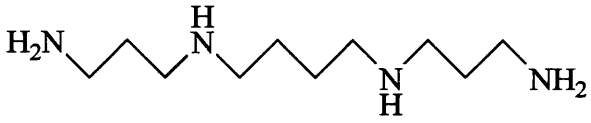
This is discussed in Chapter 4. The extension of this work to produce useful products namely optically active 2-substituted succinic acids and 2-substituted butane-1,4-

diols is discussed in Chapter 5. For comparison the addition of Grignard reagents to fumarates with one chiral auxiliary is discussed in Chapter 6

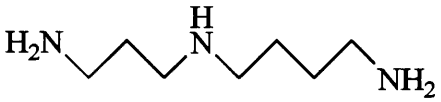
3. Polyamines and Diamine Oxidase

3.1 Polyamines

A Dutch microscopist Leeuwenhoek described crystals of polyamines over three hundred years ago. It took two centuries for these crystals to be identified as an organic base known as spermine **91**. Polyamines are ubiquitous in nature. Two polyamines, spermine **91** and spermidine **92**, are found in all cells. Putrescine **93**, and the less common diamine cadaverine **94**, also contribute to the natural polyamines found in plants and animals.



91



92

93

94

Polyamines are basic molecules which are positively charged at physiological pH. The physiological roles that these natural polyamines play are both numerous and widespread. One physiological role that highlights their importance is their involvement in cell growth and division.[60]

Putrescine has been identified in the biosynthesis of 5-membered rings containing nitrogen in many alkaloids including the pyrrolidine ring in nicotine. Polyamines have the ability to bind ionically to nucleic acids. This means that at physiological pH the protonated forms of these polyamines bind with the phosphate anions of the nucleic acids. This creates a stabilising effect on the DNA and RNA, and it also speeds up steps of the transcription and translation sequence. The overall effect of this is to improve the efficiency of the manufacture of proteins.[61]

Polyamines can also be found as conjugates. These may take the form of an amino acid as in putreamine or a peptide as in glutathionylspermidine. They have also been found forming part of an antibiotic as in bleomycin.[62]

3.1.1. Polyamine Biosynthesis

There are several biosynthetic routes to polyamines. Some of these routes are shown in Figure 3.1 (modified from Tiburcio *et al.*).[62]

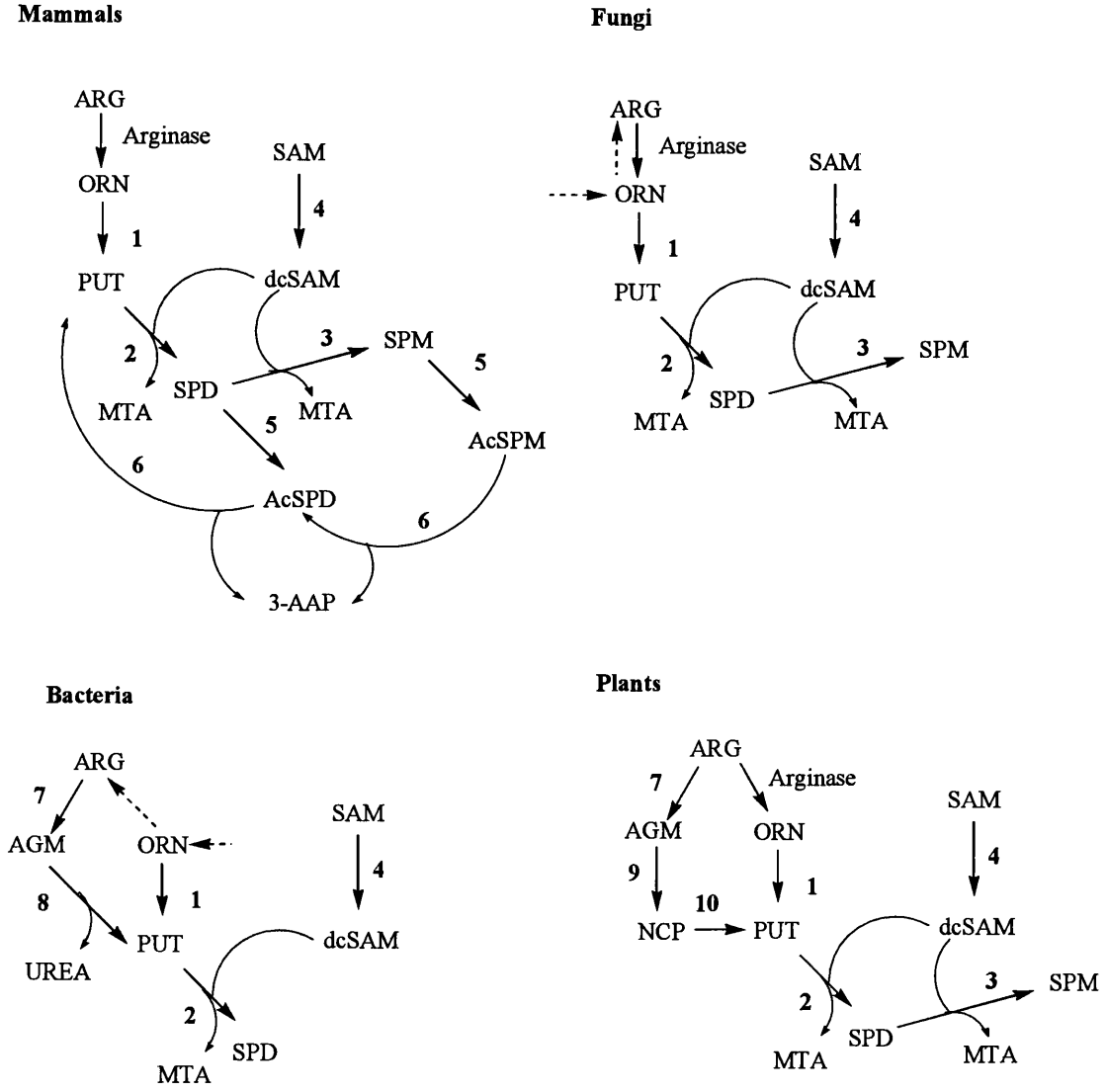


Figure 3.1 *Schematic pathway for the biosynthesis of polyamines in nature. Dotted arrows represent biosynthesis of ornithine and arginine. Abbreviations: AGM agmatine; ARG arginine; 3-AAP 3-acetamidopropanal; AcSPD acetylspermidine; AcSPM acetylspermidine; dcSAM decarboxylated S-adenosylmethionine; MTA 5'-methylthioadenosine; ORN ornithine; PUT putrescine; SAM S-adenosylmethionine; SPD*

spermidine; SPM spermine; ***1*** *ornithine decarboxylase;* ***2*** *spermidine synthase;* ***3*** *spermidine synthase;* ***4*** *S-adenosylmethionine decarboxylase;* ***5*** *acetyl coenzyme A;* ***6*** *polyamine oxidase;* ***7*** *arginine decarboxylase;* ***8*** *agmatine ureahydrolase;* ***9*** *agmatine iminohydrolase;* ***10*** N-*carbamoylputrescine amidohydrolase.*

These routes apply to bacteria, fungi, plants and animals. Some observations can be made about these pathways. It was shown that fungi are able to synthesise putrescine by only one route. Plants and bacteria possess two pathways to putrescine. One of these pathways involves ornithine and the other uses arginine. This dual pathway in plants provides a means for control of harmful fungal infections when plants are affected with fungi. The enzyme ornithine decarboxylase (ODC; EC 4.1.1.17) decarboxylates ornithine forming putrescine. This is the first and usually the rate-limiting step in the pathway.[63] This initiates the enzyme spermidine synthase to form spermidine **92** followed by the synthesis of spermine **91**. Catabolism degrades these polyamines by a process of *N*-acetylation followed by oxidative cleavage which creates the cycle converting spermine into spermidine and spermidine into putrescine.

Antifungal compounds which inhibit ODC can prevent fungi from synthesising polyamines, thus affecting cell growth and ultimately causing cell death. Plants are unharmed as they can use the arginine pathway to synthesise polyamines.

The other main metabolic pathway for polyamines is terminal polyamine catabolism which is catalysed by Cu^{2+} dependent amine oxidases. The diamine can be converted into an aminoaldehyde by the oxidative deamination of one primary amino group. The aminoaldehyde is then oxidised to an amino acid.

In summary bacteria and plants both have two pathways to polyamines. This is paramount in the synthesis of antifungal compounds where inhibition of the enzyme ornithine decarboxylase should lead to the eradication of the fungi leaving the plants unharmed.

3.1.2. Polyamine Degradation

The breakdown of natural diamines via a catabolic pathway involves the use of amine oxidase enzymes. This catabolic pathway is shown in Figure 3.2.[64]

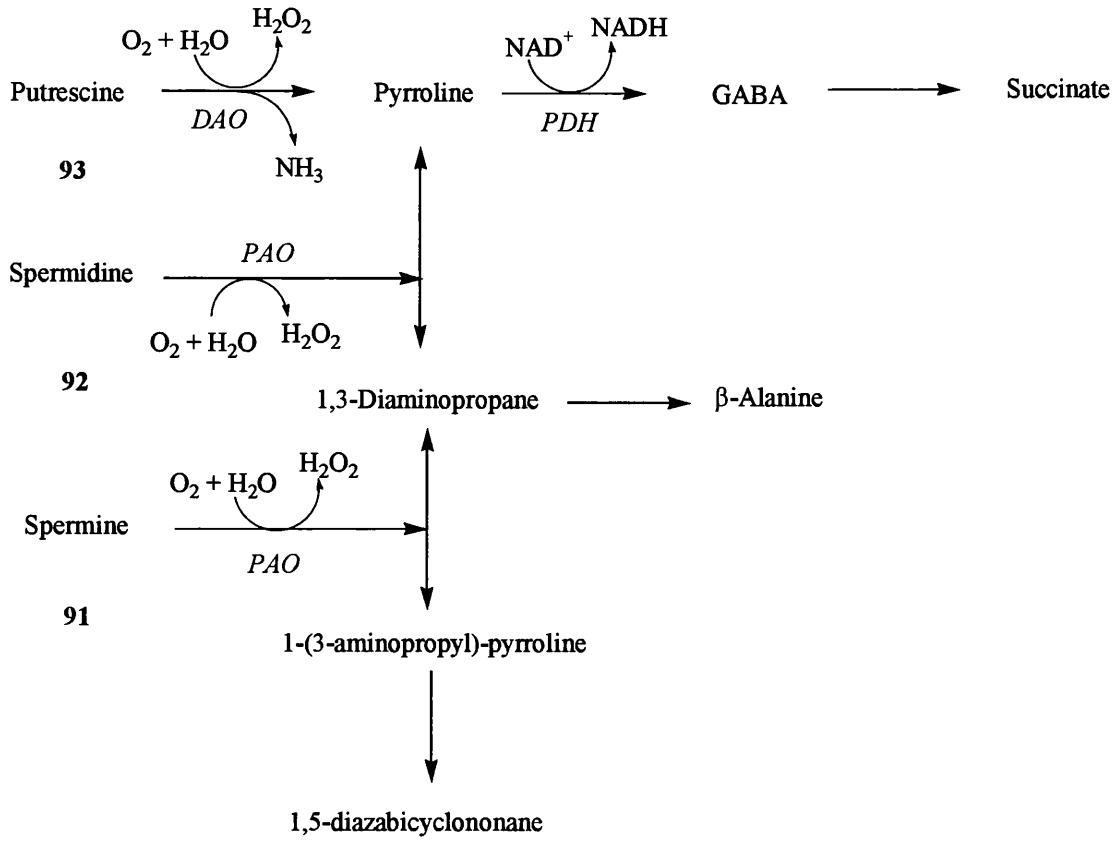


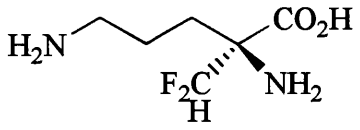
Figure 3.2

Abbreviations: DAO diamine oxidase; GABA γ-aminobutyric acid; PAO polyamine oxidase; PDH pyrroline dehydrogenase

In this scheme the diamine oxidase catalysed oxidation of putrescine produces pyrroline, hydrogen peroxide and ammonia, whereas polyamine oxidase produces pyrroline and 1,5-diazabicyclononane from spermidine and spermine, respectively, together with diaminopropane and hydrogen peroxide. Diaminopropane can then be converted into β-alanine, whereas pyrroline can be further catabolised to γ-aminobutyric acid in a reaction catalysed by pyrroline dehydrogenase. The γ-aminobutyric acid is then transaminated and oxidised to succinic acid, which is then used in the Krebs cycle.

3.1.3. Inhibition of Polyamine Synthesis

Inhibitors of polyamine biosynthesis were developed in the 1970s. These inhibitors were used to identify what happens if the concentrations of polyamines are reduced in a system. One of the inhibitors produced was α-difluoromethylornithine (DFMO) **95**.

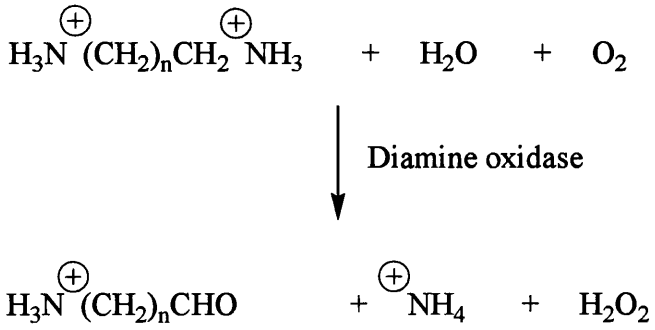


95

This inhibitor was found to bind specifically and irreversibly to ODC thereby inhibiting its action. This inhibitor permanently inactivates the enzyme; therefore DFMO is known as a suicide inhibitor. It was shown that this inhibition of ODC reduced the formation of polyamines therefore inhibiting cell growth. This property was seen to be beneficial in that DFMO is effective against tumours *in vitro* but this effect has not been seen *in vivo*.[65]

3.2 Diamine Oxidase

Diamine oxidases (DAO, EC 1.4.3.6) belong to a very large class of enzymes called quinoproteins. These proteins have a quinone co-factor and contain two identical subunits. Diamine oxidases catalyse the oxidative deamination of a range of primary diamines to their corresponding aminoaldehydes with the release of ammonium ion along with hydrogen peroxide (Scheme 3.1).

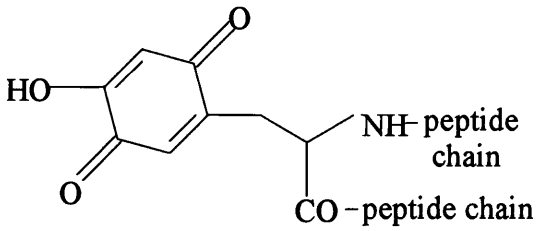


Scheme 3.1

Diamine oxidases are rather unspecific in that they catalyse the oxidation of some monoamines as well as diamines. Diamine oxidase can be found in a wide variety of biological tissues. There are two sources which are convenient for experimental use.

Kidney diamine oxidase is a commercially available enzyme and pea seedling diamine oxidase is readily extracted from 10 day old pea seedlings.[66]

Diamine oxidases are copper-containing proteins. They contain topaquinone and are referred to as topaquinoproteins **96**.



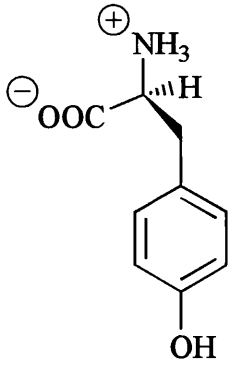
96

If copper was removed by dialysis by chelating agents deactivation of the enzyme ensued. This was shown experimentally with diamine oxidase.[67] The requirement of copper was confirmed as the activity was restored when copper was added back to the enzyme.

An organic cofactor was first identified in DAO over 50 years ago. The identity of this cofactor remained a mystery for many years. Studies showed that reagents capable of forming carbonyl derivatives were able to inhibit diamine oxidases. This suggested that the cofactor contained a carbonyl group.[68] It was first thought that the cofactor was pyridoxal phosphate. It was then reported that the cofactor is pyrroloquinoline quinone.[69] This idea has now been dismissed and the cofactor has been shown to be topaquinone.

3.2.1. Biosynthesis of Topaquinone

It was not until the amine oxidase gene from the yeast *Hansenula polymorpha* had been cloned and sequenced that it was possible to identify the precursor to topaquinone as L-tyrosine **97.**[70] This was deduced by the comparison of the DNA-derived sequence with the amino acid sequence. In other words the topaquinone co-factor is encoded by a tyrosine codon.

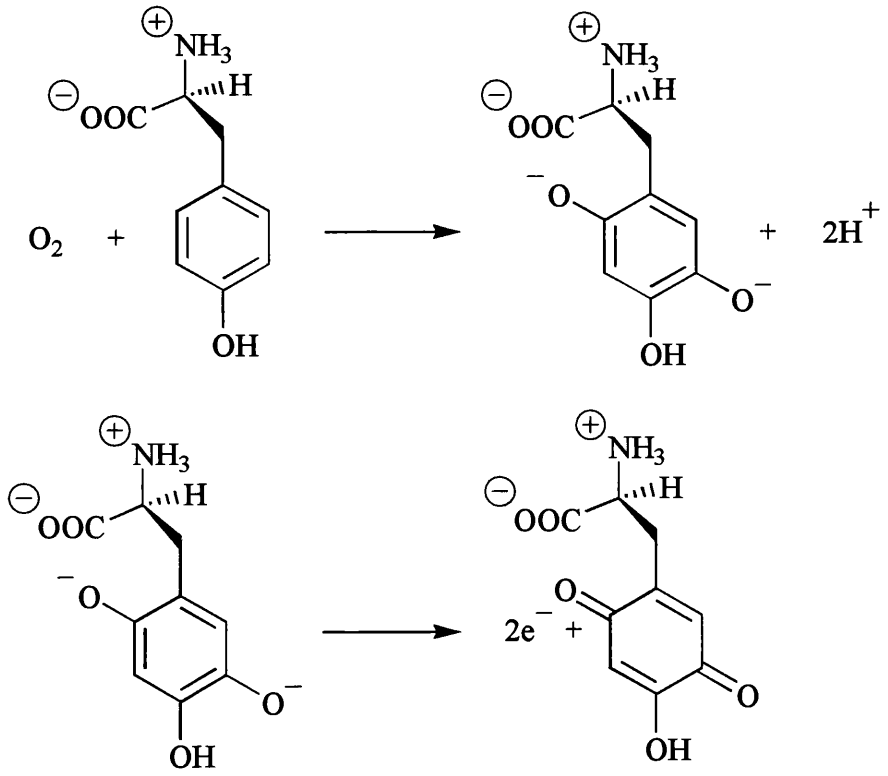


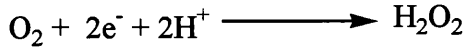
97

A number of possible pathways from tyrosine to topaquinone were postulated:[71]

- Post-translational modification of tyrosine by another enzyme, tyrosinase or tyrosine hydroxylase, or even by a yet undiscovered enzyme;
- Post-translational modification of tyrosine *in situ* by the copper.

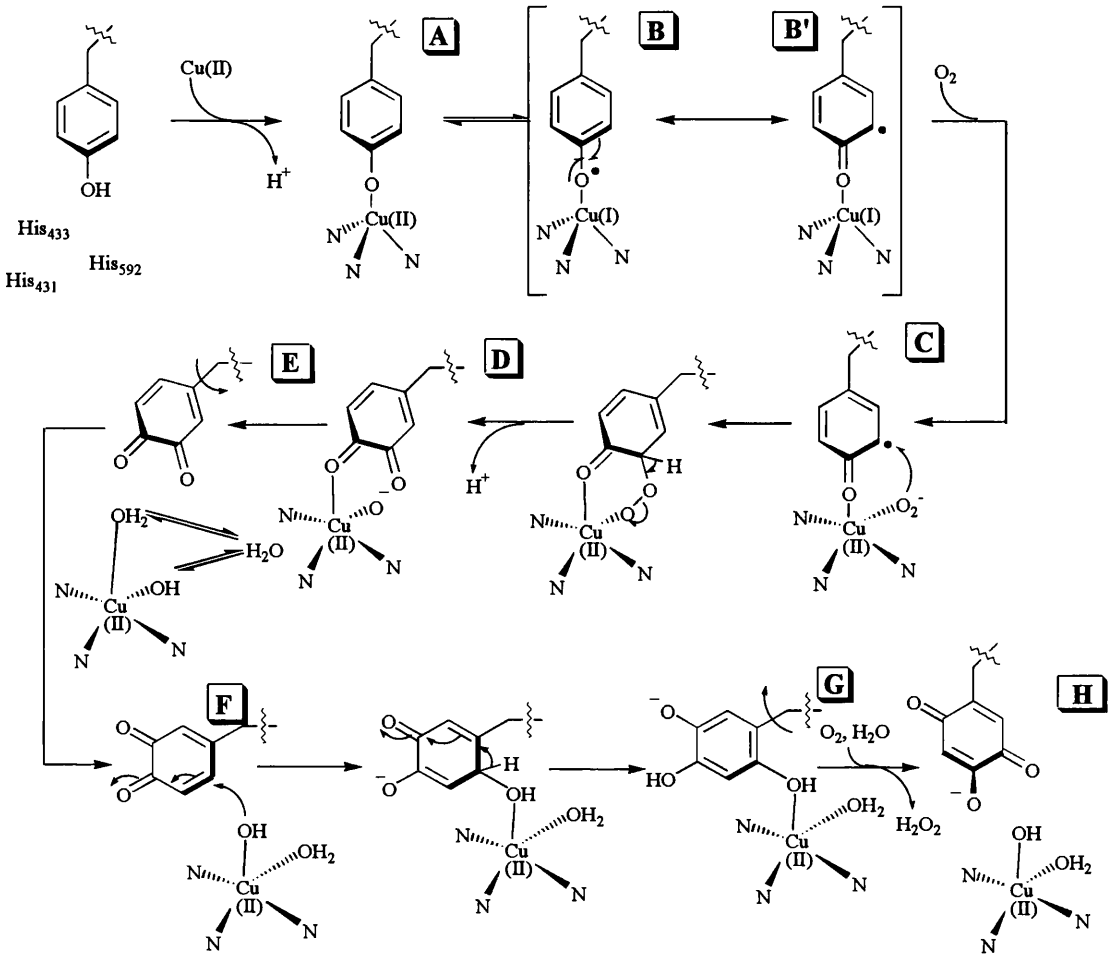
The mechanism for the oxidation of tyrosine to topaquinone is a six electron oxidation mechanism shown in Scheme 3.2.[72]





Scheme 3.2

From results of kinetic and spectroscopic studies a mechanism has been suggested which still requires structural evidence. However it does provide a rational scheme for the biosynthesis of topaquinone from tyrosine. This mechanism is shown in Scheme 3.3.[72]



Scheme 3.3

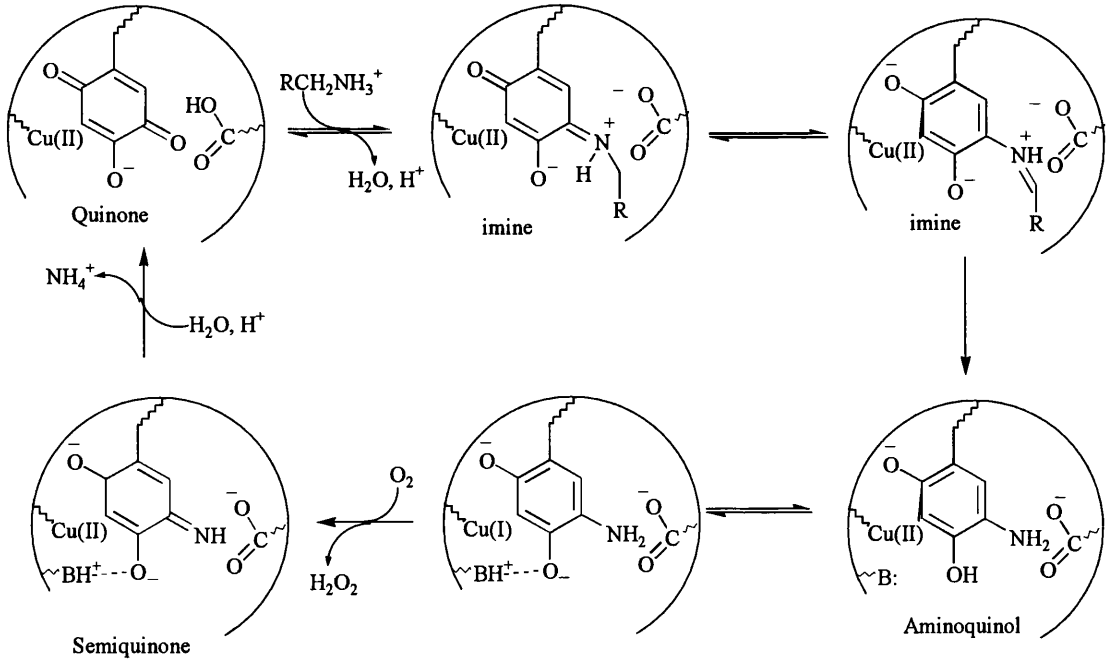
In the first step of Scheme 3.3 the Cu^{2+} binds to form a Cu(II) complex as shown by **A**. This complex is then in equilibrium with the Cu(I) radical **B**. The unpaired electron on the oxygen seen in **B** is delocalised over the aromatic ring with a resonance form **B`**, activating the ring carbons. The Cu(I) complex then reacts with dioxygen to produce an activated oxygen complex containing an oxygen superoxide bond shown in **C**. This complex then attacks the tyrosyl radical to form a dopaquinone bonded to a Cu(II) oxide/hydroxide/aqua complex **D**. This complex is in rapid exchange with solvent water thereby allowing solvent oxygen to be incorporated into topaquinone as shown by the transition of **E** to **F**. Rotation of the dopaquinone ring brings the C-2 carbon into close proximity to the water hydroxo

ligand. Nucleophilic attack results from the Cu(II)-OH^- on the dopaquinone producing **G**. Finally in the presence of dioxygen, **G** is oxidized to topaquinone and the Cu(II) atom picks up a water molecule.

At present it is believed that the synthesis of topaquinone is a self-catalytic mechanism and does not require the presence of any other enzyme. Work is presently being carried out to elucidate the mechanism fully with structural evidence.

3.2.2. Reaction Mechanism of Copper Amine Oxidases

There have been a number of methods used to try to determine the mechanisms of amine oxidases *in vivo*. These have ranged from X-ray structures and Raman spectroscopy through to site directed mutagenesis of amine oxidases. The cumulative results from various methods have been combined to give a generalised catalytic cycle as shown in Scheme 3.4.[72]



Scheme 3.4

This catalytic cycle shows the production of two imine states; one is the substrate imine and the other is the product imine. The catalytic cycle can be thought of as two separate processes. The first of these processes involves the binding of the amine to the quinone which then undergoes oxidation and cleavage. The second process involves the oxidation of the enzyme by dioxygen resulting in the loss of hydrogen peroxide and ammonia.

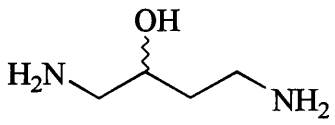
3.2.3. Structure of Amine Oxidases

The first amino acid sequence identified was that of lentil seedling amine oxidase (LSAO) which was cloned from cDNA in 1992.[73] It was not until a year later that the first crystals of an amine oxidase were identified which were those of pea seedling amine oxidase. It was found that each subunit had a M_r of ~72,000 and a weight of ~66 kDA.[74] The first X-ray structure of pea seedling amine oxidase was published in 1995. This represents a eukaryotic copper amine oxidase.[75] The active site of the enzyme is found buried deep in the structure which appears to be the trend for an enzyme that has a radical mechanism. A channel has been identified for access to this active site and it is also suggested that the active site has a gate mechanism.[72]

3.2.4. Stereoselectivity in Reactions catalysed by Copper Amine Oxidases

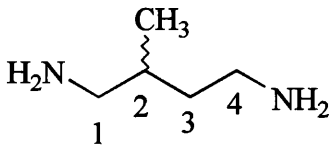
Copper amine oxidases appear to be different from most enzymes in that as a group they have no stereochemical selectivity in the removal of the hydrogen in the oxidation of the CH_2NH_2 group. Some copper amine oxidases remove the *pro-S* while others remove the *pro-R* hydrogen and some show no selectivity at all. The two main enzymes of interest in this particular research are pea seedling amine oxidase and pig kidney amine oxidase which have been shown to be selective in removing the *pro-S* hydrogen on oxidation in relation to the polyamines cadaverine **94**, putrescine **93** and tyramine.

Derivatives of these amines have also been investigated in order to give some insight into the regiochemistry of this oxidation. The first example showed that the amino group furthest away from the hydroxyl substituent of 2-hydroxyputrescine **98** and 2-hydroxycadaverine was oxidised.[76]



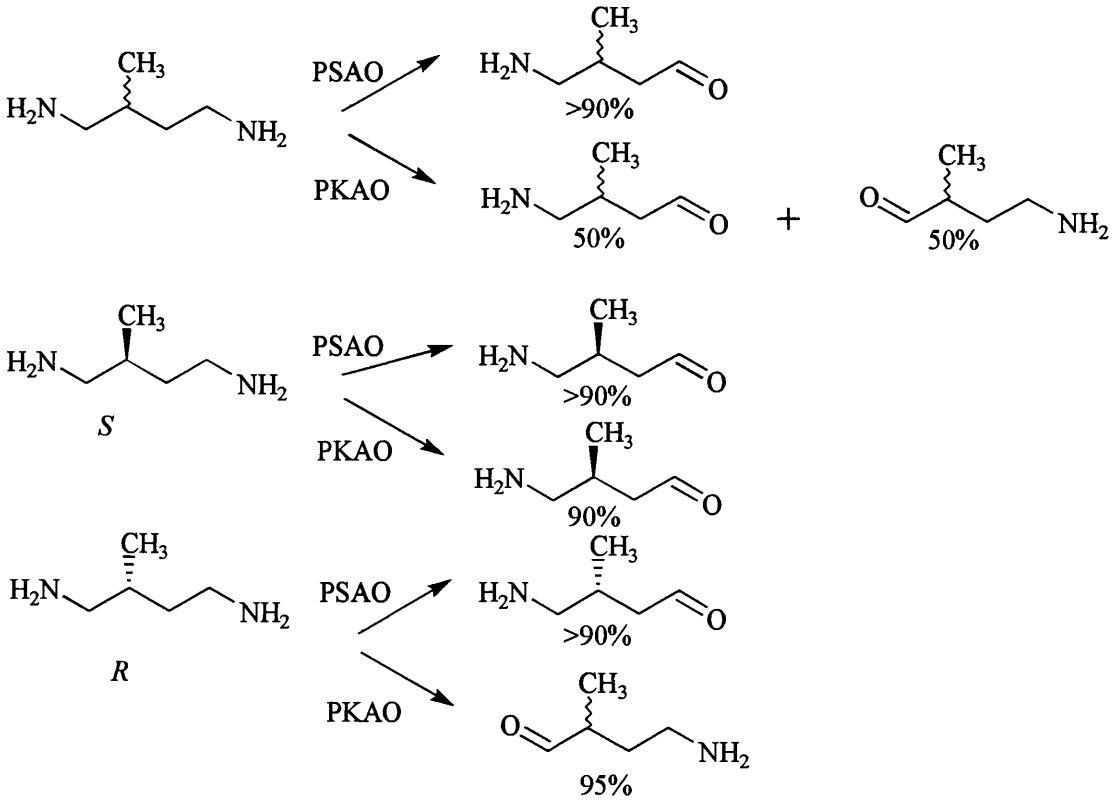
98

The next oxidation of a putrescine derivative catalysed by diamine oxidase reported in the literature involved 2-methylputrescine **99**.



99

This gave very interesting results in that pig-kidney amine oxidase showed no regioselectivity. It catalysed the oxidation of both ends of the diamine equally. However pea seedling diamine oxidase oxidised the less hindered C-4 end preferentially. The same group showed that when enantiomerically pure 2-methylputrescine was used in the same study that pea seedling amine oxidase showed no stereoselectivity and just displayed regioselectivity. On the other hand pig kidney diamine oxidase showed stereoselectivity in that both enantiomers of 2-methylputrescine were oxidised regioselectivity. The *pro-S* isomer was oxidised at the C-4 end and the *pro-R* at the C-1 end.[77,78] This situation is summarized in Scheme 3.5.



Scheme 3.5

Using our methodology that we developed for the diastereoselective conjugate addition of Grignard reagents to a homochiral fumaramide derived from Oppolzer's

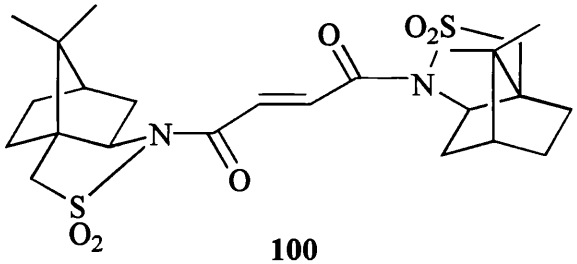
sultam, we will synthesise a range of optically active 2-substituted putrescines. This should give us valuable insight into the selectivity of the enzyme for different substrates. This work is discussed in Chapter 7.

4. Diastereoselective conjugate additions of Grignard reagents to a homochiral fumaramide derived from Oppolzer's sultam

4.1 Background

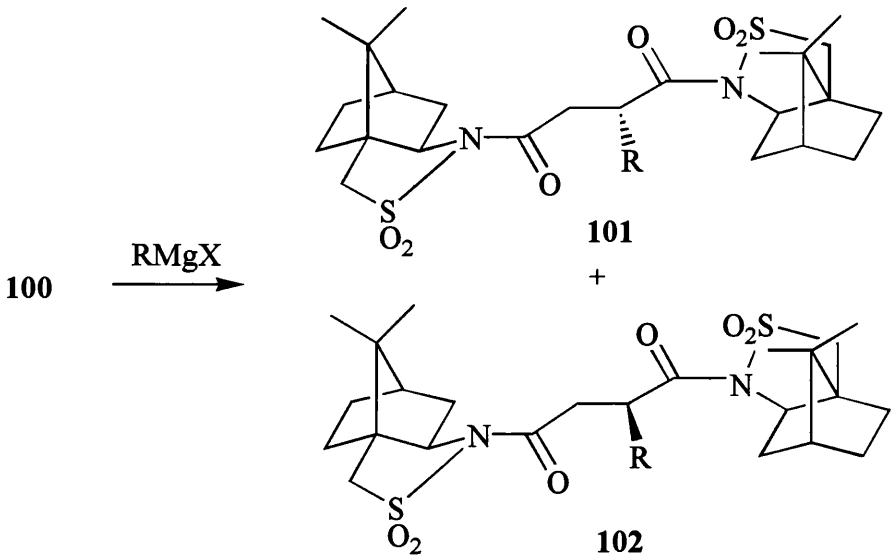
Asymmetric conjugate addition reactions to α,β-unsaturated organic compounds are some of the most useful methods for producing β-substituted products stereoselectively.[79] The introduction of chirality using a chiral auxiliary is a useful way of producing a wide variety of optically active organic compounds. Oppolzer *et al.* reported the diastereoselective conjugate addition of Grignard reagents to *N*-enoylsultams (Chapter 2.3.3.3).[55]

N,N'-Fumaroylbis[(2*R*)-bornane-10,2-sultam] **100**[80], is readily available from Oppolzer's (2*R*)-bornane-10,2-sultam. The C_2 symmetrical fumaramide **100** containing two of Oppolzer's camphorsultam moieties has previously been used in cycloaddition and dihydroxylation reactions.[80,81,82]



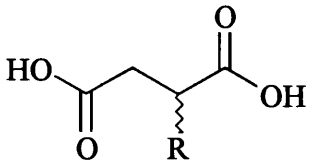
100

The [4 + 2] cycloaddition of cyclopentadiene and similar dienes to fumaramide **100** occurred with high levels of diastereofacial π-selection favouring attack on the C(α)-*re* face. Similarly the diastereoselective *syn*-dihydroxylation of fumaramide **100** using OsO_4 and 4-methylmorpholine-4-oxide occurred with excellent stereoselectivity (>98%) resulting from addition on the C(α)-*re* face. However no examples of conjugate additions to **100** have been reported. It was our aim to carry out a study of conjugate additions of Grignard reagents to fumaramide **100** (Scheme 4.1) and establish one diastereomer is produced in excess, either **101** or **102**.



Scheme 4.1

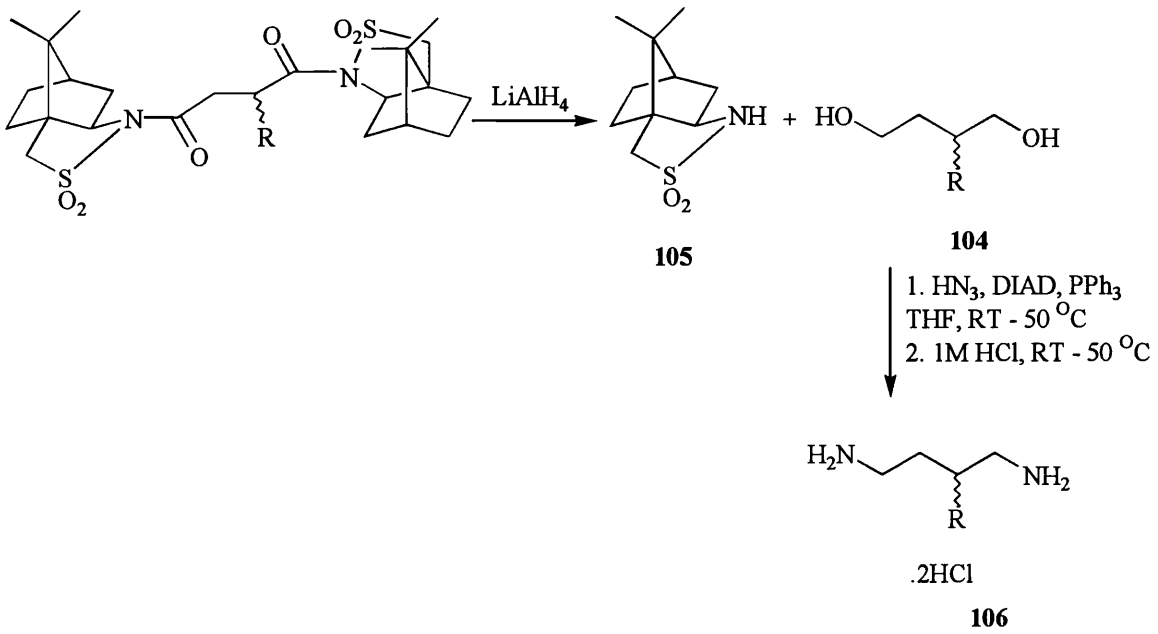
If the conjugate addition occurs with a high level of diastereoselectivity the chiral auxiliaries will be cleaved to yield enantiomerically enriched 2-substituted succinic acids **103**.



103

Substituted succinic acids are important intermediates in organic synthesis. They are building blocks for the synthesis of enantiomerically pure β-substituted β-amino acids.[83] They also have a role as structural components of natural products.[84]

Alternatively, reduction of the substituted succinamides would yield the corresponding 2-substituted butane-1,4-diols **104** together with the chiral auxiliary **105** which could be converted into the 2-substituted butane-1,4-diamines **106** (putrescines) (Scheme 4.2). We could then use these enantiomerically enriched diamines as substrates for the enzyme diamine oxidase. This would allow the study of the outcome of the oxidation of these enantiomerically enriched 2-substituted putrescines catalysed by DAO.

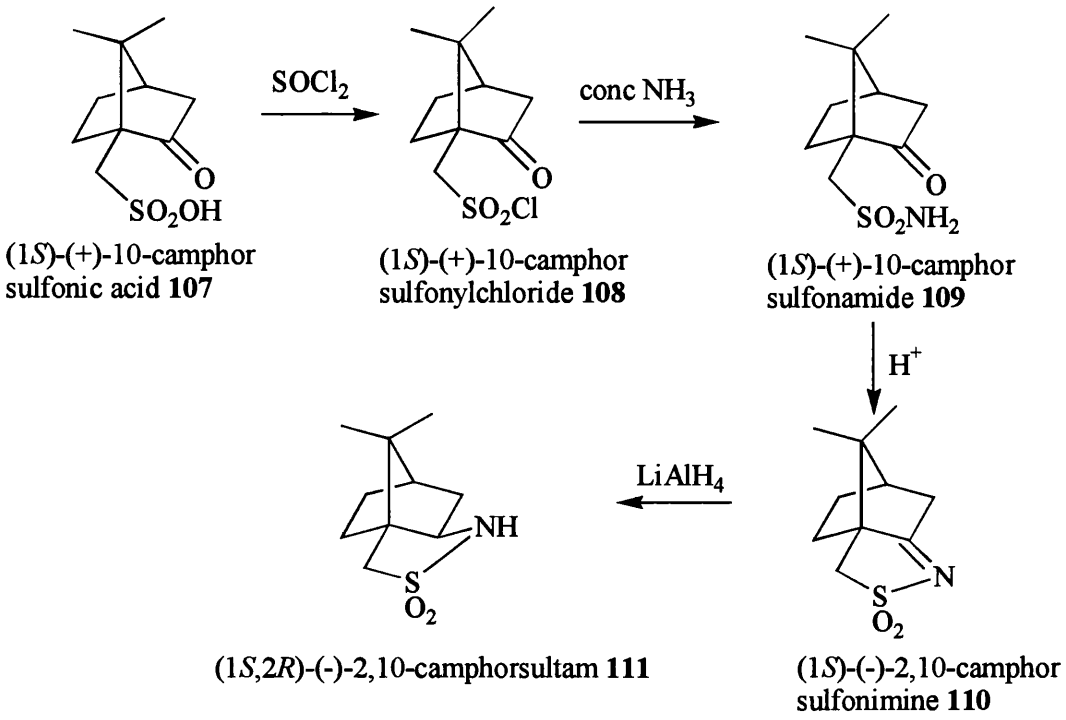


Scheme 4.2

4.2 Synthesis of Oppolzer's sultam

As Oppolzer's sultam was the auxiliary of choice it was necessary to synthesise the auxiliary from cheap starting materials as a large amount of it was required in order to carry out our study. The chiral auxiliary is commercially available at a price of £30 per gram, which was not economically viable in the quantities required. There are various synthetic routes available in the literature.[85,86] The route we used allowed the large scale production of the chiral auxiliary in pure crystalline form (Scheme 4.3).

The chiral auxiliary was readily prepared from (+)-camphor-10-sulfonic acid **107**. The sulfonyl chloride **108** was treated with ammonia and this generated the sulfonamide **109**. Azeotropic removal of water using toluene together with the acid catalyst Amberlyst 15 ion-exchange resin produced the camphorsulfonimine **110** in 95% yield. The use of a Dean-Stark apparatus in this reaction forces the equilibrium towards the imine as the water is removed as soon as it is generated. The acidic ion exchange resin was used in order to keep the pH at a reasonably low level as this assists in protonation of the OH group, making it a better leaving group. The final step was the reduction of the sulfonimine **110** to the sultam **111** using the reducing agent lithium aluminium hydride ($LiAlH_4$). This is a very good practical synthesis in that it avoids chromatography and each compound in the synthesis can be purified by crystallization.



(1*S*)-(+)-10-camphor sulfonic acid **107**

(1*S*)-(+)-10-camphor sulfonylchloride **108**

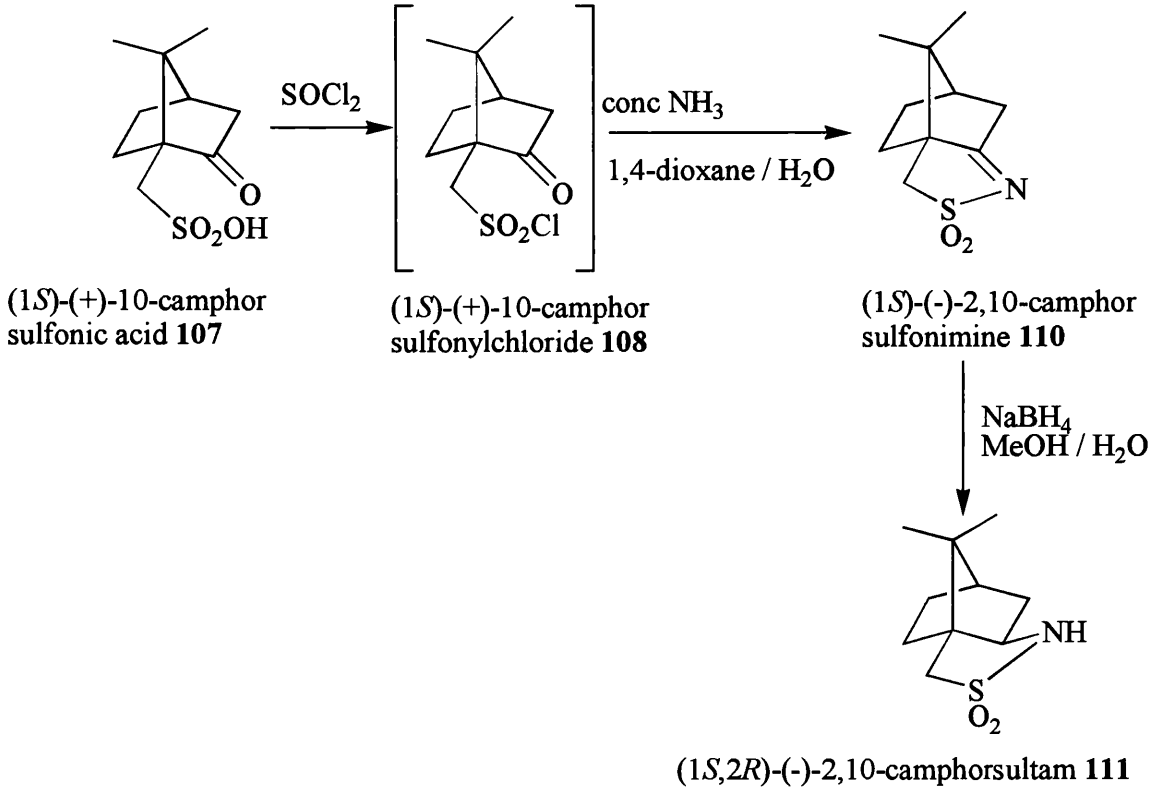
(1*S*)-(+)-10-camphor sulfonamide **109**

(1*S*,2*R*)-(-)-2,10-camphorsultam **111**

(1*S*)-(-)-2,10-camphor sulfonimine **110**

Scheme 4.3

As the project progressed another synthetic method that had previously not been identified from the literature was used as it had the added benefit of being a more efficient synthesis with fewer steps (Scheme 4.4).[87]



(1*S*)-(+)-10-camphor sulfonic acid **107**

(1*S*)-(+)-10-camphor sulfonylchloride **108**

(1*S*)-(-)-2,10-camphor sulfonimine **110**

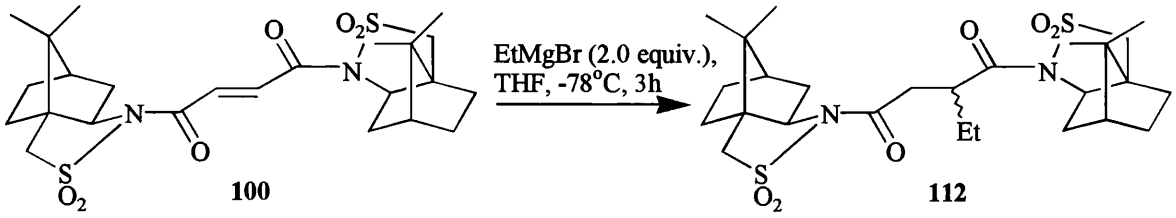
(1*S*,2*R*)-(-)-2,10-camphorsultam **111**

Scheme 4.4

This preparation of Oppolzer's sultam involved synthesising the sulfonylchloride **108**, dissolving it in 1,4-dioxane and pouring this solution into cold concentrated ammonia solution. This produces an insoluble product which could be filtered off to yield the camphorsulfonimine **110**. The imine required no purification and could be reduced by sodium borohydride in aqueous methanol to yield the chiral sultam **111**. As well as being a more efficient synthesis the reduction step is much safer than the $LiAlH_4$ reduction and also avoids the use of large amounts of tetrahydrofuran. Due to the commercial availability of both enantiomers of camphor-10-sulfonic acid this route allows access to both enantiomers of Oppolzer's sultam.

4.3 Conjugate addition of Grignard reagents to the fumaramide system

The fumaramide **100** was prepared from fumaroyl chloride and (1*S*)-(-)-2,10-camphorsultam in 81% yield using the literature method of Bauer *et al.*[80] The fumaramide **100** was treated with ethyl magnesium bromide in order to identify successful conjugate addition and also to determine the number of equivalents of Grignard reagent required for successful conjugate addition (Scheme 4.5).



Scheme 4.5

The Grignard reagent adds via a conjugate addition; however Grignard reagents would normally add via direct addition as they are classed as hard nucleophiles. It was thought that the presence of the bulky auxiliaries would direct the Grignard reagent, therefore producing the product of conjugate addition. The reaction took place cleanly with no direct addition products detected.

It appeared that the number of equivalents of Grignard reagent used has a considerable effect on the chemical yield of the reaction. The yield of **112** observed when using 2.0 equivalents of Grignard reagent was 50%. A number of exploratory reactions

were carried out looking at the influence of the number of equivalents. Further investigation into how the stereoselectivity is induced in this system indicated that the number of equivalents required must be at least three. The evidence for this stereoselective conjugate addition relates to the magnesium chelation as discussed by Oppolzer *et al.*[55] One equivalent is required for chelation to the O atoms of the C=O and SO_2 groups at each end and the C=O group adopts a *cis*-conformation with the C=C bond. This forces the camphor rings to block the *si*-face. The third equivalent then delivers its alkyl group in a conjugate manner from the *re*-face and the addition proceeds via a six-membered cyclic mechanism (Figure 4.1).

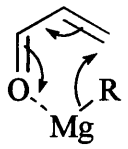


Figure 4.1

Therefore in our bis fumaramide system the reaction should proceed via the transition state shown in Figure 4.2.

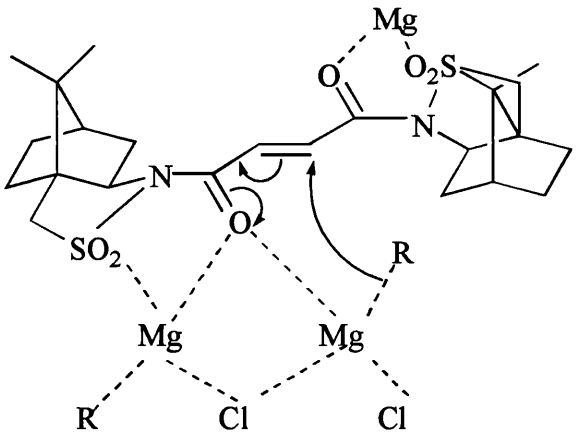


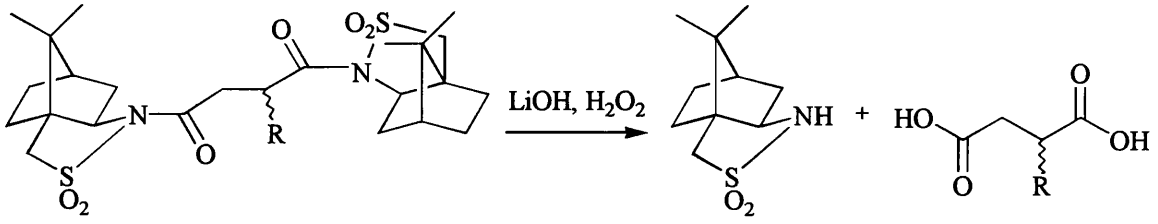
Figure 4.2

This information together with our experimental findings showed that the optimum number of equivalents of Grignard reagent required for successful addition was 3.5. Now that we had identified the best conditions to carry out the reaction we had to focus on the stereoselectivity of the conjugate addition. There were two main points that had to be addressed:

- How to determine the stereoselectivity of the conjugate addition.

- Assignment of absolute configuration of newly formed stereogenic centre to identify which diastereotopic face is being attacked.

One approach to address these points involves saponification of the succinamide products **101** and **102** to yield the enantiomerically enriched 2-substituted succinic acids **103** together with the chiral sultam **105** (Scheme 4.6). The stereoselectivity could be quantified by carrying out chiral HPLC analysis on the 2-substituted succinic acids. This might involve derivatisation of the acids to decrease their polarity increasing their mobility for liquid chromatography. Enantiomerically pure 2-substituted succinic acids have been extensively reported in the literature. Therefore the absolute configuration and sign of rotation reported could be used to identify the absolute configuration of the newly formed stereocentre of the optically active 2-substituted succinic acid synthesised by our methodology.



101 + 102 **105** **103**

Scheme 4.6

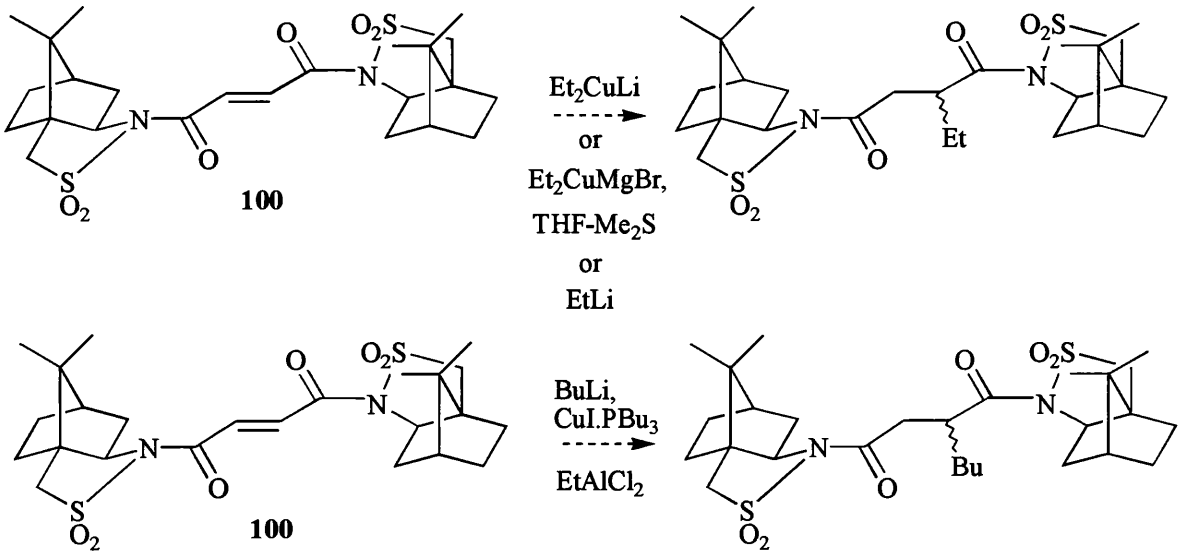
A series of diastereoselective conjugate additions using a range of Grignard reagents were carried out on fumaramide **100**. The methyl, phenyl and allyl Grignard reagents reacted with **100** to produce the direct 1,2-addition products. Oppolzer *et al.* observed the same result with the methyl Grignard reagent on *N*-enoylsultams.[55]

Table 4.1 Diastereoselective conjugate additions to fumaramide 100

Entry	2-substituted succinamide	Isolated yield (%)
1	Ethyl **113**	73
2	Isopropyl **114**	89
3	Propyl **115**	69
4	Butyl **116**	76
5	Cyclohexyl **117**	78
6	Octyl **118**	97
7	Benzyl **119**	71
8	Isobutyl **120**	51
9	Hexyl **121**	80
10	Cyclohexylmethyl **122**	75

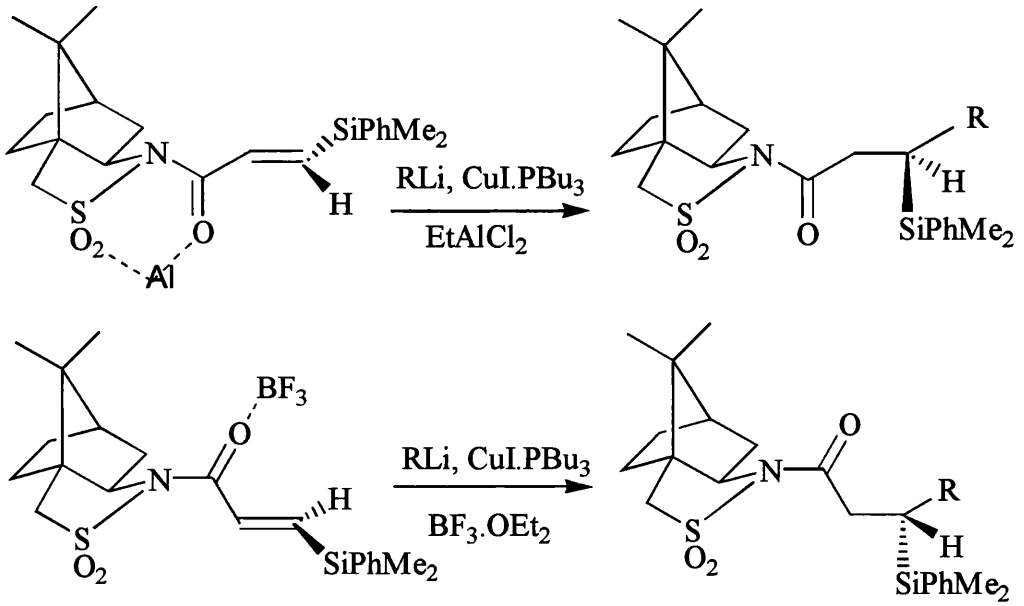
4.3.1 Addition of other organometallic reagents

Various different methods were attempted to add organocuprates to fumaramide **100**. However the fumaramide **100** was unreactive and only starting material was isolated from the reaction mixtures. Organolithium reagents were also used but again fumaramide **100** was unreactive. Even when Oppolzer's method was used which incorporated the use of a Lewis acid and BuLi as the alkyl donor the fumaramide **100** did not react (Scheme 4.7). Oppolzer had shown that this method of cuprate addition was very successful in carrying out conjugate addition to an *N*-enoylsultam system. By changing the Lewis acid both diastereomers could be obtained with good diastereoselectivities (Scheme 4.8).[54]



Scheme 4.7

It was disappointing that our system did not behave in a similar manner as this would have allowed access to both epimers without the need to use the other enantiomer of the chiral auxiliary.

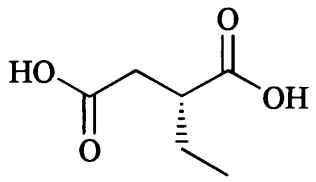


Scheme 4.8: Oppolzer's results

4.4 Synthesis of enantiomerically enriched 2-substituted succinic acids

This reaction involves the removal of the chiral auxiliaries under hydrolysis conditions to yield the 2-substituted succinic acids **103** (Scheme 4.6). The method of hydrolysis used was the hydrogen peroxide-assisted lithium hydroxide saponification which has been previously used for this type of hydrolysis.[88] The reaction was reasonably straight-forward but the workup required careful control of pH in order to extract both products successfully. On workup it was essential for the pH of the aqueous phase to be below 3 in order to get successful extraction of the succinic acid into ethyl acetate. The aqueous extract was then made basic to about pH 8 and extracted with ethyl acetate to yield the chiral auxiliary which could be recycled.

The first substituted succinic acid synthesised using this method was 2-ethylsuccinic acid **123**. From the optical rotation of the 2-ethylsuccinic acid **123** its absolute configuration corresponded to the (*R*)-enantiomer by comparison with the optical rotation reported in the literature.[89]



123

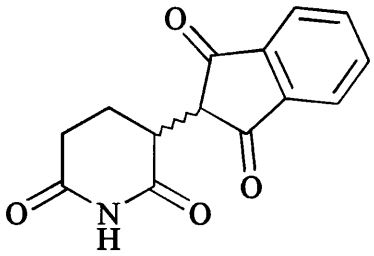
However the specific rotation observed for the ethyl succinic acid (+34) was much higher than the literature value (+24) which could be due to the following factors.

- The original rotation in the literature was not of the pure enantiomer or there could be some error in the measurements reported.
- The rotation obtained for our sample could be subject to errors in the measurements obtained (estimated to be ± 10%).

The next step was to quantify the enantiomeric excess of the optically active 2-substituted succinic acids. The analytical method that was appropriate for this was chiral HPLC. Chiral chromatography involves the use of a chiral stationary phase in gas or liquid chromatography. The disadvantage in using chiral chromatography is that a sample of the racemate is usually required in order to prove separation of enantiomers.

Chromatographic separation depends on the difference in affinity of a mixture of compounds between the stationary phase and the mobile phase. The stationary phase is usually the solid material which the mixture is passed through such as silica. The mobile

phase is the solvent (eluent) travelling through the stationary phase. If we consider the two enantiomers of a racemate they have the same physical properties. However when they are present in a chiral environment they can behave differently. Enantiomers usually have different biological properties when present in a biological system. In a biological system enantiomers are differentiated by interactions with enantiomerically pure molecules that are present in the system. This was realised in an unfortunate situation when the drug Thalidomide was administered to pregnant women and resulted in birth defects. The drug was manufactured and sold as a racemic mixture of *N*-phthalylglutamic acid imide **124**. It was found that the (*R*)-(+)-isomer produced the desired physiologically activity whereas the corresponding (*S*)-(-)-enantiomer was teratogenic and caused serious foetal malformations. This led to the United States Food and Drug Administration recommending that each enantiomer of all new racemic drugs should be individually tested.



124

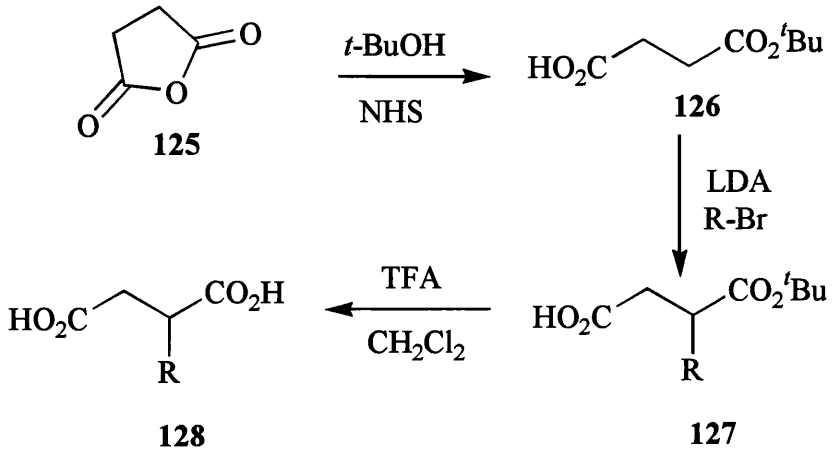
Similarly in chromatography the stationary phase can be made chiral. The different enantiomers will have a different affinity for the chiral stationary phase thus allowing separation to occur. There are five general types of chiral stationary phases:

- Protein based phases bonded to silica.
- Small molecular weight compounds bonded to silica (the Pirkle phases).
- Cellulose and amylose polymers that are coated onto silica gel.
- Macrocyclic glycopeptides that are bonded to silica.
- Cyclodextrin based materials that are also bonded onto silica.

The stationary phase is chemically bonded to a silica substrate and is stable to a wide range of solvents. The chiral stationary phase columns that are available in our department are celluose polymer coated silica. The cellulose is derivatized with tris(3,5-dimethylphenyl carbamate.

In order for the successful identification of each enantiomer peak in the chromatograph samples of racemic 2-subtituted succinic acids were required. The racemic acid should give two peaks when run on a chiral LC column and would allow comparison

with our mixture of enantiomers. A literature synthesis was used for the preparation of racemic 2-substituted succinic acids (Scheme 4.9).[90]



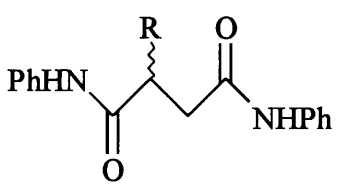
Scheme 4.9

This route worked extremely well with inexpensive starting materials. Succinic anhydride **125** was subjected to ring opening and one carboxyl group was protected as the *tert*-butyl ester **126**. The advantage in using the *tert*-butylsuccinate **126** is that it is soluble in ethereal solvents and thus minimizes self-condensation. The dianion produced from treatment of *tert*-butylsuccinate **126** with LDA in THF was alkylated at the α-carbon of the ester with various alkyl halides producing the 2-substituted succinate derivatives **127**. It was found that for successful alkylation of the isopropyl and propyl substituents the halide source had to be iodide, wheras the bromides of the other R groups were successful in alkylation of **126**. The ester protecting group was removed using trifluoroacetic acid in dichloromethane to yield the 2-substituted succinic acids **128** (Table 4.2).

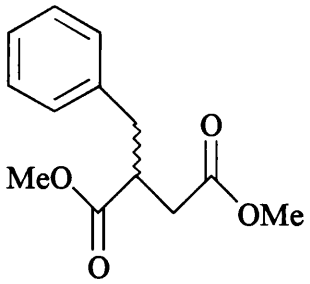
The substituted succinic acids could not be analysed directly by chiral chromatography as they were too polar for the chiral columns available within the department and therefore they required derivatisation. In order to incorporate a chromophore that would show a good absorption in the ultraviolet detector of the HPLC spectrometer and also decrease the polarity, the alkyl substituted succinic acids were converted into their dianilide derivatives **147**. The aromatic substituted succinic acids were simply derivatised as their corresponding dimethyl esters **148** as they already contain a chromophore in the form of an aromatic ring.

Table 4.2 2-Substituted succinic acids

Entry	Substituent	Substituted *tert*-butyl ester (% yield)	Substituted succinic acid (% yield)
1	R = ethyl	**129** (72)	**138** (81)
2	R = isopropyl	**130** (38)	**139** (79)
3	R = propyl	**131** (16)	**140** (74)
4	R = butyl	**132** (70)	**141** (81)
6	R = octyl	**133** (85)	**142** (83)
7	R = benzyl	**134** (89)	**143** (81)
8	R = isobutyl	**135** (14)	**144** (52)
9	R = hexyl	**136** (20)	**145** (87)
10	R = cyclohexylmethyl	**137** (14)	**146** (94)



147
R = alkyl

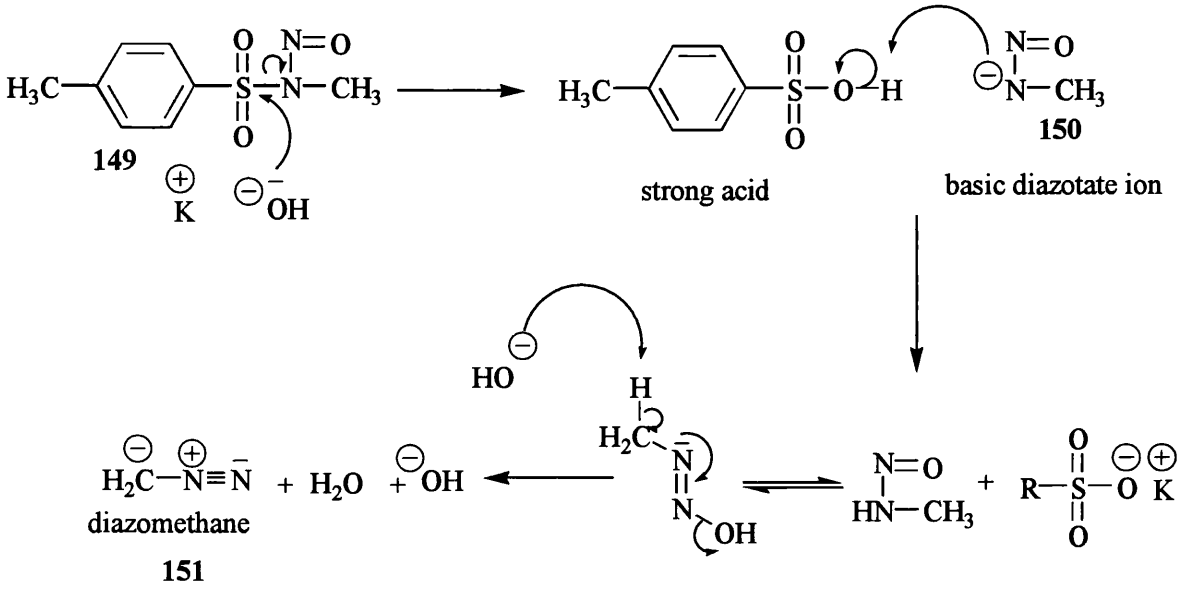


148

The preparation of the dimethyl esters was carried out using diazomethane generated using the Aldrich MNNG (*N*-methyl-*N'*-nitro-*N*-nitrosoguanidine) Diazomethane Kit. We used the modified procedure previously described by Ngan *et al.* which replaces MNNG with Diazald (*N*-methyl-*N'*-nitroso-*p*-toluenesulfonamide) as the precursor to diazomethane.[91] The Aldrich MNNG Diazomethane Kit was ideal for our purposes as it allowed the generation of diazomethane in a closed system on a millimole scale without the need for distillation. Apparatus used to prepare diazomethane that requires distillation has the added risk of the diazomethane exploding. Diazomethane has been known to explode both as a gas or in solution, and ground glass joints and alkali metals were found to be initiators. Due to the highly toxic and explosive nature of diazomethane it was very important that the safest possible method was utilised.

The first stage in generating diazomethane involves saponification of *N*-methyl-*N'*-nitroso-*p*-toluenesulfonamide **149** using potassium hydroxide to give a basic diazotate ion

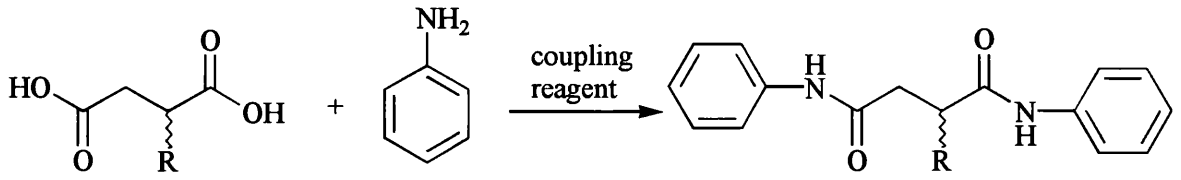
150. This diazotate ion is rapidly converted to diazomethane **151** by the basic conditions of the reaction (Scheme 4.10).



Scheme 4.10

As the diazomethane is generated it reacts with the 2-substituted succinic acid to give the corresponding succinate diesters in moderate yields of 54-86%. The succinate diesters required no further purification and could be used directly for chiral HPLC anaylsis. The racemic dimethyl 2-benzylsuccinate **152** resolved well on the commercially available chiral stationary phase column, Diacel Chemical Industries CHIRALCEL-OD-H. The dimethyl 2-benzylsuccinate **153** produced in our asymmetric Grignard reaction gave a good chromatograph displaying an enantiomeric excess of 92%. Racemic dimethyl 2-methylsuccinate was also synthesised in an attempt to identify if it was resolvable by the HPLC system. It was detectable but did not give two distinct peaks corresponding to both enantiomers.

As previously mentioned the alkyl substituted succinic acids **154** can be derivatised as their corresponding dianilides **147** (Scheme 4.11). However it proved very problematic and time consuming to identify optimum reaction conditions for this coupling. A number of different coupling reagents were used such as DCC (dicyclohexylcarbodiimide), EDCI [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] and cyanuric chloride (Table 4.3).



154 **147**

Scheme 4.11

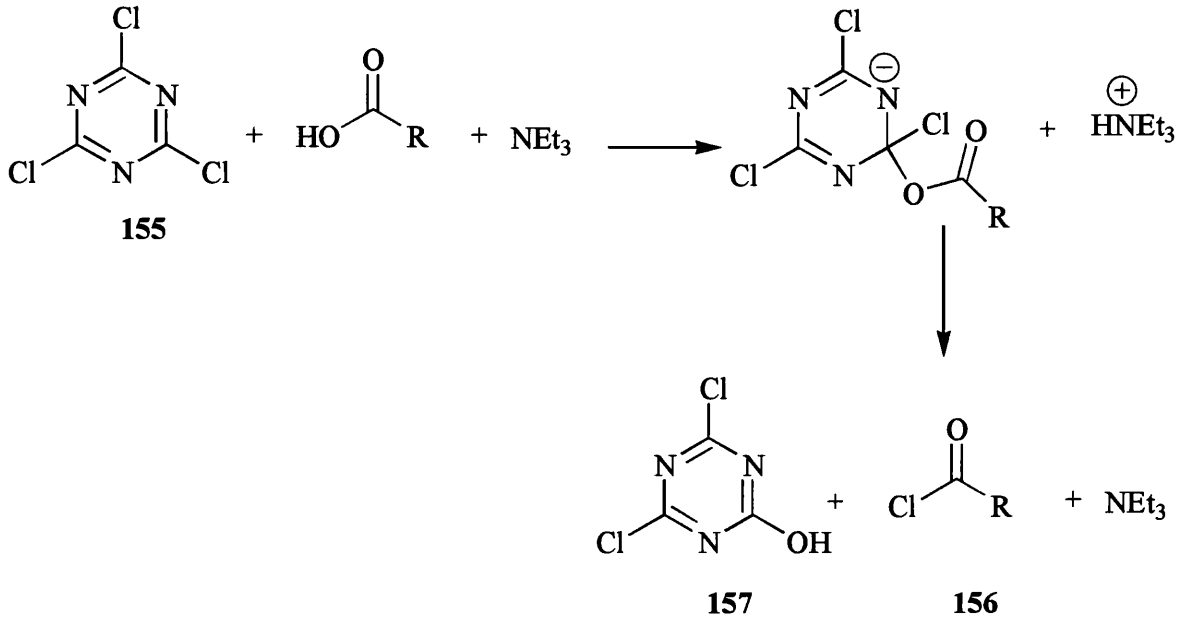
Table 4.3 Summary of coupling reaction conditions attempted

Reaction conditions	Reaction outcome
Aniline 2 equiv.,DCC 2 equiv. DMAP 10 mol %, acetonitrile Solvent: THF	reaction unsuccessful
Aniline 2.2 equiv., EDCI 2.2 equiv. Solvent: DCM	reaction unsuccessful
Aniline 2.2 equiv., EDCI 2.2 equiv. Solvent: THF	reaction unsuccessful
Aniline 4 equiv., cyanuric chloride 3 equiv. Triethylamine 2.2 equiv. Solvent: Acetone	reaction successful but problems in purification
Aniline 4 equiv., EDCI 2.2 equiv. Solvent: DMF	reaction successful

The reactions attempted involved the use of a coupling reagent, in our examples DCC and the water soluble equivalent EDCI. The coupling reagent reacts with the carboxylic acid to form an imidate which is susceptible to nucleophilic attack from aniline producing the corresponding dianilide and in the case of DCC the by-product dicyclohexylurea. Dicyclohexylurea is difficult to remove from the product and purification usually requires chromatography. The benefit of using EDCI is that excess reagent and the urea by-product can be easily removed by washing with dilute acid or water. In summary the coupling reagent activates the carboxyl group by transforming it into a good leaving group.

The use of cyanuric chloride (CC) **155** as a reagent allows carboxylic acids to be converted into chlorides, esters, amides and peptides.[92] It was shown that succinic acid was converted into the dianilide in 55% yield using CC. When CC is dissolved in dry acetone

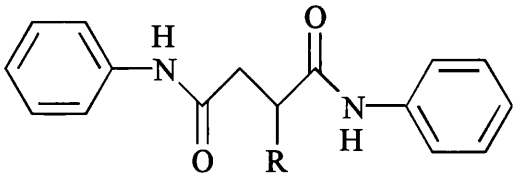
along with the carboxylic acid and triethylamine the acid chloride **156** is formed from a nucleophilic attack of the carboxylate anion on CC. CC is then converted into the insoluble dichlorohydroxy- or chlorodihydoxy-s-triazine **157** (Scheme 4.12). The acid chloride is then subject to attack from the corresponding amine to form the amide.



Scheme 4.12

The use of CC as a reagent to synthesise our dianilides did work but purification could not be achieved and as we wanted to carry out this coupling on a 50 mg scale purification must be straightforward. Use of EDCI and DMF (dimethylformamide) as the reaction solvent, was successful in synthesising the corresponding dianilides in good yield (57-85%).

Racemic *N,N*-diphenyl-2-methylsuccinamide **158** was synthesised in order to check if chiral HPLC could resolve the enantiomers. The enantiomers showed good separation. The racemic 2-substituted succinic acids previously synthesised were derivatised as the corresponding dianilides (Figure 4.3).



R = Et **159**, iPr **160**, Bu **161**, Oct **162**, iBu **163**, iPr **164**, Hex **165** and cyHexMe **166**

Figure 4.3

Now with a system in place for determination of the enantiomeric excesses of the 2-substituted succinic acids, a set of results was produced (Table 4.4).

Table 4.4 Removal of chiral auxiliaries yielding (*R*)-substituted succinic acids

Entry	2-substituted succinic acid	Isolated yield (%)	Configuration	Ee (%)[a]
1	Ethyl **167**	65	(*R*)[93]	63 **177**
2	Isopropyl **168**	67	(*R*)[94]	0 **178**
3	Propyl **169**	71	(*R*)[95]	52[b] **169**
4	Butyl **170**	67	(*R*)[96]	72[b] **179**
5	Cyclohexyl **171**	63	(*R*)[97]	9 **180**
6	Octyl **172**	74	(*R*)	90 **181**
7	Benzyl **173**	71	(*R*)[98]	92[c] **182**
8	Isobutyl **174**	76	(*R*)	8 **183**
9	Hexyl **175**	65	(*R*)[99]	37 **184**
10	Cyclohexylmethyl **176**	66	(*R*)	**185** dianilide not resolved

[a]Determined by chiral HPLC of dianilide derived from diacid. [b]Not resolved by chiral HPLC, % ee based on optical rotation of substituted succinic acid compared with literature value. [c]Diacid converted into dimethyl ester.

The results showed a range of stereoselectivities relating to the conjugate addition of Grignard reagents to fumaramide **100**. There was no obvious trend and it was difficult to explain why there was no stereoselectivity for the isopropyl substituent and a high stereoselectivity for the benzyl substituent. A suggestion for the low levels of stereoselectivity could be a result of non-chelation of the magnesium. Comparative semi-empirical PM3 and *ab initio* STO 3 21G calculations suggest that at 193 K four conformations of **100** can exist.[100] There are two symmetrical and two unsymmetrical species with the symmetrical conformations making up 96% and the nonsymmetrical

conformations 4% of the total. If chelation did not occur the existence of these other conformations could explain the low values obtained.

Attempts were also made to separate the diastereomeric mixtures of the substituted succinamides by column chromatography. It became apparent from the ^{1}H NMR spectra of the individual diastereomers that specific signals could be identified. The chemical shifts of these signals are characteristic for each diastereomer. This should allow determination of the diastereomeric excess from the ^{1}H NMR spectra of each crude mixture.

4.5 Determination of diastereomeric excess from ^{1}H NMR spectra

The conjugate addition of Grignard reagents to *N,N'*-fumaroylbis[(2*R*)-bornane-10,2-sultam] **100** produced a mixture of diastereomers **101** and **102** (Scheme 4.1). Attempts to determine the stereoselectivity of the conjugate addition from the mixture of diastereomers produced were made. Initially the technique of GC-MS was used which consists of coupling a mass spectrometer to the effluent of a gas chromatograph. This gives the combination of the analytical capability of mass spectrometry together with the high degree of separation by gas chromatography. However this technique was not successful as the compounds have too high molecular weights to be volatile for GC.

A method was developed to determine the diastereomeric excesses from the ^{1}H NMR spectra of the crude mixtures (Figure 4.4).

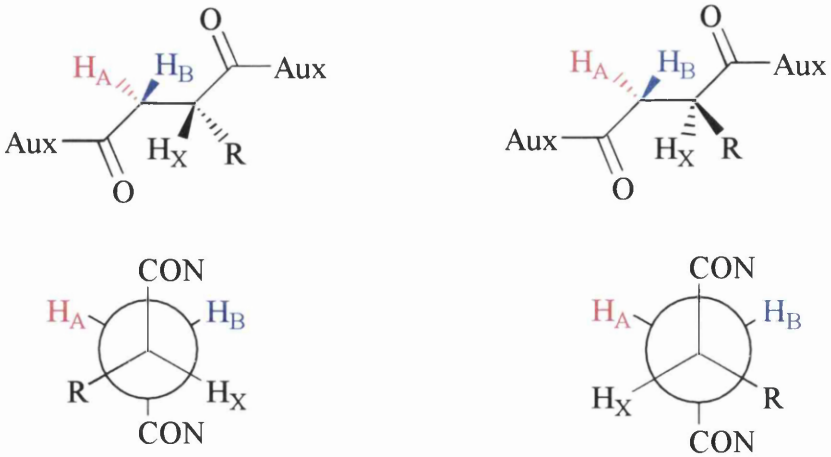
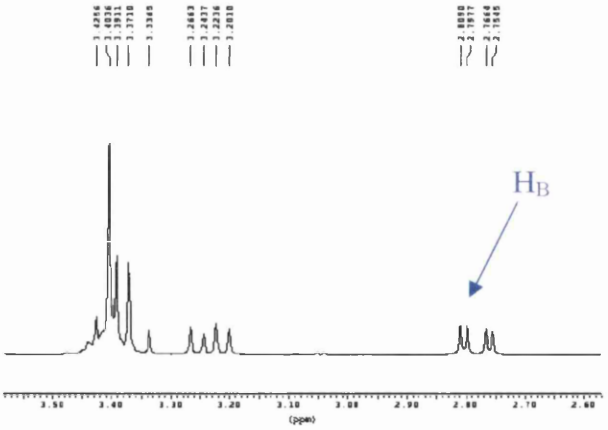
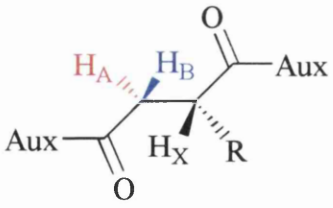


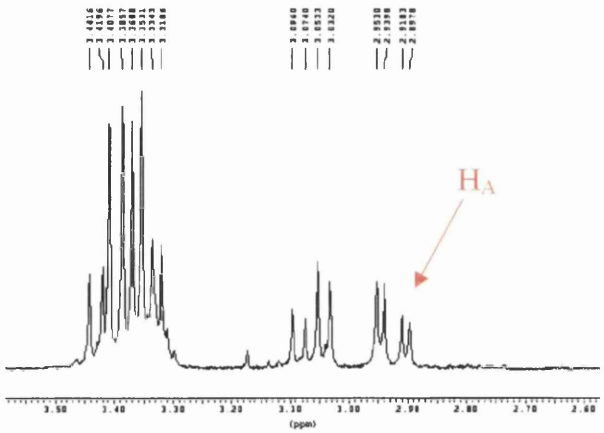
Figure 4.4

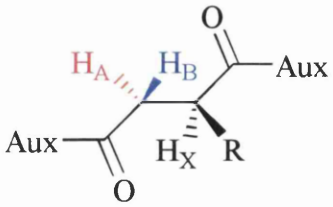
The ABX system of the succinamide protons resonated at different chemical shifts for each pair of diastereomers except for the benzylsuccinamide. The ABX system in our example arises from proton H_A and H_B being diastereotopic giving an AB system which is further split by H_X to give a double doublet for both H_A and H_B (Figure 4.5). H_X also displays a double doublet but this is masked in Figure 4.5 as a result of the CH_2SO_2 signal of the camphorsultams. As shown in Figure 4.5 the chemical shift of H_B of the major diastereomer is lower than H_A of the minor diastereomer. Integration of the signals for H_A and H_B gives an estimate of the diasteromeric ratio from which the diastereomeric excess can be calculated. The ABX system of the major diastereomer was consistently at a lower δ value than the minor diastereomer. Therefore the ratio of diastereomers **101** and **102** was determined by ^{1}H NMR spectroscopy (Scheme 4.1, Table 4.5). The table of results was both interesting and alarming as we were expecting to observe analogous results to those obtained from the chiral HPLC work on the derivatised 2-substituted succinic acids (Table 4.4).





major





minor

Figure 4.5

Results from both methods are tabulated in Table 4.6. We consider that the results obtained from the ^{1}H NMR spectra of the diastereomeric mixtures are more reliable as this is a direct method of estimating the stereoselectivity. In summary the succinic acids with propyl, butyl and octyl substituents show an increase in optical purity after removal of the chiral auxiliary, whereas succinic acids with isopropyl, cyclohexyl, isobutyl and hexyl substituents show a decrease in optical purity.

Table 4.5 Conjugate addition to fumaramide 100

Entry	**RMgX**	**Isolated yield (%)**	**Dr[a] (major/minor)**	**De (%)**
1	R = ethyl	76	81:19 (**186/187**)	62
2	R = isopropyl	89	66:34 (**188/189**)	32
3	R = propyl	69	68:32 (**190/191**)	36
4	R = butyl	76	77:23 (**192/193**)	54
5	R = cyclohexyl	87	66:34 (**194/195**)	32
6	R = octyl	62	76:24 (**196/197**)	52
7	R = benzyl	78	N/A (**198**)	N/A
8	R = isobutyl	87	72:28 (**199/200**)	44
9	R = hexyl	80	76:24 (**201/202**)	53
10	R = cyclohexyl methyl	75	69:31 (**203/204**)	38

[a]Diastereomeric ratios were estimated from by ^{1}H 400 MHz NMR spectra of the crude reaction mixtures.

Table 4.6 Comparison of stereoselectivity results

Entry	Substituent	Ee obtained from 2-substituted succinic acids	De obtained from ^{1}H NMR of succinamides
1	R = ethyl	63	62
2	R = isopropyl	0	32
3	R = propyl	52	36
4	R = butyl	72	54
5	R = cyclohexyl	9	32
6	R = octyl	90	52
7	R = benzyl	92	N/A
8	R = isobutyl	8	44
9	R = hexyl	37	53
10	R = cyclohexylmethyl	N/A	38

The results suggest that there is epimerisation of the succinate stereogenic centre during the basic hydrolysis. This can be explained by enolate **B** formation during the basic hydrolysis of **A**. It is also likely that each amide group of a diastereomer is hydrolysed at a different rate so **C** and **D** (less likely) could also be formed (Figure 4.6). The final product could also be present as an enolate **E**. It should be noted that the IR C=O absorption of succinamide **A** is 1680-1690 cm^{-1} and therefore **A** behaves like a ketone with a localised lone pair on the nitrogen.

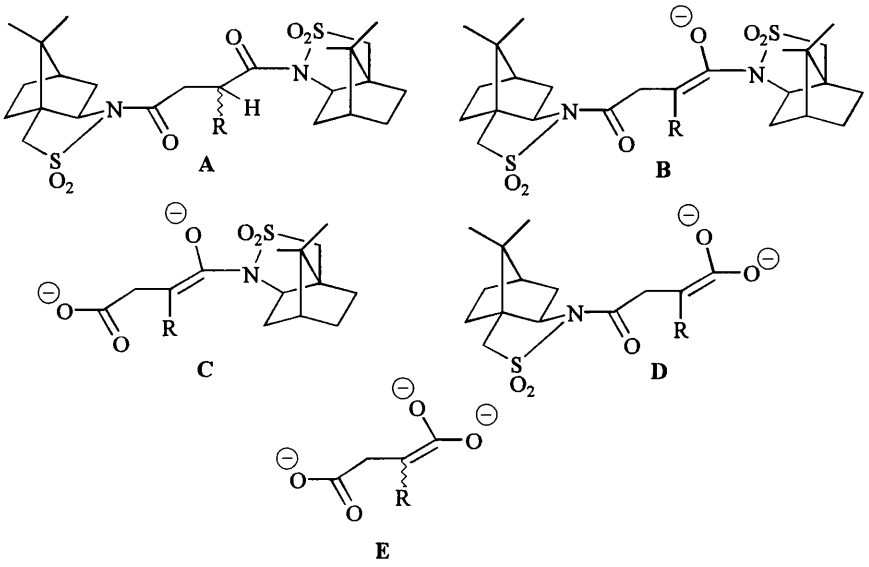
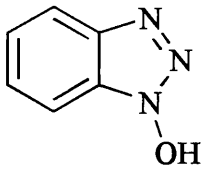


Figure 4.6

The combination of hydrogen peroxide and lithium hydroxide to cleave chiral auxiliaries attached by an amide has been routinely used with no loss of optical purity.[88,101,102]

Another explanation for change in optical purity could be a result of epimerisation during the coupling of aniline to the 2-substituted succinic acids. In the preparation of peptides one problem that was encountered was racemization of the activated ester when DCC or other related carbodiimide coupling reagents were used. In an attempt to address this problem racemization suppressing additives were used; the most popular being 1-hydroxybenzotriazole (HOBt) **205**.[103] HOBt intercepts the activated ester forming a new intermediate which does not racemize, allowing the second amino acid to attack the HOBt ester producing the dipeptide. Even with the use of additives a small amount of racemization can still occur. This problem could also apply to our system in which the stereogenic centre epimerises when the activated ester is formed. However this would only account for the decrease in stereoselectivity and not the increase observed for some 2-susbtituted succinic acids.



205

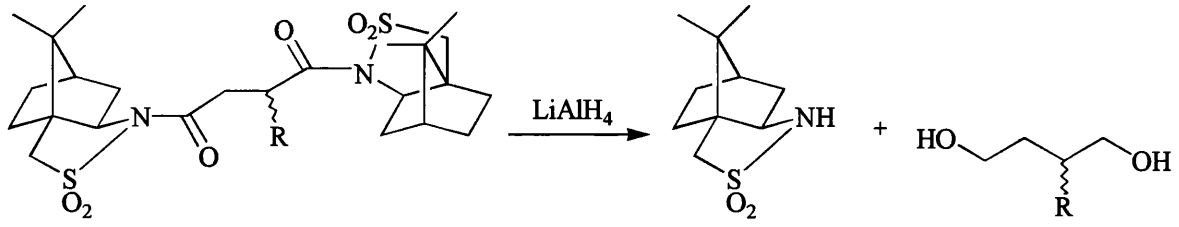
It was decided to try the following modifications to the hydrolysis of the succinamide and the coupling reaction to form the dianilide.

- Hydrolysis attempted under acidic conditions.
- Hydrolysis attempted in the presence of lithium hydroxide but without hydrogen peroxide.
- Coupling reaction attempted using HOBt as an additive.

Firstly we attempted to hydrolyse the octyl substituted succinamide by refluxing in dilute HCl and 1,4-dioxane to give the succinic acid and chiral sultam. However this was unsuccessful with the starting succinamide being the only product isolated from the reaction. Although these hydrolysis conditions were vigorous it was disappointing as this was shown to be effective for hydrolysing substituted succinamides without any trace of racemization.[104] The hydrolysis was attempted using only lithium hydroxide without the use of hydrogen peroxide and the products displayed marginally less epimerisation. The

use of HOBt to promote the coupling reaction was unsuccessful in minimising epimerisation on forming the dianilide.

A better method was required that would confirm the results obtained from the initial conjugate addition. We decided to focus on the synthesis of the 2-substituted diols **104** where no epimerisation should occur from reduction of the amides **101** and **102** with lithium aluminium hydride (Scheme 4.13).



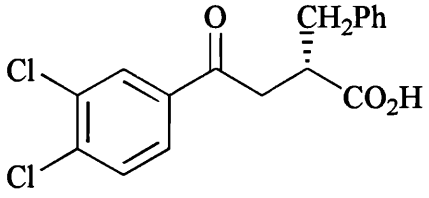
101 + 102 **105** **104**

Scheme 4.13

4.6 Future Work

4.6.1 Asymmetric synthesis of aryloxobutanoic acids for treatment of neurodegenerative diseases

The neuronal damage that results from disorders like Alzheimer's disease or Parkinson's disease or following strokes cannot be prevented by currently available drugs.[105] The kynurenines are metabolites of tryptophan and inhibitors of kynurenine 3-hydroxylase which should have a neuroprotective effect.[105] The aryloxobutanoic acid **206** is a good inhibitor of kynurenine 3-hydroxylase.[106] It was shown that the (*S*)-isomer was 5x more active than the (*R*)-isomer.



206

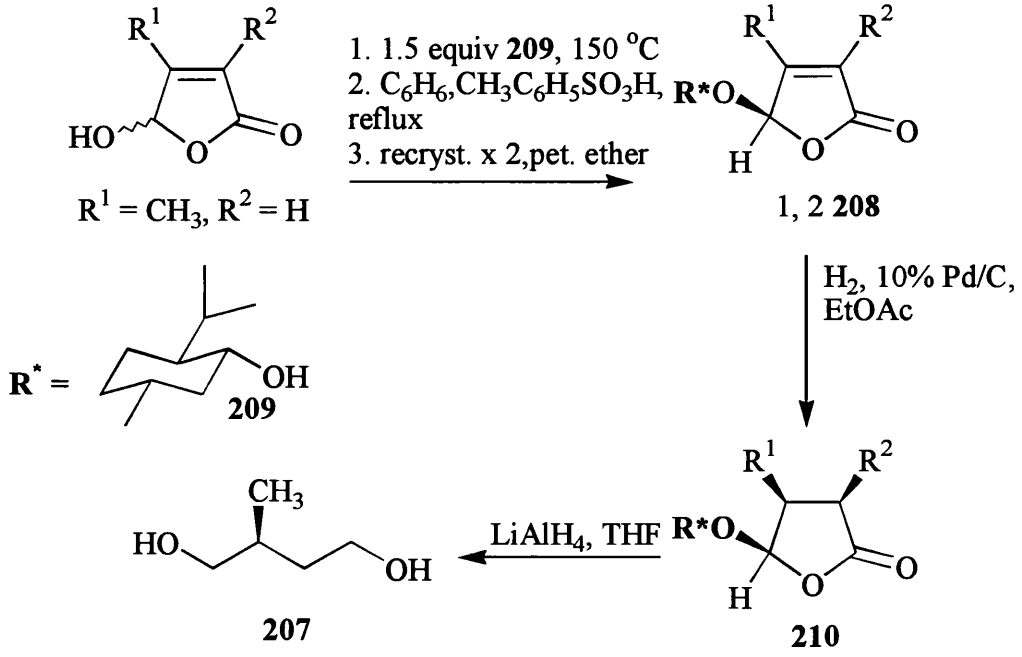
We have developed a route to optically active (*R*)-2-benzylsuccinic acid in high 92% ee. The synthesis of (*R*)- and (*S*)-2-benzylsuccinic acid and related compounds with substitutents on the aromatic ring (e.g. *p*-methoxy, *p*-methyl, *p*-fluoro) could be carried out. The optically active succinic acids could be converted into corresponding anhydrides

and these could be reacted with 1,2-dichlorobenzene using Friedel Crafts conditions to give optically active aryloxobutanoic acids. Testing of these compounds for the inhibition of kynurenine 3-hydroxylase could be carried out.

5. Synthesis of enantiomerically enriched 2-substituted butane-1,4-diols

5.1 Background

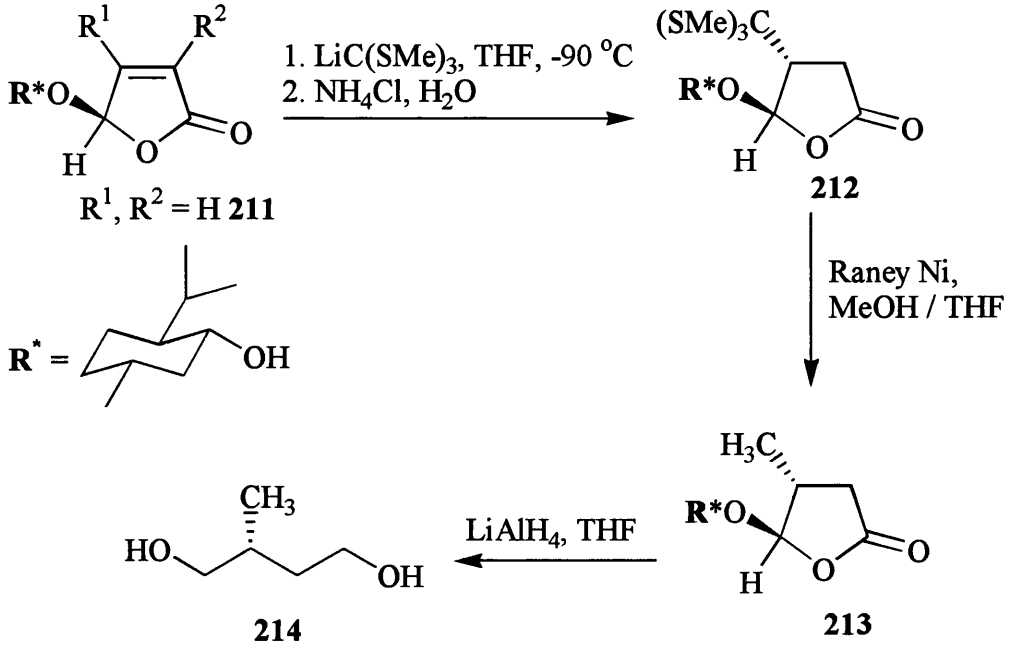
Previous asymmetric syntheses of 2-substituted butane-1,4-diols have been accomplished by the use of chiral auxiliaries and chiral catalysts. Feringa *et al.* reported the synthesis of (*S*)-2-methyl-1,4-butanediol **207** by hydrogenating enantiomerically pure γ-(menthyloxy)butenolides **208** prepared from 5-hydroxy-2(5*H*)-fuaranone and (-)-menthol **209** to produce enantiomerically pure lactones **210** (Scheme 5.1).[107] These lactones were then reduced using lithium aluminium hydride to give the corresponding enantiomerically pure 2-methyl-1,4-butanediol.



Scheme 5.1

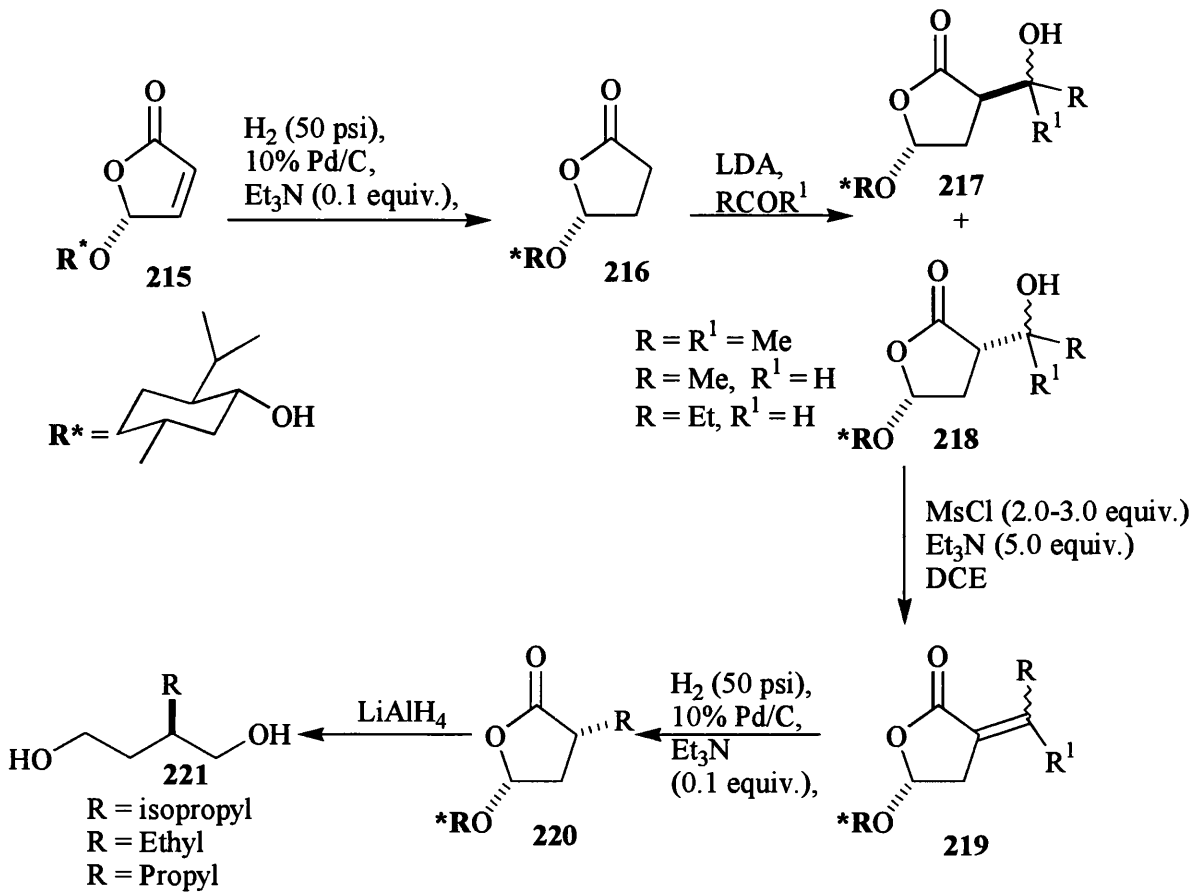
An alternative approach reported the conjugate addition of lithiotris(methylthio)methane to enantiomerically pure γ-(menthyloxy)butenolides (R^1 and R^2 = H) **211** followed by quenching with NH_4Cl to give the corresponding lactone **212** (Scheme 5.2).[108] Desulfurization using Raney-nickel gave lactone **213** which was reduced using lithium aluminum hydride to give (2*R*)-methylbutane-1,4-diol **214**. Stereoselectivity of the conjugate addition was due to the bulky γ-menthyloxysubstitutent **R*** which directs

attack from the less hindered bottom face producing selectively the *R* enantiomer of 2-methylbutane-1,4-diol.



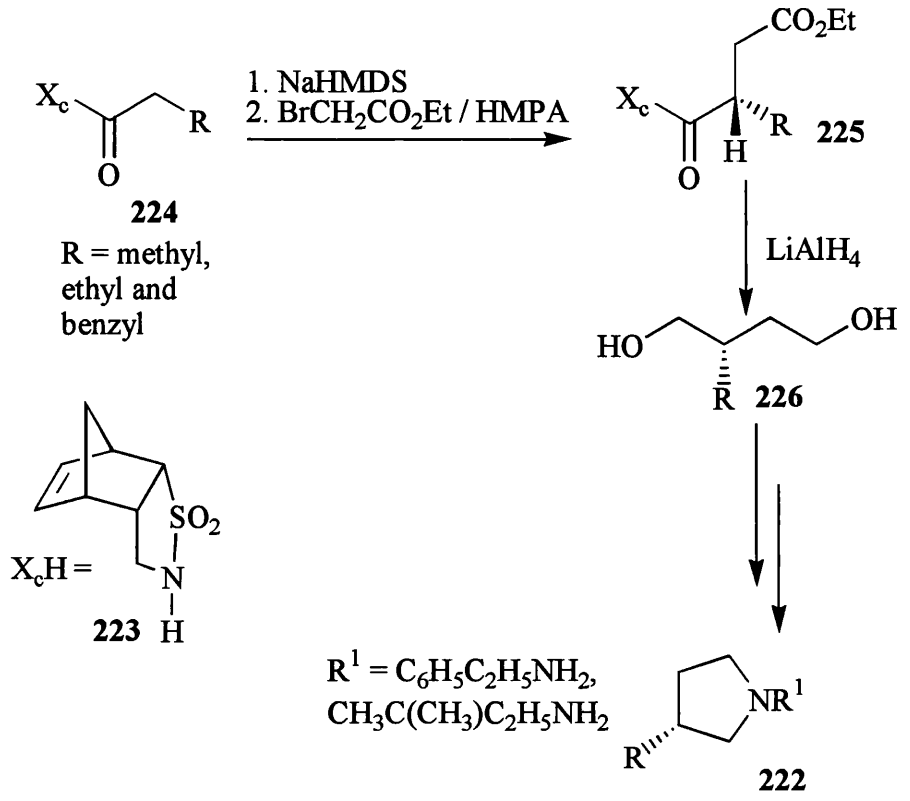
Scheme 5.2

A modification of this methodology led to the synthesis of optically pure (*R*)- and (*S*)-2-ethyl-, 2-propyl- and 2-isopropyl-1,4-butanediols (Scheme 5.3).[109] It involved the hydrogenation of 5-(*R*)-[-(-)-menthyloxy]butenolide **215** to give the butyrolactone **216**. The lactone was then lithiated with LDA followed by trapping the enolate with acetone, acetaldehyde or propionaldehyde producing the aldol products **217** and **218**. The diastereomeric mixtures of aldol products were treated with methanesulfonyl chloride to produce the mesylates which on heating at reflux underwent elimination to give *exo*-double bonded butenolides **219** (no detection of *endo*-double bonded butenolides). It is suggested that the *exo*-double bonded butenolides are the thermodynamic products as attempts were made to convert *exo* products into *endo* isomers by treating with DBU using various solvents (dichloromethane, acetonitrile and 1,2-dichloroethane) at reflux which proved unsuccessful. These *exo*-butenolides were hydrogenated in the presence of triethylamine. Hydrogenation occurred with complete stereocontrol to give the corresponding butyrolactone **220** and reduction using lithium aluminium hydride produced the corresponding (*R*)-2-alkyl-1,4-butanediols **221**. The stereoselectivity results from delivery of hydrogen from the opposite side to the bulky C-5 group of the lactone **219**.



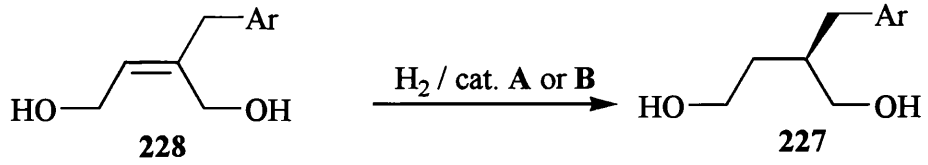
Scheme 5.3

Enantiomerically pure 2-substituted butane-1,4-diols can be used as precursors to 1,3-substituted pyrrolidines **222**.[110] Chiral pyrrolidines have been shown to be subunits of natural and unnatural products which exhibit interesting and diverse biological activities. The enantiopure norbornene sultam **223** was an effective chiral auxiliary to induce stereoselectivity when *N*-acylnorbornene sultams **224** were alkylated with α-bromoalkanoates. Lithium aluminium hydride reduction of the alkylated *N*-acylnorbornene sultams **225** produced the corresponding chiral 2-substituted butane-1,4-diols **226**. Treatment of the diols with tosyl chloride yielded the corresponding ditosylates which could be reacted with the relative amine to yield the chiral substituted pyrrolidines **222** (Scheme 5.4).

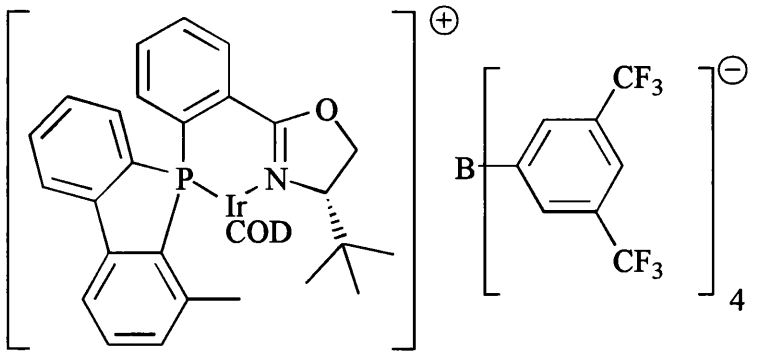


Scheme 5.4

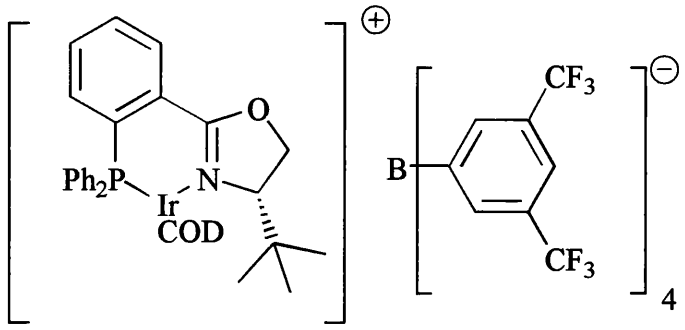
Kamlage *et al.* reported the synthesis of optically active aromatic 2-substituted butane-1,4-diols **227** via hydrogenation using chiral catalysts from aromatic 2-substituted butenediols **228**.[111] Various catalysts were used and Ir(I)-phosphinooxazoline catalysts **A** and **B** displayed the highest levels of stereoselectivity (58-82% ee) (Scheme 5.5).



Scheme 5.5



A

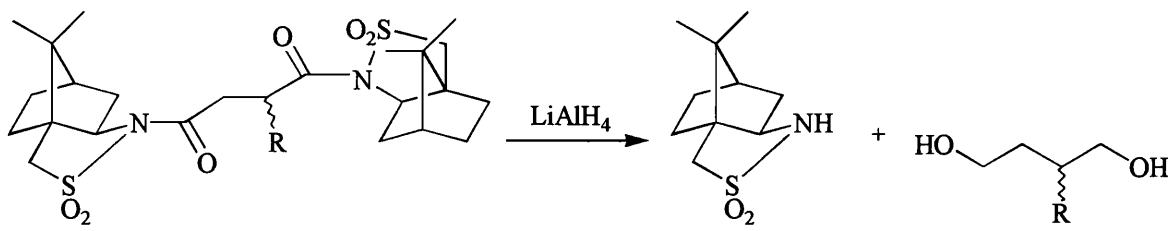


B

Our approach would provide a quick and efficient synthesis to both epimers of optically active 2-substituted butane-1,4-diols.

5.2 Synthesis of enantiomerically enriched 2-substituted butane-1,4-diols

In order to confirm the estimates for diastereomeric excesses obtained from the ^1H NMR spectra of the succinamide products from the conjugate addition of Grignard reagents with fumaramide **100**, the substituted succinamides were reduced with lithium aluminium hydride to produce the corresponding 2-substituted butane-1,4-diols **104** and camphorsultam **105**, which were separated by column chromatography (Scheme 5.6).



105 **104**

Scheme 5.6

The camphorsultam **105** was recovered in 90-95% yield and showed no loss of enantiomeric purity. The diols were isolated in moderate yields and the absolute configuration of diols **229, 230, 231** and **233** was determined to be (*R*) by comparison of the specific rotations with those reported in the literature (Table 5.1).

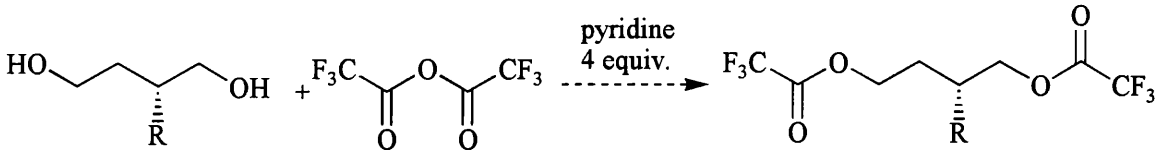
Table 5.1 Reduction of substituted succinamides yielding optically active 2-substituted butane-1,4-diols

Entry	2-substituted diol	Isolated yield (%)	Configuration[a]
1	Ethyl (**229**)	44	(*R*)[89]
2	Isopropyl (**230**)	43	(*R*)[109]
3	Propyl (**231**)	46	(*R*)[109]
4	Butyl (**232**)	56	
5	Cyclohexyl (**233**)	38	(*R*)[b]
6	Octyl (**234**)	79	
7	Benzyl (**235**)	75	
8	Isobutyl (**236**)	85	
9	Hexyl (**237**)	75	

[a]Compared with specific rotations reported in the literature.

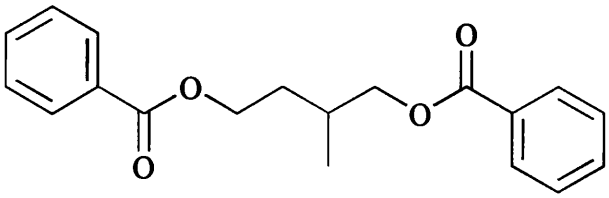
[b](*S*) previously reported with opposite sign.[112]

A method was required to determine the enantiomeric excess of the optically active 2-substituted butane-1,4-diols. From the literature there was no obvious method so we decided first to try chiral GC. Chiral GC can be used in the same way as chiral HPLC previously discussed. The columns are packed with a chiral stationary phase. It was found that the diols were not volatile enough for this technique. Attempts were made to trifluoroacetylate the diols in order to make the compounds more volatile and suitable for chiral GC (Scheme 5.7).



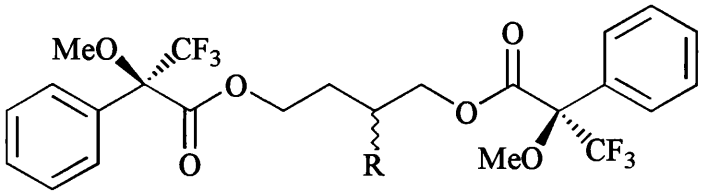
Scheme 5.7

A lot of time was spent on what appeared to be a straightforward reaction but we could never isolate the bis-trifluoroacetate, only a mixture of the mono- and bis-trifluoroacetate products. The mixture could not be separated as the mono- and bis- trifluoroacetylated compounds had the same R_f value. We then focused on synthesising the dibenzoate derivative and using chiral HPLC to determine the stereoselectivity.[107] This method was used by Feringa *et al.* although the chiral column used [Chiracel OB (Daicel)] was not available within our department. We did however hope that the dibenzoate might be resolved on similar columns that are available. The racemic 2-methylbutane-1,4-diol was converted into the dibenzoate **238** but could not be resolved on the chiral columns available.



238

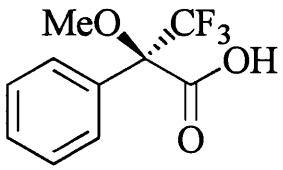
An NMR technique was attempted which involved making bis Mosher esters **239** of the diols and then using ^{19}F NMR spectroscopy to determine the enantiomeric excess of each mixture of diatereomers.



239

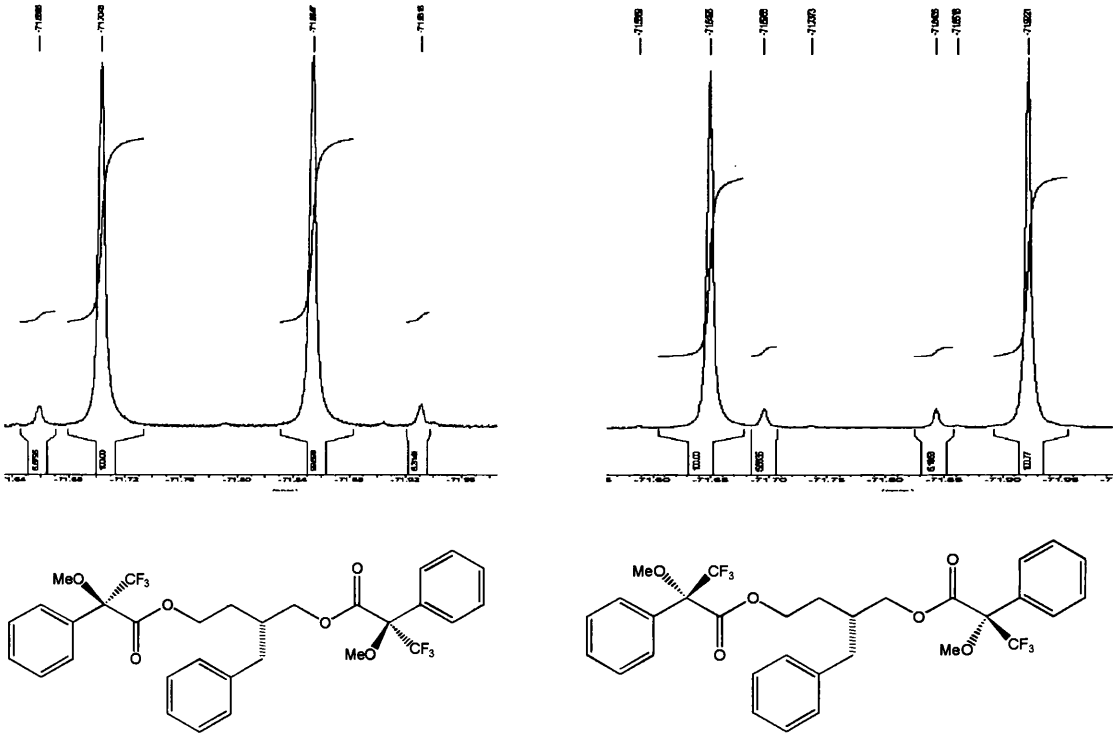
The presence of the CF_3 group would allow the ratio of diastereomers to be measured from integration of the two singlets in the ^{19}F NMR spectrum.

The use of α-methoxy-α-(trifluoromethyl)phenylacetic acid **240** (MTPA, Mosher's acid) as a reagent for determination of the enantiomeric excess of alcohols or amines was pioneered by Mosher.[113] This reagent is useful as it is resistant to racemization under reaction conditions of acid, base or extreme temperatures during preparation of derivatives. The presence of the trifluoromethyl group allows the use of ^{19}F NMR spectroscopy which produces fluorine signals that are simple and in uncongested regions. The disadvantage of using proton NMR spectra to determine enantiomeric excesses is that some proton signals can overlap other proton signals resulting in unreliable results.



R enantiomer **240**

Initially racemic 2-methylbutane-1,4-diol was esterified with both (*R*)- and (*S*)-MTPA but failed to produce diastereomeric mixtures observable by proton or fluorine NMR spectroscopy. It is proposed that the methyl substituent is too small to have an effect in the chemical environment of the two diastereomers. Esterification using both (*R*)- and (*S*)- MTPA with the rest of the enantiomerically enriched 2-substituted butane-1,4-diols produced diastereomeric MTPA diesters as shown in Figure 5.1 for 2*R*-benzylbutane-1,4-diol **235**.



RRR ***SRS***

Figure 5.1

When using the *R* enantiomer of Mosher's acid the major diastereomer produced has the *RRR* configuration with the minor diastereomer having the *RSR* configuration. Alternatively using the *S* enantiomer of Mosher's acid the major diastereomer has the *SRS* configuration with the minor being *SSS*. Each spectra displays four signals, two large

signals corresponding to the major diasteromer with two small signals corresponding to the minor diastereomer. By measuring the area of the major signals in relation to the area of the minor signals the diastereomeric excess could be quantified which corresponds to the enantiomeric excess of the starting enantiomerically pure 2-substituted diol.

The coupling of the MTPA acid with the diols was straight forward using EDCI (5 equiv.) as the coupling reagent together with a catalytic amount of DMAP (10%) to give the corresponding MTPA diester in good yield (Table 5.2).

Table 5.2 Synthesis of MTPA diesters and determination of diasteromeric excess

Entry	2-substituted diol	(*R*) –MTPA diester (% yield)	De (%)[a]	(*S*) –MTPA diester (% yield)	De (%)[a]	Average de (%)
1	Ethyl **229**	**238** (87)	70	**239** (77)	76	73
2	Isopropyl **230**	**240** (47)	28	**241** (78)	30	29
3	Propyl **231**	**242** (77)	46	**243** (82)	44	45
4	Butyl **232**	**244** (91)	56	**245** (77)	56	56
5	Cyclohexyl **233**	**246** (84)	33	**247** (92)	33	33
6	Octyl **234**	**248** (80)	56	**249** (82)	52	54
7	Benzyl **235**	**250** (92)	89	**251** (79)	90	90
8	Isobutyl **236**	**252** (66)	50	**253** (66)	49	50
9	Hexyl **237**	**254** (48)	61	**255** (82)	59	60

[a]Diastereomeric excesses were determined by analysis of the fluorine NMR spectra of the MTPA diester measured in $CDCl_3$.

Now that we had a good method for determining the enantiomeric excess of the 2-susbtituted butane-1,4-diols it allowed us to compare the different values of diastereomeric excesses obtained for each substituent using the chiral HPLC method and the ^1H NMR spectra of the mixture of succinamides (Table 5.3).

Table 5.3 Comparison of diastereomeric excess values obtained by three different methods

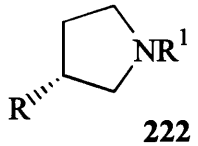
Entry	Substituent	De obtained from derivatives of 2-substituted succinic acids	De from ^{1}H NMR of succinamides	De from ^{19}F NMR of MTPA diesters of 2-substituted butane-1,4-diols
1	R = Ethyl	63	62	73
2	R = Isopropyl	0	32	29
3	R = Propyl	52	36	45
4	R = Butyl	72	54	56
5	R = Cyclohexyl	9	32	33
6	R = Octyl	90	52	54
7	R = Benzyl	92	N/A	90
8	R = Isobutyl	8	44	50
9	R = Hexyl	37	53	60

The table of results confirms that the determination of the diastereomeric excesses from the derivatives of 2-substituted succinic acids gives the least reliable results. The diastereomeric excesses obtained from the ^{1}H NMR spectra of the succinamides and from the fluorine NMR spectra of the MTPA diesters complement each other in most cases. The latter method is taken to be more accurate as it is the average of two independent measurements. This new method incorporating Mosher's acid to produce the diesters has proved very useful as a technique for the determination of the enantiomeric excess of enantiomerically enriched 2-substituted butane-1,4-diols. This technique avoids the requirement of a racemic sample of the diol as was required with the chiral HPLC analysis of the 2-substituted succinic acids. This technique should be applicable for other optically active diols.

5.3 Future Work

5.3.1 Asymmetric synthesis of novel 1,3-substituted pyrrolidines

An extension of this work could be to develop this methodology to the synthesis of optically active 1,3-substituted pyrrolidines **222**.



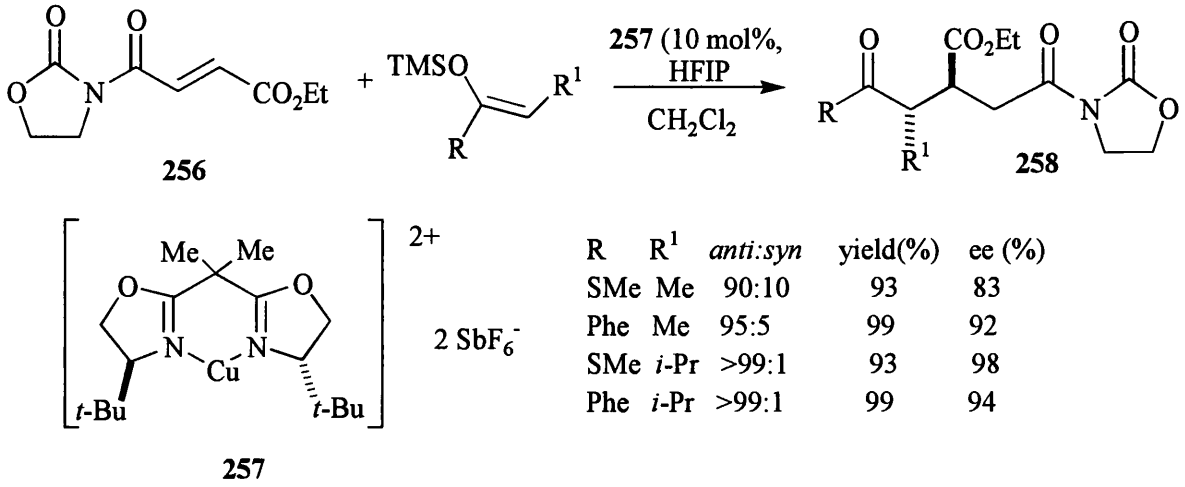
222

The chiral 2-substituted butane-1,4-diols produced by the conjugate addition of a Grignard reagent on fumaramide **100** followed by reduction can be converted to the corresponding ditosylates. The ditosylates would be reacted with an amine to form the desired optically active 1,3-substituted pyrrolidine **222**. These novel pyrrolidines could be assessed for biological activity.

6. Diastereoselective conjugate additions of Grignard reagents to differentially functionalised fumarates

6.1 Background

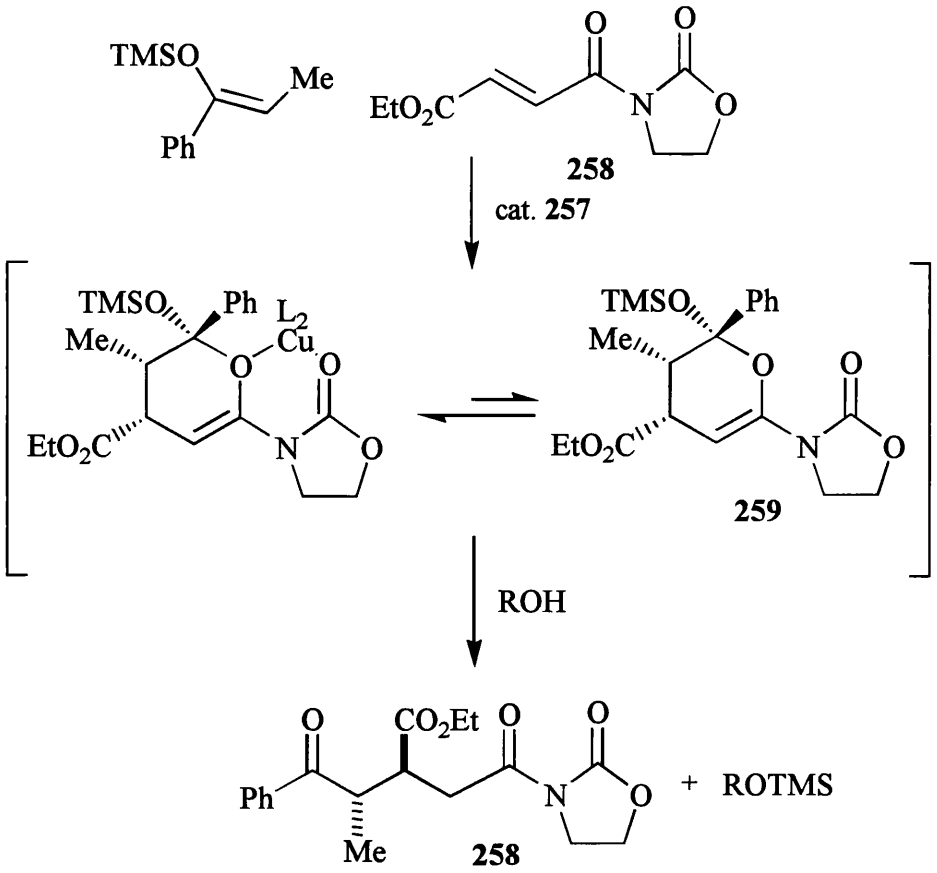
Differentially protected fumarates have been used as substrates to synthesise enantiomerically enriched succinamides. Evans *et al.* reported the stereoselective conjugate addition of enol silanes to oxazolidinone fumarates **256** using a chiral Cu(II)bis(oxazoline) catalyst **257** (Scheme 6.1).[114]



R	R^1	*anti:syn*	yield(%)	ee (%)
SMe	Me	90:10	93	83
Phe	Me	95:5	99	92
SMe	*i*-Pr	>99:1	93	98
Phe	*i*-Pr	>99:1	99	94

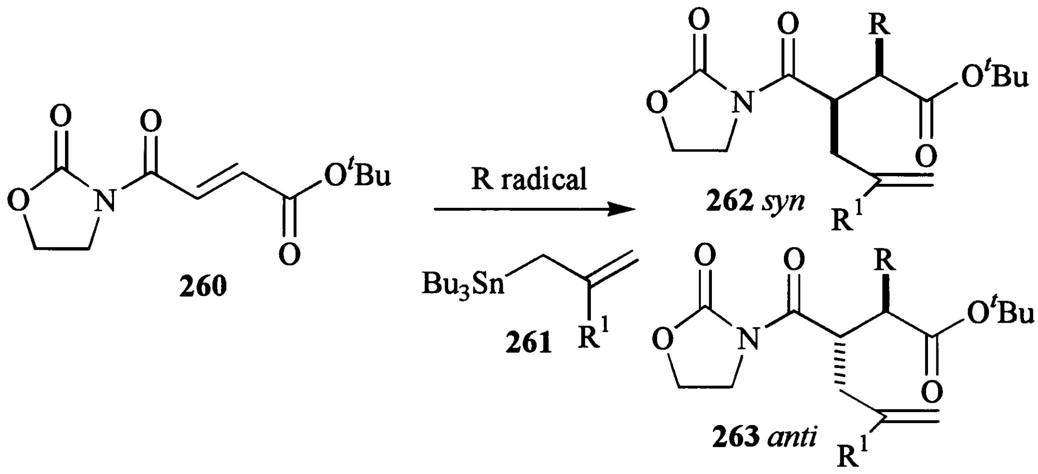
Scheme 6.1

The use of (*Z*)-enol silanes gave *syn*-adducts whereas using (*E*)-enol silanes gave *anti*-adducts. The use of hexafluoro-2-propanol (HFIP) greatly enhanced the rate of reaction without affecting the stereochemical outcome of the reaction. It is believed that the alcohol acts as the silicon group acceptor, as the product **258** forms the dihydropyran intermediate **259** transfers the silicon group to the alcohol (Scheme 6.2). The presence of intermediate **259** suggests that the reaction could be thought of as a hetero Diels-Alder reaction.



Scheme 6.2

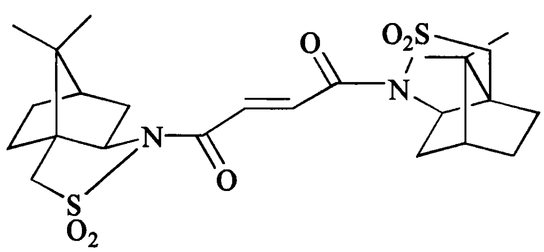
Sibi *et al.* used a similar fumarate system to synthesise disubstituted succinates with high levels of diastereoselectivity.[115] The differentially protected fumarate **260** was shown to undergo regio- and stereo-controlled radical additions with the radical intermediate being trapped with a variety of allystannes **261** to provide the corresponding *syn* **262** and *anti* **263** products (Scheme 6.3). The effect of Lewis acids on the radical addition/trapping was investigated and it was found that the lanthanide triflates of yttrium and samarium produced the best chemical yields. The stereochemistry of the reactions always favoured the *anti*-product in a >99:1 ratio. Various different radical species were shown to give good yields with the exception of the adamantyl radical. When the R group of the allyl stannane was changed from H to CH_3 the yield decreased only marginally, however when R = CH_2OAc the reaction gave a low yield of product (28%).



Scheme 6.3

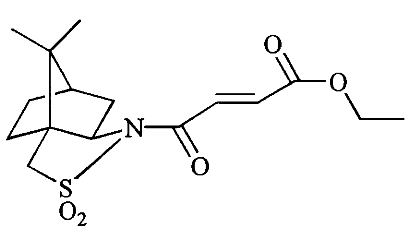
6.2 Conjugate addition of Grignard reagents to two differentially protected fumarates

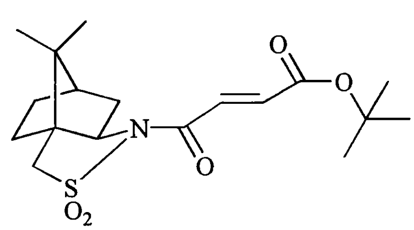
The initial aim of the project was to investigate the diastereomeric conjugate addition of Grignard reagents to a fumaramide system **100** containing two identical chiral auxiliaries.



100

For comparative purposes we decided to apply the same methodology to two differentially protected fumarates **264** and **265**.

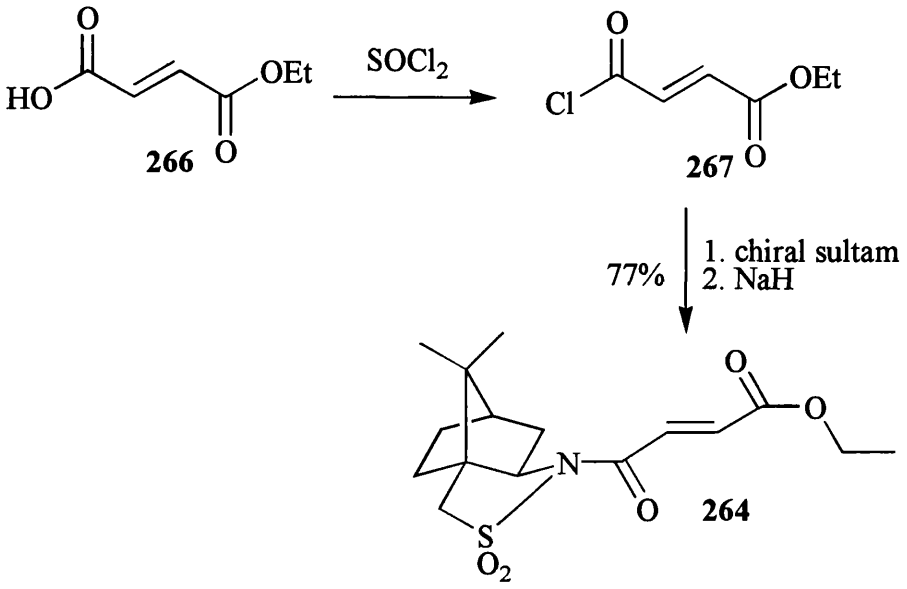




264 **265**

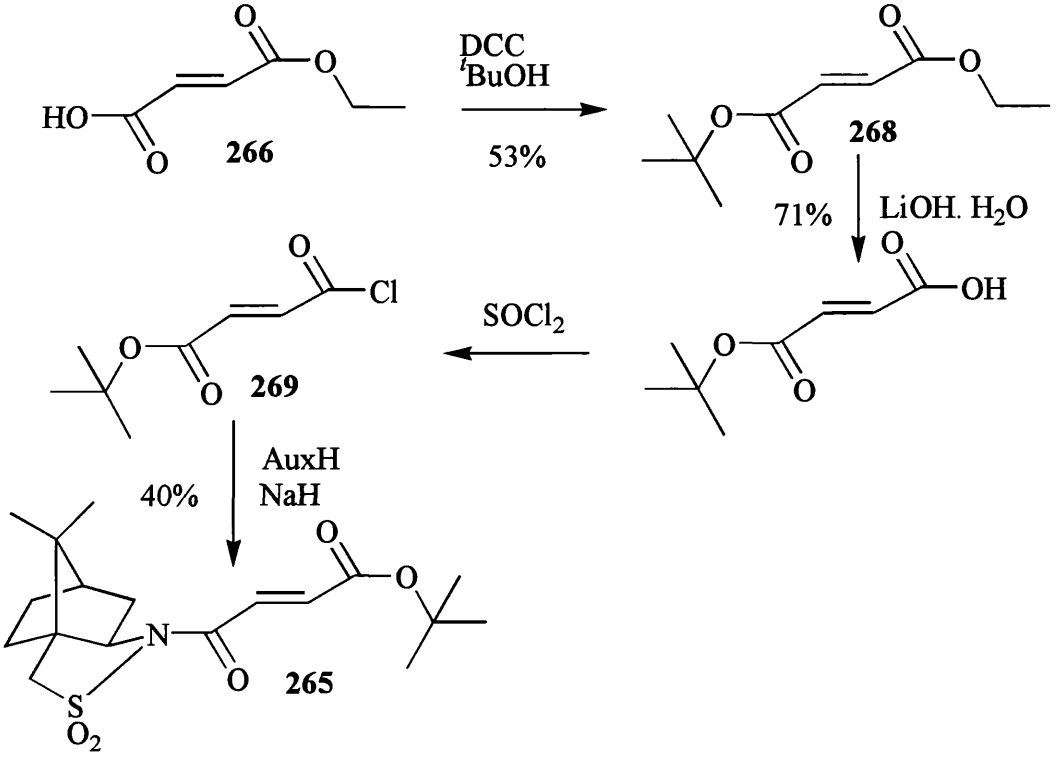
Fumarate **264** is easily accessible from commercially available fumaric acid monoethyl ester **266**.[116] The fumaric acid was converted to the fumaroyl chloride **267** using

thionyl chloride and then coupled to Oppolzer's sultam to give fumarate **264** in 77% yield (Scheme 6.4).



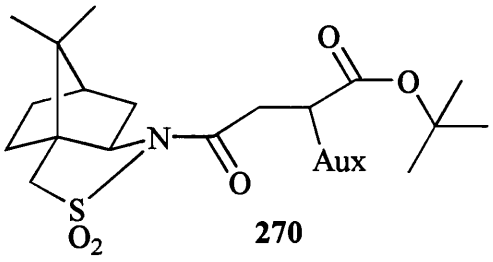
Scheme 6.4

In order to study the effect of using a sterically more hindered ester, fumarate **265** was prepared from fumaric acid monoethyl ester **266**. t-Butanol was coupled to the carboxylic acid using DCC. The ethyl ester **268** was selectively hydrolysed with lithium hydroxide and converted into the fumaroyl chloride **269** followed by coupling to Oppolzer's sultam (Scheme 6.5).

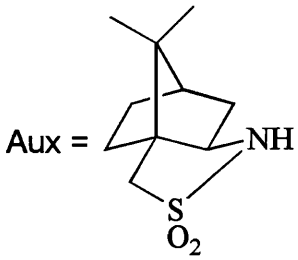


Scheme 6.5

The formation of the fumarate **265** from the coupling of Oppolzer's sultam with the acid chloride **269** was low yielding due to a side reaction forming the product **270** from conjugate addition of the sultam on **260**. The only way this reaction could be minimised was by monitoring the reaction by tlc and when the appearance of the spot relating to **270** was visible the reaction was worked up.



270



Diastereomeric conjugate additions were carried out on the protected fumarate **264** using a series of Grignard reagents. Diastereomeric excesses could not be determined from proton NMR spectra of the reaction mixtures. The selectivity of the Grignard reagent to add exclusively in a 1,4-manner with **264** was not observed and a mixture of 1,2-addition products and 1,4-addition products could be identified from the proton NMR spectra. After column chromatography of each reaction mixture the 1,4-addition product was always the major product isolated. In order to determine the stereoselectivity of the conjugate addition the succinates were reduced to the corresponding diols using lithium aluminium hydride. This allowed the assignment of the new stereocentre by comparing the optical rotations obtained with those in the literature. All the enantiomerically enriched 2-substituted butane-1,4-diols displayed the *R* configuration. This is the same stereoselectivity as previously shown with **100** resulting from attack from the *re*-face. The diols were then converted into both (*R*)-and (*S*)-Mosher diesters and analysed by fluorine NMR spectroscopy to determine the diastereomeric excesses (Table 6.1). The fumarate **264** is not as good at inducing stereoselectivity as the fumaramide **100**. It was expected that fumarate **265** would produce better selectivity than **264** both from a regio- and stereo-chemical aspect due to the bulkier tertiary butyl protecting group.

Table 6.1 Conjugate addition to fumarate 264 followed by reduction to 2-substituted diols

Entry	2-substituted fumarate	Isolated Yield (%)	Enantiomeric excess[a]
1	R = Ethyl **271**	79	50 (*R*)[89]
2	R = Benzyl **272**	41	63
3	R = Isoproyl **273**	37	9 (*R*)[109]
4	R = Butyl **274**	52	59

[a]Enantiomeric excesses were determined by synthesis of both (*R*)- and (*S*)-Mosher's diesters of each diol and were analysed by ^{19}F NMR spectra.

The reaction of fumarate **265** with Grignard reagents displayed only conjugate addition products. Once again diastereomeric excesses could not be determined from proton NMR spectra of the reaction mixtures. Therefore the diastereomeric excess was determined from the bis-Mosher diester of each diol (Table 6.2). The stereoselectivity displayed using fumarate **265** was comparable to that observed for fumarate **264** (Tables 6.1 and 6.2).

Table 6.2 Conjugate addition to fumarate 265 followed by reduction to 2-substituted diols

Entry	2-substituted fumarate	Isolated Yield (%)	Enantiomeric excess[a]
1	R = Ethyl **275**	67	55 (*R*)[89]
2	R = Benzyl **276**	75	56
3	R = Isoproyl **277**	73	6 (*R*)[109]
4	R = Butyl **278**	75	68

[a]Enantiomeric excesses were determined by synthesis of both (*R*)- and (*S*)-Mosher's diesters of each diol and were analysed by ^{19}F NMR spectra.

The stereoselectivity obtained with fumarates **264** and **265** was not as good as the stereoselectivity observed using fumaramide **100**. The presence of the two auxiliaries is

clearly necessary for better stereoselective conjugate addition due to the bulk of the camphorsultam. It was surprising that the tertiary butyl fumarate **265** was only marginally better at inducing stereoselectivity in the conjugate addition reaction than the ethyl fumarate **264**.

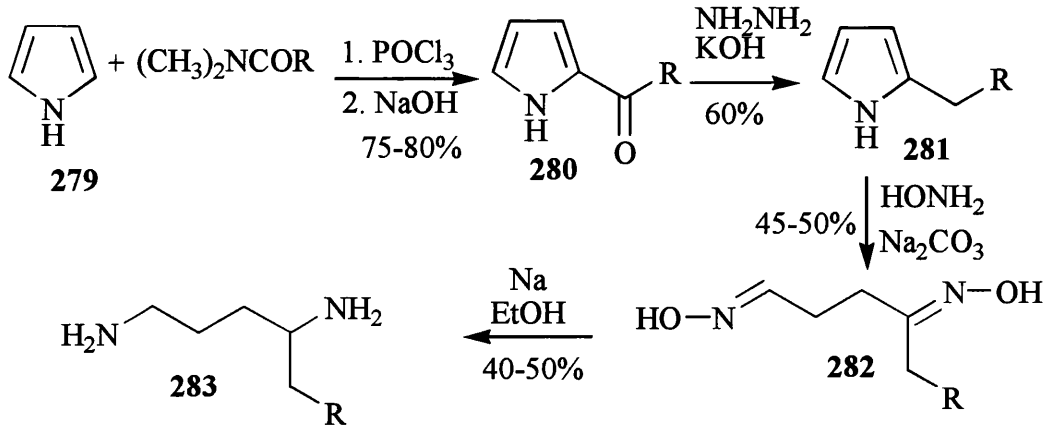
7. Synthesis and enzymatic studies of optically active 2-substituted putrescines

7.1 Background

The work carried out by Santaniello *et al.* discussed in Chapter Three described how the enantiomers of 2-methylputrescine could be distinguished by PKAO, but not by PSAO.[78] It was our aim to synthesise a series of 2-substituted putrescines in an attempt to identify potential substrates for PSAO. This would allow the study of the outcome of the DAO catalysed oxidation of these enantiomerically enriched 2-substituted putrescines. This should give us valuable insight into the selectivity of the enzyme for different substrates.

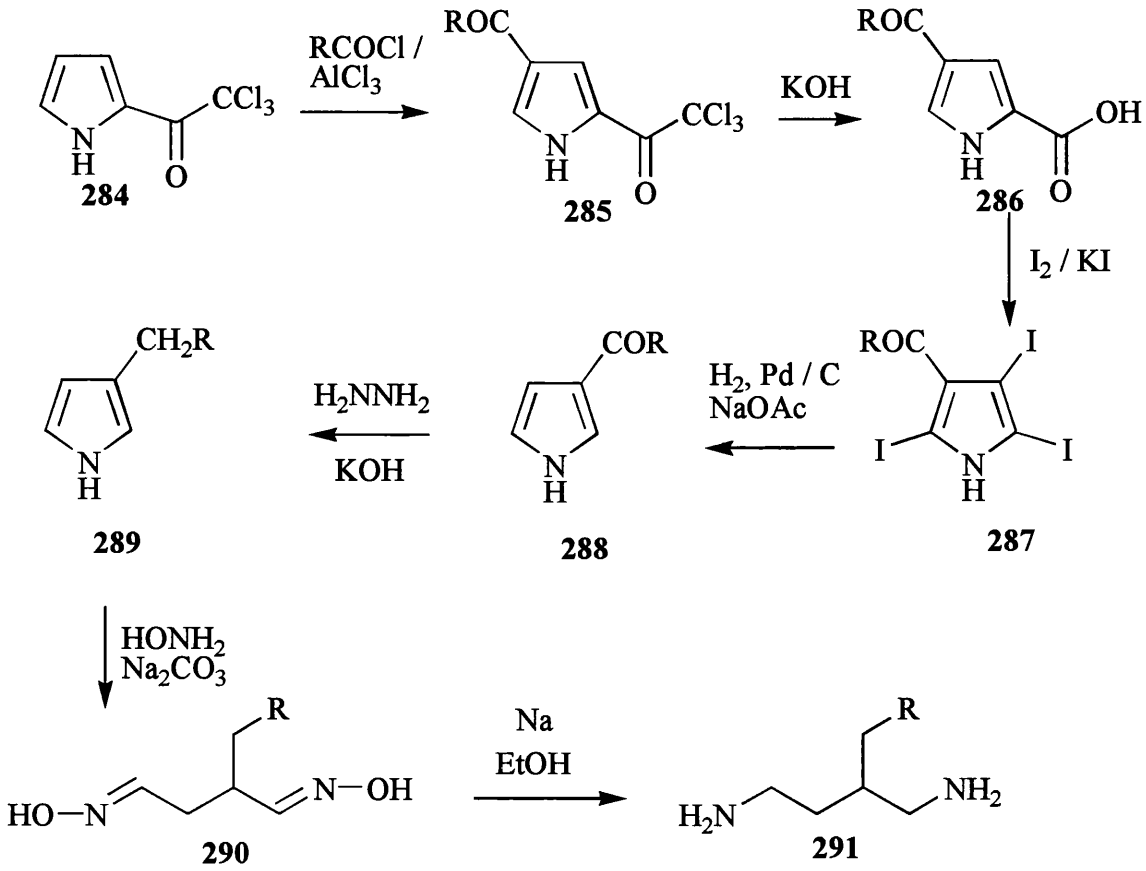
There have been no literature reports of a general synthesis to optically pure 2-substituted putrescines (1,4-diaminoalkanes), however there have been a few papers published reporting the synthesis of racemic 2-subtituted putrescines.

Frydman *et al.* published the synthesis to 1-substituted putrescines prepared from pyrroles.[117] Pyrroles **279** are easily substituted and are useful synthons for substituted putrescines (Scheme 7.1). Acylation of pyrrole was facilitated under Vilsmeier conditions and the acylpyrroles **280** were reduced to the 2-alkylpyrroles **281** using potassium hydroxide and hydrazine. Ring opening of the 2-alkylpyrroles **281** was achieved by heating with hydroxylamine hydrochloride in the presence of sodium bicarbonate yielding the corresponding dioximes **282**. The 1-substituted putrescines **283** were prepared by reduction of the dioximes **282** using sodium in ethanol at reflux. A number of alkyl substituted putrescines were prepared in this way ranging from R = H to R = *n*-$C_{11}H_{23}$.



Scheme 7.1

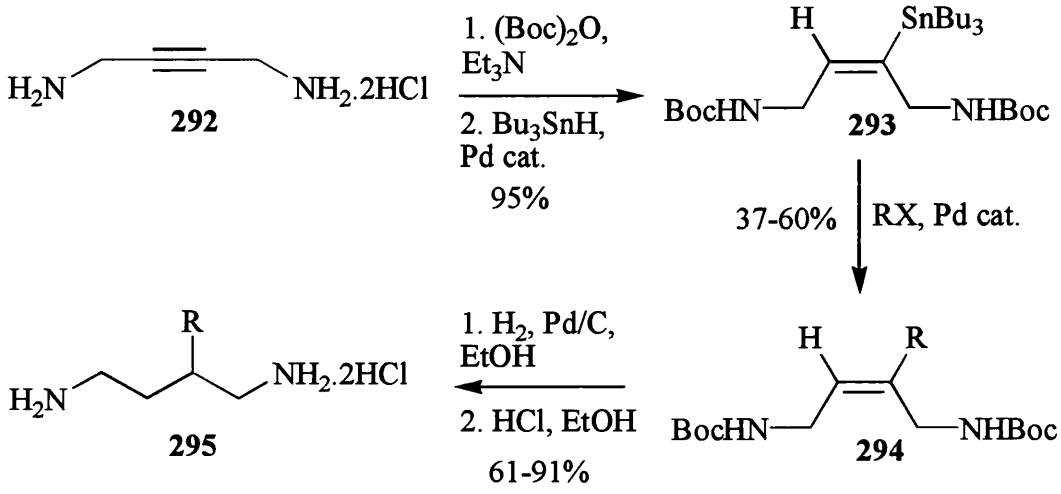
This methodology was extended to the synthesis of 2-substituted putrescines from 3-alkylpyrroles.[118] The synthesis of 3-alkylpyrroles is not as straightforward as that previous shown for 2-alkylpyrroles. The use of Vilsmeier reaction conditions or Friedel-Crafts conditions produces the corresponding 2-substituted pyrrole. An indirect method is usually required to produce 3-substituted pyrroles. The preparation of 2-(trichloroacetyl)pyrrole **284** made it possible under Freidel Crafts acylation conditions to produce 4-acyl-2-(trichloroacetyl)pyrroles **285**. When treated with potassium hydroxide the corresponding 2-pyrrolecarboxylic acids **286** were prepared. Decarboxylation of **286** was achieved by treating with iodine to give the triiodoacylpyrroles **287**. Hydrogenation of **287** using 10% palladium on charcoal gave the 3-acylpyrroles **288**. The 3-acylpyrroles **288** were reduced using potassium hydroxide and hydrazine to give the 3-alkylpyrroles **289** which were ring opened to the dioximes **290** and reduced to produce the corresponding 2-substituted putrescines **291** (Scheme 7.2).



Scheme 7.2

A different approach to 2-subtituted putrescines was reported by Carboni *et al.* in which both alkyl and aryl substituted putrescines were prepared in three steps.[119] The synthesis started from 1,4-diaminobut-2-yne **292** which was protected as the *N*-di-*tert*-

butyloxycarbonyl derivative. A hydrostannylation reaction using tributylstannane and a catalytic amount of palladium tetrakis(triphenylphosphine) produced the corresponding vinylstannane **293**. Cross-coupling of the vinylstannane **293** with a range of electrophiles in the presence of a palladium catalyst produced the 2-substituted-1,4-di-*tert*-butyloxycarbonylaminobut-2-enes **294**. Compounds **294** were hydrogenated using palladium on carbon (10%) and deprotected to give the corresponding 2-alkyl- and 2-aryl-putrescine dihydrochlorides **295** (Scheme 7.3).



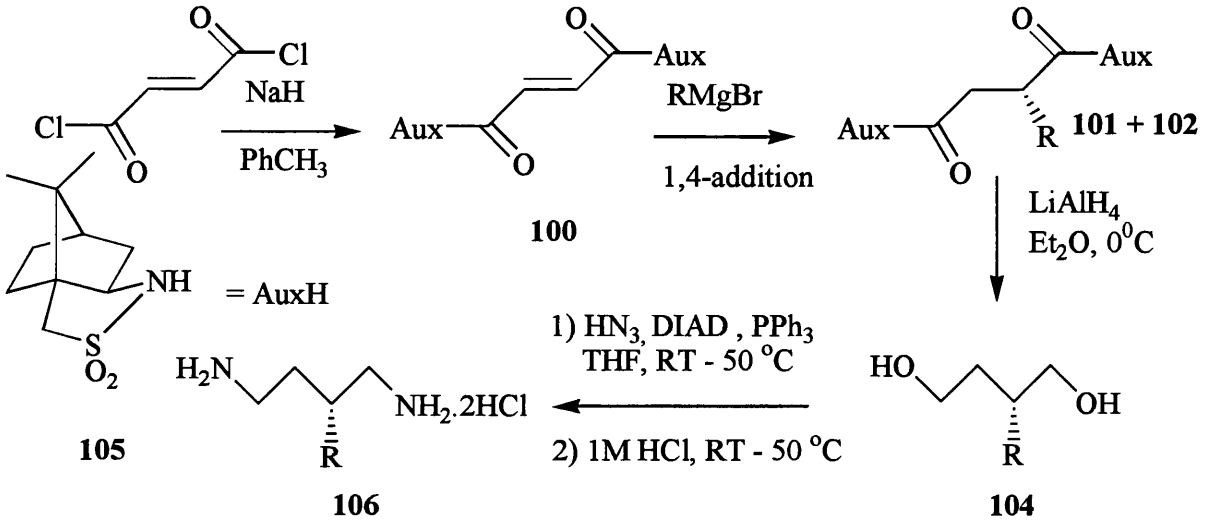
R = *n*-C_3H_7, $CH_2CH(CH_3)CO_2Et$, benzyl, 4-*tert*-butylcyclohexyl, phenyl and 3-pyridyl

Scheme 7.3

It was our aim to devise a new route to both racemic and optically pure 2-substituted putrescines in an attempt to identify potential substrates for PSAO and investigate the regio- and stereo-selectivity of the enzyme.

7.2 Synthesis of Optically Active 2-Substituted Putrescines

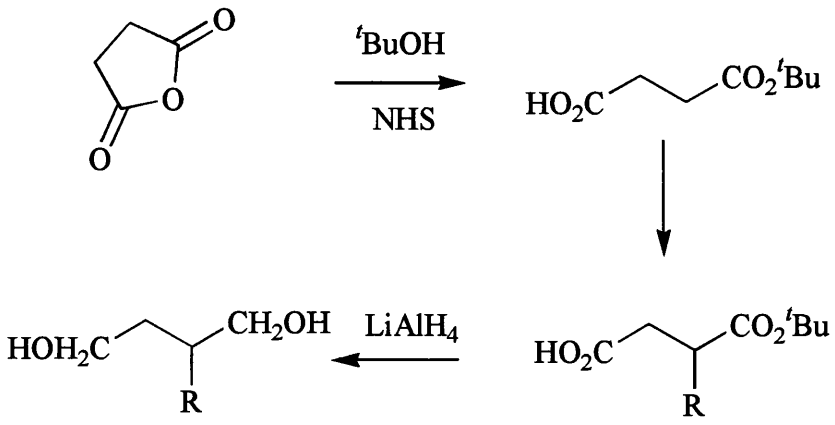
Our synthetic approach to synthesise enantiomerically pure 2-substituted putrescines **106** is shown in **Scheme 7.4**.



Scheme 7.4

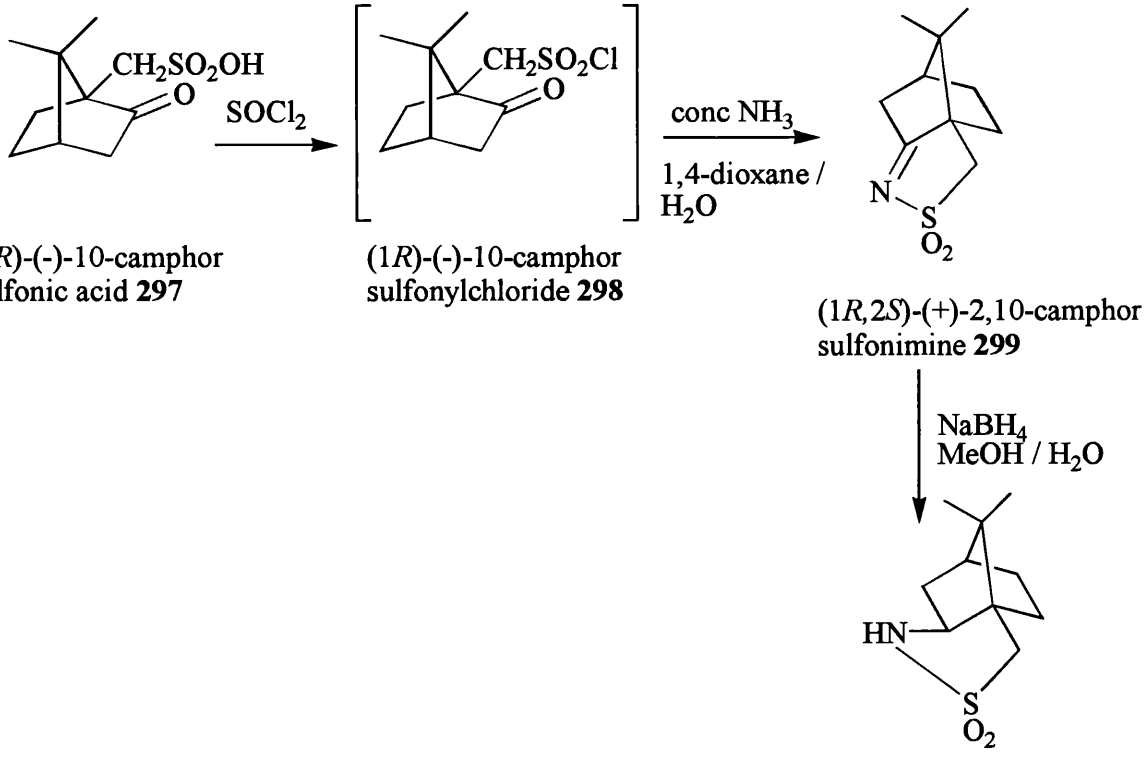
This route is based on the previous methodology developed in this work using Grignard reagents to add to fumaramide **100** stereoselectively in a conjugate manner. Removal of the chiral auxiliaries using lithium aluminium hydride produced the corresponding enantiomerically enriched 2-substituted butane-1,4-diols **104**. The enantiomeric excess of these diols could be improved to >95% by separation of the major and minor diastereomers of the adducts **101** and **102** using column chromatography or recrystallisation. The enantiomeric excesses of the corresponding enantiomerically pure diols were determined by using fluorine NMR spectroscopy of the Mosher diesters. The conversion of the diols into the diamines **106** was achieved using a one-pot conversion of alcohols into amines devised by Golding *et al.*[120] It involves a Mitsunobu reaction using hydrazoic acid followed by an *in situ* Staudinger reaction.[121,122]

For purposes of the enzyme studies we also required racemic 2-substituted putrescines. We proposed to synthesise the racemic diamines from 2-substituted succinic acids prepared previously (Chapter 4). These can be converted into the corresponding diols by a borane reduction and subsequently converted into the diamines (Scheme 7.5).



Scheme 7.5

Use of Oppolzer's auxiliary **105** [(1*S*,2*R*)-(-)-2,10-camphorsultam] shown in Scheme 7.4 allows access to the (*R*)-enantiomer of the 2-substituted diol. Alternatively using the other enantiomer (1*R*,2*S*)-(+)-2,10-camphorsultam **296** of the auxiliary allows access to the (*S*)-enantiomer of the 2-substituted diol. This enantiomer of Oppolzer's auxiliary was synthesised using the same synthetic route previously used (Scheme 7.6).



(1*R*)-(-)-10-camphor sulfonic acid **297**

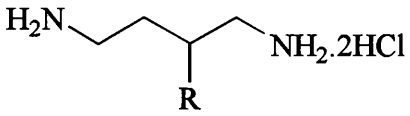
(1*R*)-(-)-10-camphor sulfonylchloride **298**

(1*R*,2*S*)-(+)-2,10-camphor sulfonimine **299**

(1*R*,2*S*)-(+)-2,10-camphorsultam **296**

Scheme 7.6

Initially we selected two alkyl substituted and two aromatic substituted putrescines to synthesise in racemic form together with the corresponding enantiomers (Figure 7.1).

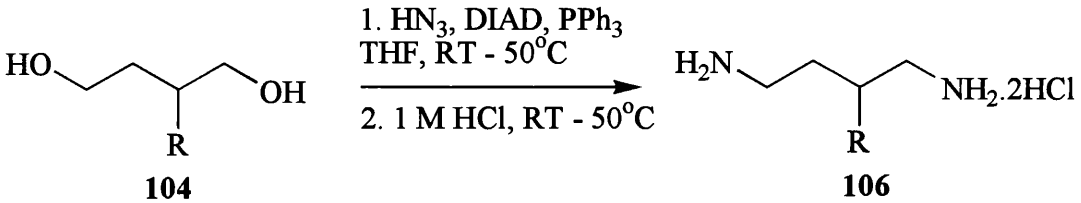


R = rac, *R* and *S* Me
R = rac, *R* and *S* Et
R = rac, *R* and *S* Ph
R = rac, *R* and *S* Bn

Figure 7.1

The starting 2-methyl and 2-phenyl substituted succinic acids were commercially available in racemic and enantiomerically pure form. The optically pure methyl and phenyl substituted putrescines could not be prepared by our stereoselective method. As previously discussed the methyl and phenyl Grignard reagents added in a 1,2-addition manner to fumaramide **100**. It was proposed that we would prepare the optically pure ethyl and benzyl substituted putrescines using the diastereoselective conjugate addition of Grignard reagents to fumaramide **100**.

The reaction in the synthetic route which concerned us the most was the conversion of the diols into the diamines (Scheme 7.7). This transformation was carried out previously in the group with a low yield of product (29%). We were optimistic we could produce the desired products in higher yields.



104 **106**

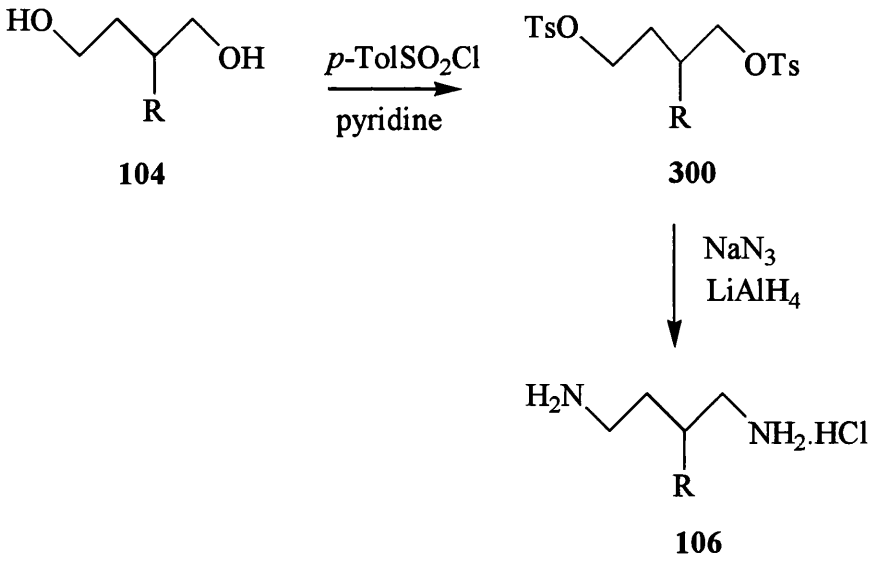
Scheme 7.7

The transformation involves conversion of the diol **104** into the corresponding diazide. The diazide formed is then reduced *in situ* by triphenylphosphine in a reaction known as the Staudinger reaction to the diamine which on workup yields the diammonium dihydrochloride salt **106**. The Mitsunobu reaction is a method of converting the hydroxyl group into an electrophile using phosphorus and then a S_N2 displacement with a

nucleophile can occur. Triphenylphosphine is used in the Mitsunobu reaction but is also the reducing agent in the Staudinger reaction so it plays a dual role in the above reaction.

A number of attempts to convert **104** to **106** were made, but they were very low yielding. There were a number of problems. One possible problem was the synthesis of a cyclic ether by an intramolecular cyclization of the activated alcohols. The two examples shown in the literature which involve a diol being converted into a diamine contained either an alkene bond or an alkyne bond in the aliphatic chain which enforces a rigidity preventing cyclization.[120] Another problem of this route is that the diamines produced are extremely volatile so they are converted into their diamine dihydrochloride salts. This however prevents purification by chromatography. The drawback of the Mitsunobu reaction is the requirement to remove excess triphenylphosphine, triphenylphosphine complexes and the by-product triphenylphosphine oxide by chromatography. The major impurity with the diamine dihydrochloride salts is triphenylphosphine oxide, which makes purification difficult. This problem can be addressed by using commercially available polymer-bound triphenylphosphine.[123] The triphenylphosphine impurities are now polymer-bound and can be removed by filtration. As the triphenylphosphine is on a solid support this can reduce its reactivity due a sterically less accessible reactive centre. Attempts to counter the lower reactivity could be to use more equivalents of the reagent but as the polymer supported reagent is expensive this may not be desirable. It was also questionable if the polymer bound triphenylphosphine would reduce the azide functionality successfully in the Staudinger reaction. Polymer bound triphenylphosphine proved successful in removal of the triphenylphosphine by-products; however the yields were still low.

In order to synthesise these diamines in good yields another synthetic approach was attempted. This involves the conversion of the diols into the sulfonate diesters **300**, then substitution by sodium azide. The sulfonate groups are very good leaving groups and can be easily displaced by different nucleophiles. The diazides are directly reduced to the diamines using lithium aluminium hydride (Scheme 7.8). This method has previously been applied successfully to 2-alkyl-1,3-propanediols.[124] This method worked reasonably well with the ditosylates synthesised in 32-73% yield. The subsequent nucleophilic substitution with sodium azide yielded the diazides in 52-95% yield, however conversion of the azides into the diamines was much more problematic (Table 7.1).



104 **300** **106**

Scheme 7.8

The diamine dihydrochloride salts **326**, **328** and **329** were very hygroscopic and difficult to purify and handle. The benzyl substituted putrescines could not be isolated. The more stable of the 2-substituted putrescine salts **325**, **327** and **330** were tested as substrates for the enzyme PSAO.

Table 7.1 Synthesis of 2-substituted putrescines

Substituent	Diol (% yield)	Ditosylate (% yield)	Diazide (% yield)	Substituted Putrescine (HCl salt) (% yield)
rac-Methyl	**301** (85)	**309** (39)[a]	**317** (95)	**325** (40)
R-Methyl	**302** (75)	**310** (26)[a]	**318** (55)	**326** (51)[b]
S-Methyl	**303** (95)	**311** (51)	**319** (52)	**327** (29)
rac-Ethyl	**304** (81)	**312** (73)	**320** (81)	**328** (66)[b]
R-Ethyl	**305** (58)	**313** (65)	**321** (65)	extremely hygroscopic
S-Ethyl	**306** (62)	**314** (61)	**322** (53)	**329** (49)[b]
rac-Phenyl	**307** (79)	**315** (32)	**323** (74)	**330** (35)
rac-Benzyl	**308** (58)	**316** (38)	**324** (53)	extremely hygroscopic

[a]Synthesised as diphenylsulfonyl diester.

[b]Found to be hygroscopic.

7.3 Enzymatic studies

The diamines produced were examined as substrates of PSAO. Kinetic data was obtained through calculations of K_M and V_{max} using the putrescines as substrates in an assay with PSAO.

PSAO is an enzyme, which is a biological catalyst. Catalysts increase the rate of chemical reactions but are chemically unchanged when the reaction is complete. A distinctive feature of enzyme catalysed reactions is that their reaction rates V have a saturation point known as V_{max}. The reaction rate is first order for low substrate concentrations [S] although as the concentration of the substrate increases reaction rate reaches a maximum known as V_{max} (Figure 7.2).

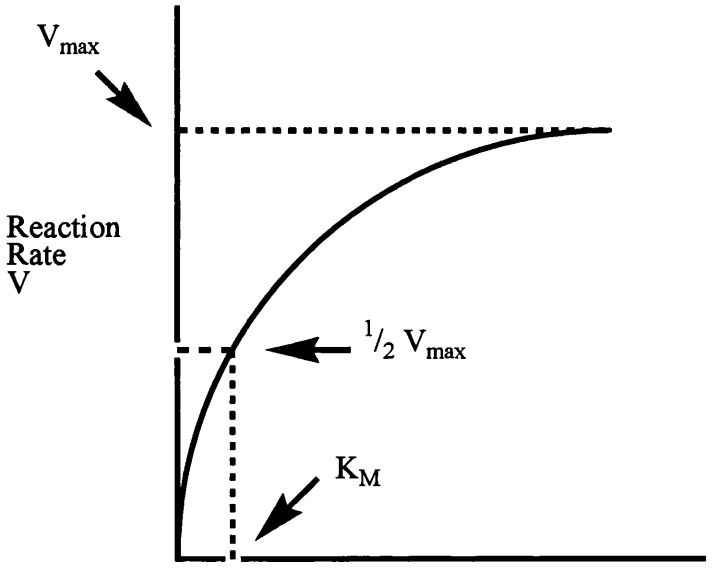


Figure 7.2

In 1913 Michaelis and Menten pointed out that these observations can be explained with the mechanism (Scheme 7.9).[125]

$$E + S \underset{K_2}{\overset{K_1}{\rightleftharpoons}} ES \xrightarrow{K_3} E + P$$

Scheme 7.9

The enzyme E and substrate S combine to give an enzyme substrate complex, ES. This complex can dissociate and form the starting materials or can release the products and enzyme. The Michaelis–Menten equation has been derived to explain enzyme kinetics and introduces V_{max} and K_M (Eq. 7.1). K_M is the concentration of substrate that gives a reaction rate half its maximal value.

$$V = \frac{V_{max}[S]}{K_M + [S]}$$

Eq. 7.1

A graph of the Michaelis–Menten equation is difficult to use for determination of V_{max} and K_M as it is curved. It approaches the maximum point slowly and attempts to find three consistent points to determine the V_{max} are difficult. As a result of the line being curved values recorded for low [S] cannot be extrapolated. Other methods were sought and it was found that the best sets of data to work with were those with a linear relationship known as a linear transform. In 1934 Lineweaver and Burke produced a linear relationship by inverting the Michaelis–Menten equation (Eq. 7.2). This relationship corresponded to the equation $y = mx + c$.

$$\frac{1}{V} = \frac{K_M}{V_{max}}\left(\frac{1}{[S]}\right) + \frac{1}{V_{max}}$$

Eq. 7.2

This produces a straight line if 1/V is plotted against 1/[S] (Figure 7.3)

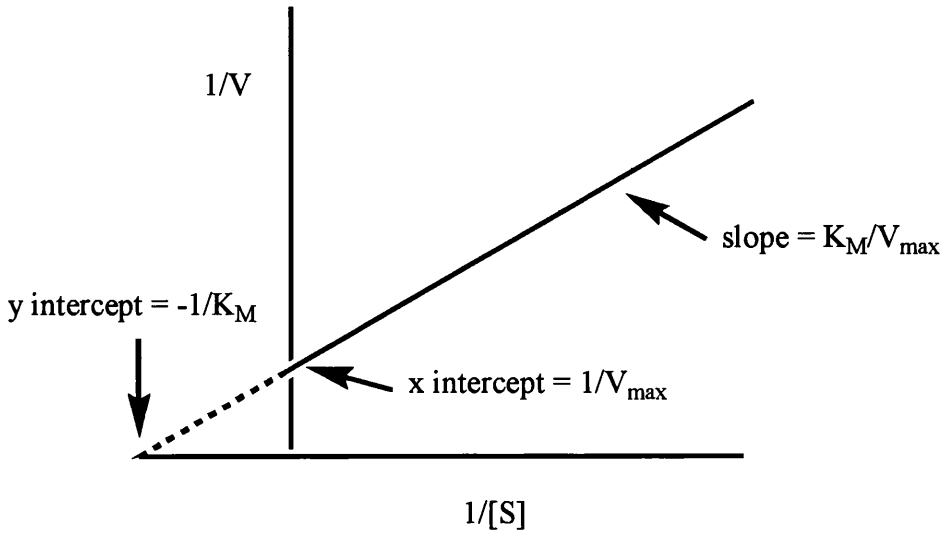


Figure 7.3

The intercept of the extrapolated straight line with the horizontal axis is used to obtain the Michaelis constant, K_M. The intercept with the vertical axis is used to determine V_{max}.[126] The values obtained from the Lineweaver-Burke equation were criticised as being unreliable as the measurements are recorded at low [S] values due to the reciprocal being taken. The smaller and more error prone experimental values now become the largest in the plot, which are the least accurate. Another method for determination of K_M and V_{max} was derived by Eadie and Hofstee. The principle of this is that Lineweaver–Burke equation is multiplied by $V.V_{max}$ (Eq. 7.3):

$$V.V_{max}\left(\frac{1}{V}\right)=\left\{\left(\frac{K_M}{V_{max}}\right)\left(\frac{1}{[S]}\right)\right\}V.V_{max}+\left(\frac{1}{V_{max}}\right)V.V_{max}$$

$$V = -K_M\left(\frac{V}{[S]}\right)+ V_{max}$$

Eq. 7.3

A graph is obtained by plotting V against V/[S] (Figure 7.4).

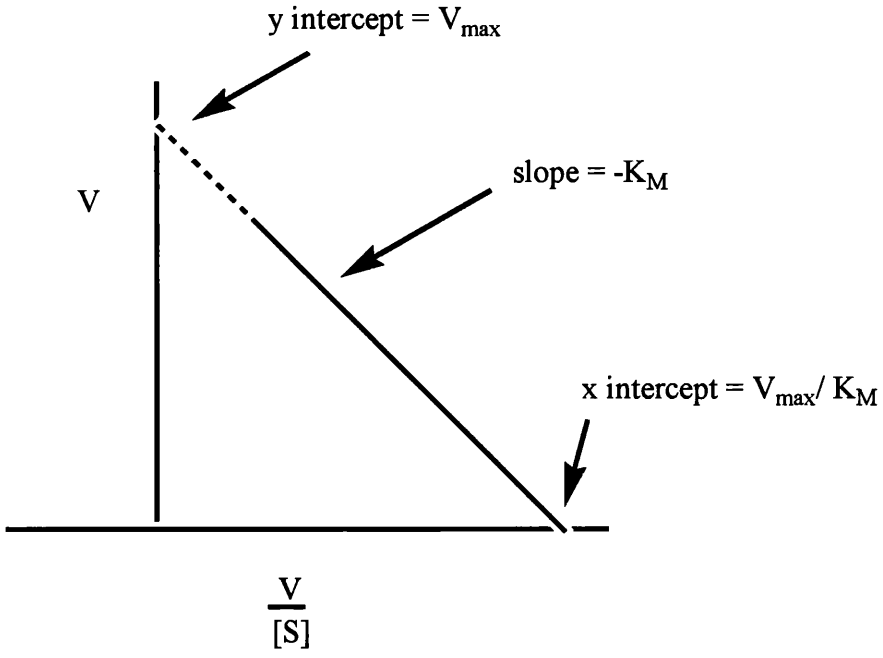


Figure 7.4

V_{max} is obtained from the intercept on the vertical axis and K_M is obtained from the gradient taking the opposite sign. The advantage of this method is that the value of K_M is

derived directly from the slope. However when data are scattered as a result of errors intercepts can be inaccurate. Due to the substrate concentration being expressed in reciprocal form the Eadie-Hofstee method has the same drawback as the Lineweaver-Burk plot.

Another linear method is known as the Woolf Hanes plot. This method avoids taking reciprocal concentrations and is the preferred method for statistical correctness of data analysis. The x-axis is [S] and the y-axis is [S]/V. The gradient is $1/V_{max}$ and the x intercept is K_M/V_{max}, (Figure 7.5).

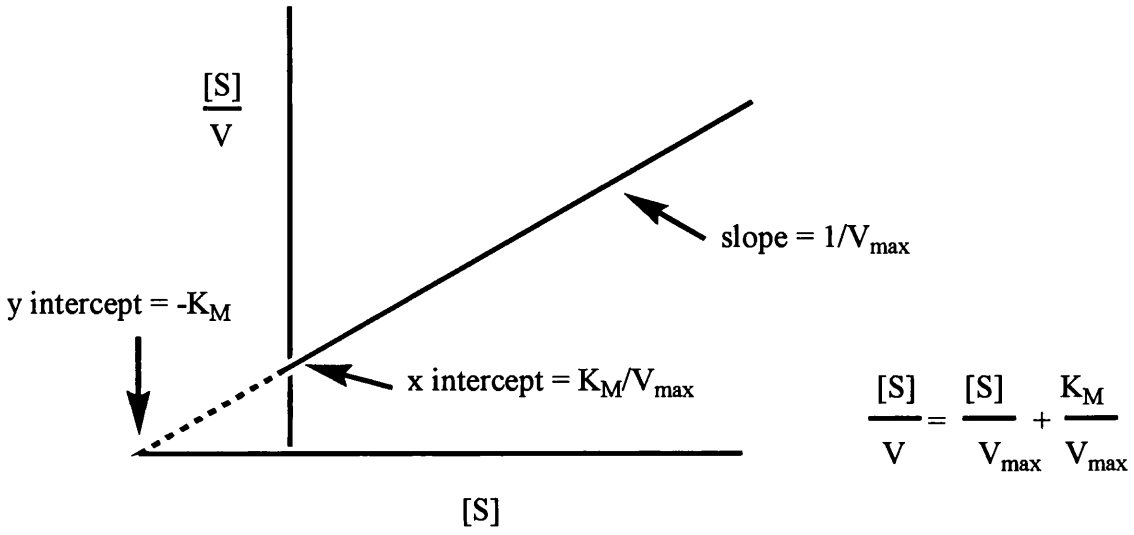


Figure 7.5

7.4 Kinetic Data

Three of the 2-substituted putrescines produced were tested as substrates in an assay with PSAO with putrescine as a reference. Kinetic data were obtained through calculations of K_M and V_{max}. K_M is the concentration of substrate that gives a reaction rate half its maximal value. K_M can be used as a measure of the strength of the complex: a high K_M means that the complex is loosely bound and vice versa. V_{max} is the maximal rate when the enzyme substrate binding sites are saturated. Rate data were analysed for K_M and V_{max} by least squares fitting of Lineweaver-Burke, Eadie-Hofstee and Woolf Hanes plots. All experiments were carried out three times with all data quoted being the mean of nine determinations. The enzyme PSAO was isolated from pea-seedlings by a process of

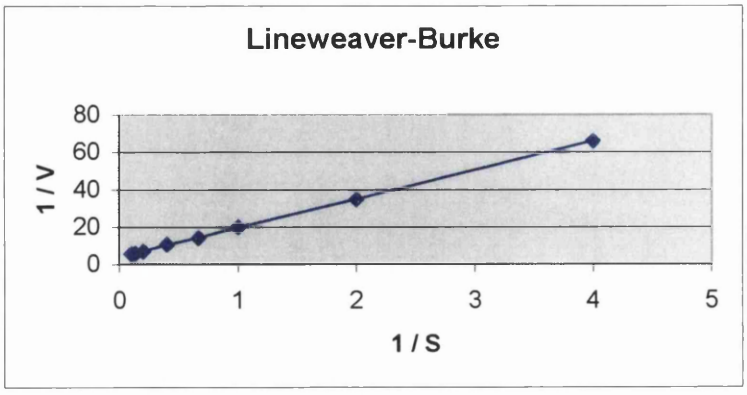
extraction, dialysis and purification as described in the experimental section. The results are shown in **Table 7.2.**

Table 7.2 Determination of K_M and V_{max} values for various 2-subtituted putrescines

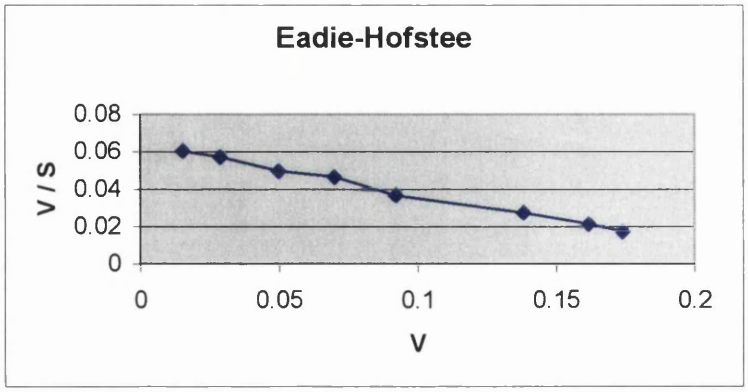
2-substitued Putrescine	K_M (mM)	V_{max} (μmol mg^{-1} h^{-1})
Putrescine	1.97	0.47
(±)-2-methyl **325**	3.14	0.22
(2*S*)-methyl **327**	2.70	0.22
(±)-2-phenyl **330**	52.9	0.26

The data show that the substituted putrescines tested all have an affinity for DAO. They were compared to putrescine which is a natural substrate of DAO. The V_{max} values of the substituted putrescines were about half that of putrescine. There was a difference in the extent of binding expressed as K_M between the racemic 2-methylputrescine **325** and the (*S*) enantiomer **327**. The 2-phenylputrescine **330** had a high K_M value but displayed a good level of substrate reactivity towards the enzyme.

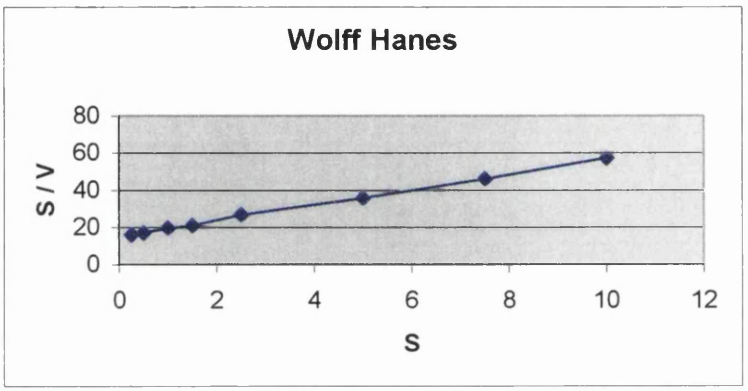
The following graphs are the plots generated for diamine **325** using the equations explained.



Lineweaver-Burke plot using the data for **325**



Eadie-Hofstee plot using the data for **325**

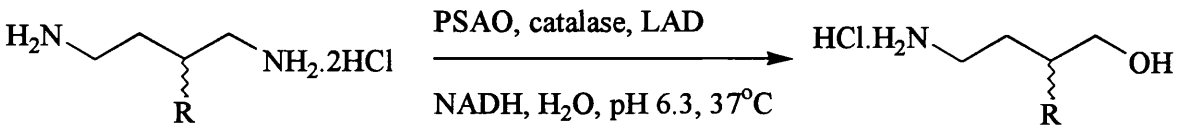


Wolff Hanes plot using the data for **325**

7.5 Future Work

7.5.1 Experiments to isolate the products of the oxidation catalysed by PSAO

We did not progress as far as we had hoped with the kinetic studies of the 2-substituted putrescines. The 2-substituted putrescines could be isolated as the oxalate salts which should not be hygroscopic. We would like to study the outcome of the oxidation of optically pure 2-substituted putrescines catalysed by DAO. It is proposed that biotransformations can be carried out for selected 2-substituted putrescines shown from kinetic studies to be good substrates for PSAO. The products of these biotransformations could be isolated through product trapping experiments. This method uses another enzyme known as liver alcohol dehydrogenase (LAD) which converts the aldehyde into an alcohol (Scheme 7.9).



Scheme 7.9

The products once isolated would be examined for optical purity. This would allow some insight into the stereo- and regio-selectivity of PSAO.

8. Experimental

8.1 General Details

All reactions were carried out under nitrogen with anhydrous solvents unless otherwise stated. Tetrahydrofuran and diethyl ether were dried by distillation from sodium and benzophenone immediately before use. Toluene and dichloromethane were dried by distillation from CaH_2 immediately before use. Reagents were purchased from commercial suppliers and used without further purification unless otherwise stated.

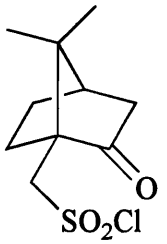
Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained on a Bruker DPX-400 spectrometer or Bruker WP-200 spectrometer. Chemical shifts are given relative to residual chloroform ($\delta_H = 7.27$ and $\delta_C = 77.2$) as internal standards unless otherwise stated. All coupling constants are reported in Hertz (Hz). Infra red spectra were recorded on either a Nicolet Impact 410 FT-IR or Perkin Elmer 500 spectrometer and mass spectra were obtained using a JOEL JMS-700 spectrometer. Combustion analysis was carried out using an Elemental Analyser MOD 1106. All of the thin layer chromatography plates used were Merck aluminium oxide 60 F_{254} neutral (type E) with layers of 0.2 mm thickness or Merck silica gel 60 F_{254} with layers of 0.25 mm thickness. The plates were visualised by illumination with UV light, or staining with permanganate or vanillin solution. Optical rotations were recorded on a Polaar 2000 polarimeter with path length 10 cm. $[\alpha]_D$ values are measured in 10^{-1} deg cm^2 g^{-1}.

For known compounds the only spectroscopic data given are the ^1H NMR spectra, except where new data are being reported.

8.2 Experimental for Chapter 4

8.2.1 Synthesis of chiral auxiliary according to literature method[127,85]

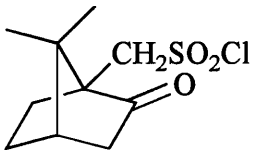
8.2.1.1 (1*S*)-(+)-10-Camphorsulfonyl chloride 108[127]



108

Compound **108** was prepared in 95% yield on a 43 mmol scale by the method of Knox and co-workers[127] and gave mp 67-68 °C (lit.[127] 65-66 °C); δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, s, C*H*$_3$CCH$_3$), 1.14 (3 H, s, C*H*$_3$CCH$_3$), 1.46-1.52 (1 H, m, alkyl-H), 1.74-1.81 (1 H, m, alkyl-H), 1.97 (1 H, d, *J* 18.6, alkyl-H), 2.05-2.18 (2 H, m, alkyl-H), 2.40-2.50 (2 H, m, alkyl-H), 3.71 (AB system, 1 H, d, *J* 14.6, CH*H*SO$_2$) and 4.29 (AB system, 1 H, d, *J* 14.6, CH*H*SO$_2$).

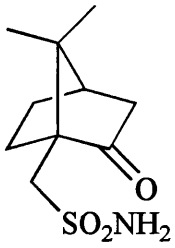
8.2.1.2 (1*R*)-(-)-10-Camphorsulfonyl chloride 298[127]



298

Compound **298** was prepared in 95% yield on a 0.17 mol scale by the method of Knox and co-workers[127] and gave mp 66-68 °C (lit.[80] 65-66 °C). Spectral data were identical to enantiomer **108**.

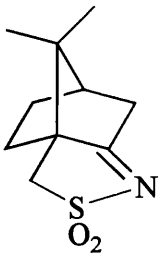
8.2.1.3 (1*S*)-(+)-10-Camphorsulfonamide 109[85]



109

Compound **109** was prepared in 70% yield on an 80 mmol scale by the method of Davis and co-workers[85] and gave mp 127-129 °C (lit.[85] 127-130 °C); δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, s, C*H*$_3$CCH$_3$), 1.01 (3 H, s, C*H*$_3$CCH$_3$), 1.44-1.51 (1 H, m, alkyl-H), 1.60 (1 H, d, *J* 20.0, alkyl-H), 2.03-2.10 (2 H, m, alkyl-H), 2.15-2.22 (1 H, m, alkyl-H), 2.39-2.46 (1 H, m, alkyl-H), 3.11 (AB system, 1 H, d, *J* 15.0, CH*H*SO$_2$), 3.47 (AB system, 1 H, d, *J* 15.0, CH*H*SO$_2$) and 5.41 (2 H, broad s, N*H*$_2$).

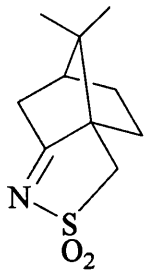
8.2.1.4 (1*S*, 2*R*)-(-)-10-Camphorsulfonimine 110[85]



110

Compound **110** was prepared in 95% yield on a 23 mmol scale by the method of Davis and co-workers[85] and gave mp 222-224 °C (lit.[85] mp 225 °C); $[\alpha]_D$ –34.3 (*c* 1.89, $CHCl_3$) [lit.[86] –32.73 (*c* 1.89, $CHCl_3$)]; δ_H(400 MHz; $CDCl_3$) 0.87 (3 H, s, C*H*$_3$CCH$_3$), 1.09 (3 H, s, C*H*$_3$CCH$_3$) 1.46-1.53 (1 H, m, alkyl-H), 1.72-1.80 (1 H, m, alkyl-H), 2.02-2.13 (2 H, m, alkyl-H), 2.26-2.28 (1 H, m, alkyl-H), 2.38 (1 H, d, *J* 19.3, alky-H), 2.74-2.80 (1 H, m, alkyl-H), 2.96 (AB system, 1 H, d, *J* 13.3, CH*H*SO$_2$) and 3.18 (AB system, 1 H, d, *J* 13.3, CH*H*SO$_2$).

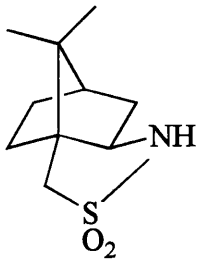
8.2.1.5 (1*R*, 2*S*)-(+)-2,10-Camphorsulfonimine 299[85]



299

Compound **299** was prepared in 90% yield on a 0.17 mol scale by the method of Davis and co-workers[85] and gave mp 224-226 °C (lit.[85] mp 225 °C); $[\alpha]_D$ +31.0 (*c* 1.0, $CHCl_3$) [lit.[85] +31.47 (*c* 2.11, $CHCl_3$)]. Spectral data were identical to enantiomer **110**.

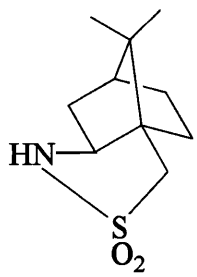
8.2.1.6 (1*S*,2*R*)-(-)-2,10-Camphorsultam 111[85]



111

Compound **111** was prepared in 45% yield on a 18 mmol scale by the method of Davis and co-workers[85] and gave mp 182-183 °C (lit.[85] 183-184 °C); $[\alpha]_D$ –31.2 (*c* 2.0, $CHCl_3$) [lit.[85] –30.5, (*c* 4.0, $CHCl_3$)]; δ_H(400 MHz, $CDCl_3$) 0.94 (3 H, s, C*H*$_3$CCH$_3$), 1.14 (3 H, s, C*H*$_3$CCH$_3$), 1.29-1.36 (1 H, m, alkyl-H), 1.42-1.49 (1 H, m, alkyl-H), 1.84-2.02 (5 H, m, alkyl-H), 3.08 (AB system, 1 H, d, *J* 13.7, CH*H*SO$_2$), 3.13 (AB system, 1 H, d, *J* 13.7, CH*H*SO$_2$), 3.42-3.45 (1 H, m, C*H*N) and 4.12 (1H, broad s, N*H*).

8.2.1.7 (1*R*,2*S*)-(+)-2,10-Camphorsultam 296[85]

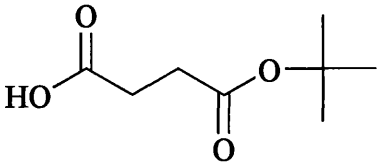


296

Compound **296** was prepared in 80% yield on a 0.17 mol scale by the method of Davis and co-workers[85] and gave mp 177-179 °C (lit.[85] 183-184 °C); $[\alpha]_D$ +32.1 (*c* 1.0, $CHCl_3$) [lit.[85] +32.5, (*c* 1.0, $CHCl_3$)]. Spectral data were identical to enantiomer **111**.

8.2.2 Synthesis of racemic 2-substituted succinic acids according to literature methods.[90]

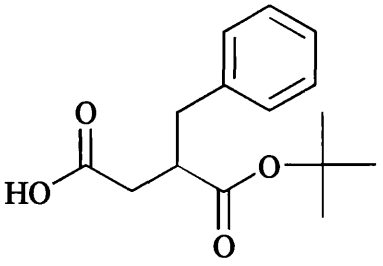
8.2.2.1 *tert*-Butyl succinate 126[128]



126

Compound **126** was prepared in 51% yield on a 20 mmol scale by the method of Miller and co-workers[128] and gave mp 51 °C (lit.[128] 49-51 °C); δ_H(400 MHz; $CDCl_3$) 1.45 (9 H, m, $(CH_3)_3$) and 2.45-2.58 (4 H, m, CH_2CH_2); δ_C($CDCl_3$) 28.4 (3 x CH_3), 29.6 (CH_2), 30.4 (CH_2), 81.4 (*C*), 171.8 (*C*=O) and 179.0 (*C*=O).

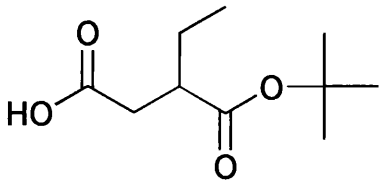
8.2.2.2 *tert*-Butyl (±)-2-benzylsuccinate 134[90]



134

Compound **134** was prepared in 89% yield on an 8.6 mmol scale by the method of Bergmeier and co-workers.[90] δ_H(400 MHz; $CDCl_3$) 1.40 (9 H, s, CCH_3), 2.42 (ABX system, 1 H, dd, *J* 4.4 and 17.0, COCH*H*CH), 2.67 (ABX system, 1 H, dd, *J* 8.8 and 17.0, COCH*H*CH), 2.74-2.81 (1 H, m, $COCH_2CH$), 2.99-3.06 (2 H, m, $PhCH_2$) and 7.19-7.33 (5 H, m, ArC*H*).

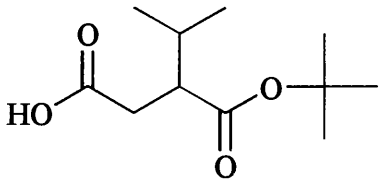
8.2.2.3 *tert*-Butyl (±)-2-ethylsuccinate 129[90]



129

Compound **129** was prepared in 72% yield on an 8.6 mmol scale by the method of Bergmeier and co-workers.[90] δ_H(400 MHz; $CDCl_3$) 0.94 (3 H, t, *J* 7.2, CH_3CH_2), 1.45 (9 H, s, CCH_3), 1.58-1.68 (2 H, m, CH_3CH_2), 2.42 (ABX system, 1 H, dd, *J* 3.0 and 14.4, COCH*H*CH) and 2.64-2.74 (ABX system, 2 H, m, 1 from COCH*H*CH and 1 from $COCH_2CH$).

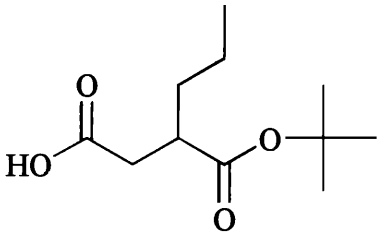
8.2.2.4 *tert*-Butyl (±)-2-isopropylsuccinate 130[90]



130

Compound **130** was prepared in 38% yield on an 8.6 mmol scale by the method of Bergmeier and co-workers.[90] δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6.8, CH_3CH), 0.96 (3 H, d, *J* 6.8, CH_3CH), 1.45 (9 H, s, CCH_3), 1.98-2.02 (1 H, m, CH_3CH), 2.40 (ABX system, 1 H, dd, *J* 3.6 and 16.4, COCH*H*CH), 2.55-2.61 (ABX system, 1 H, m, $COCH_2CH$) and 2.71 (ABX system, 1 H, dd, *J* 10.8 and 16.4, COCH*H*CH).

8.2.2.5 *tert*-Butyl (±)-2-propylsuccinate 131

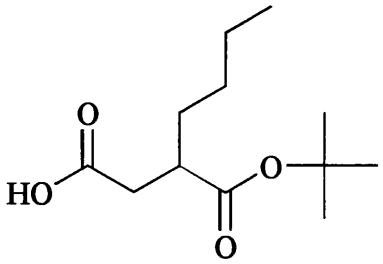


131

Compound **131** was prepared in 16% yield on an 8.6 mmol scale by the method of Bergmeier and co-workers[90] and was isolated as a colourless oil. υ_{max}(NaCl)/cm^{-1} 3060 (OH), 2962 (CH_3), 2873 (CH) and 1714 (C=O); δ_H(400 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 7.2,

CH_3CH_2), 1.26-1.40 (3 H, m, CH_3CH_2CHH), 1.44 (9 H, s, CCH_3), 1.57-1.68 (1 H, m, CH_3CH_2CHH), 2.40-2.47 (1 H, m, COCH*H*CH) and 2.64-2.74 (2H, m, COCH*H*C*H*); δ_C(100 MHz) 13.9 (CH_3), 20.1 (CH_2), 27.0 (3 x CH_3), 34.1 (CH_2), 35.8 (CH_2), 41.7 (*C*H), 80.8 (*C*), 174.2 (*C*=O) and 177.6 (*C*=O); *m/z* (FAB+) 217 [$(M+H)^+$, 30%] and 161 ($(M+H)^+$-^tBu, 100); [Found (FAB+): $(M+H)^+$ 217.1440; $C_{11}H_{20}O_4$ requires 217.1440].

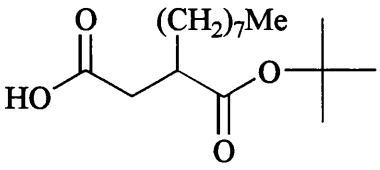
8.2.2.6 *tert*-Butyl (±)-2-butylsuccinate 132[90]



132

Compound **132** was prepared in 70% yield on an 8.6 mmol scale by the method of Bergmeier and co-workers.[90] δ_H(400 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 6.8, CH_3CH_2), 1.31-1.66 (15 H, m, alkyl-H), 2.40-2.47 (1 H, m, COCH*H*CH) and 2.66-2.73 (2 H, m, COCH*H*C*H*).

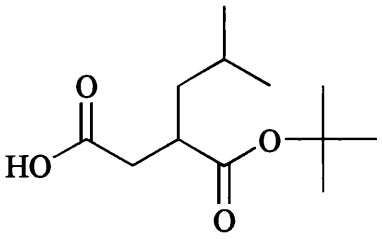
8.2.2.7 *tert*-Butyl (±)-2-octylsuccinate 133[90]



133

Compound **133** was prepared in 85% yield on an 8.6 mmol scale by the method of Bergmeier and co-workers.[90] δ_H(400 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 7.0, CH_3CH_2), 1.22-1.29 (12 H, m, alkyl-H), 1.44 (9 H, s, CCH_3), 1.81-1.89 (2 H, m, alkyl-H), 2.38-2.45 (1 H, m, COCH*H*CH) and 2.64-2.72 (2 H, m, COCH*H*C*H*).

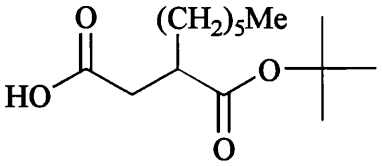
8.2.2.8 *tert*-Butyl (±)-2-isobutylsuccinate 135



135

Compound **135** was prepared in 14% yield on an 8.6 mmol scale by the method of Bergmeier and co-workers[90] and was isolated as a colourless oil. υ_{max}(NaCl)/cm^{-1} 2960 (CH_3), 2873 (CH) and 1716 (C=O); δ_H(400 MHz; $CDCl_3$) 0.91 (3 H, d, *J* 6.4, C*H*$_3$CHCH$_3$), 0.95 (3 H, d, *J* 6.4, C*H*$_3$CHCH$_3$), 1.24-1.31 (1 H, m, CH$_3$C*H*CH$_3$), 1.45 (9 H, s, CC*H*$_3$), 1.55-1.67 (1 H, m, CH$_3$CHCH*H*), 2.43 (ABX system, 1 H, dd, *J* 4.7 and 16.5, COCH*H*CH) and 2.62-2.81 (ABX system, 2 H, m, COCH*H*CH and COCH$_2$C*H*); δ_C(100 MHz) 22.6 (*C*H$_3$), 23.0 (*C*H$_3$), 26.2 (*C*H), 28.3 (3 x *C*H$_3$), 29.5 (*C*H$_2$), 40.5 (*C*H), 41.6 (*C*H$_2$), 81.2 (*C*), 174.8 (*C*=O) and 178.0 (*C*=O); *m/z* (FAB+) 231 [(M+H)$^+$, 29%] and 175 ((M+H)$^+$-*^{t}Bu*, 100); [Found (FAB+): (M+H)$^+$ 231.1597; $C_{12}H_{22}O_4$ requires 231.1596].

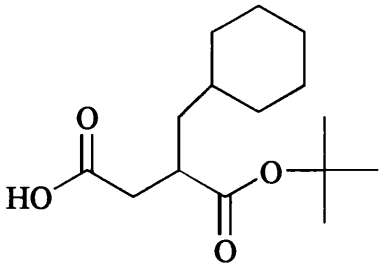
8.2.2.9 *tert*-Butyl (±)-2-hexylsuccinate 136



136

Compound **136** was prepared in 20% yield on a 5.7 mmol scale by the method of Bergmeier and co-workers[90] and was isolated as a colourless oil. υ_{max}(NaCl)/cm^{-1} 2929 (CH_3), 2860 (CH) and 1713 (C=O); δ_H(400 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.28-1.31 (8 H, m, alkyl-H), 1.41-1.66 (11 H, m, alkyl-H), 2.44 (ABX system, 1 H, dd, *J* 8.7 and 20.4, COCH*H*CH) and 2.68-2.74 (ABX system, 2 H, m, COCH*H*CH and COCH$_2$C*H*); δ_C(100 MHz) 14.5 (*C*H$_3$), 23.0 (*C*H$_2$), 27.1 (*C*H$_2$), 28.4 (3 x *C*H$_3$), 29.4 (*C*H$_2$), 32.0 (*C*H$_2$), 32.3 (*C*H$_2$), 36.2 (*C*H$_2$), 42.2 (*C*H), 81.2 (*C*), 174.6 (*C*=O) and 178.1 (*C*=O); *m/z* (CI$^+$ mode, isobutane) 259 [(M+H)$^+$, 66%], 203 ((M+H)$^+$-*^{t}Bu*, 100) and 185 (25); [Found (CI$^+$ mode, isobutane): (M+H)$^+$ 259.1907; $C_{14}H_{26}O_4$ requires 259.1909].

8.2.2.10 *tert*-Butyl (±)-2-cyclohexylmethylsuccinate 137

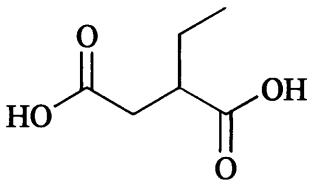


137

Compound **137** was prepared in 14% yield on a 5.7 mmol scale by the method of Bergmeier and co-workers[90] and was isolated as a colourless oil. υ_{max}(NaCl)/cm^{-1} 2924 (CH_3), 2852 (CH) and 1712 (C=O); δ_H(400 MHz; $CDCl_3$) 0.84-0.92 (3 H, m, alkyl-H), 1.12-1.32 (5 H, m, alkyl-H), 1.44 (9 H, s, CC*H*$_3$), 1.50-1.83 (5 H, m, alkyl-H), 2.42 (ABX system, 1 H, dd, *J* 4.7 and 16.7, COCH*H*CH), 2.65 (ABX system, 1 H, dd, *J* 9.5 and 16.7, COCH*H*CH) and 2.76-2.81 (ABX system, 1 H, m, $COCH_2CH$); δ_C(100 MHz) 26.6 (2 x CH_2), 26.9 (CH_2), 28.4 (3 x CH_3), 33.3 (CH_2), 33.6 (CH_2), 35.6 (*C*H), 36.7 (CH_2), 39.7 (*C*H), 40.0 (CH_2), 81.1 (*C*), 175.0 (*C*=O) and 178.0 (*C*=O); *m/z* (CI$^+$ mode, isobutane) 271 [(M+H)$^+$, 8%], 215 ((M+H)$^+$-^{t}*Bu*, 100) and 197 (35); [Found (CI$^+$ mode, isobutane): (M+H)$^+$ 271.1908; $C_{15}H_{26}O_4$ requires 271.1909].

8.2.3 Conversion of *tert*-butyl 2-substituted succinates into 2-substituted succinic acids.

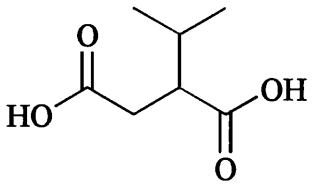
8.2.3.1 (±)-2-Ethylsuccinic acid 138[90]



138

Compound **138** was prepared in 81% yield on a 1.5 mmol scale by the method of Bergmeier and co-workers[90] and gave mp 96-97 °C (lit.[90] 93 °C). δ_H(400 MHz; d_6-DMSO) 0.86 (3 H, t, *J* 7.5, CH_3CH_2), 1.47-1.58 (2 H, m, CH_3CH_2), 2.32 (ABX system, 1 H, dd, *J* 4.7 and 16.2, COCH*H*CH) and 2.49-2.68 (ABX system, 2 H, m, COCH*H*CH and $COCH_2CH$).

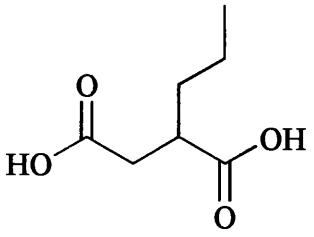
8.2.3.2 (±)-2-Isopropylsuccinic acid 139[90]



139

Compound **139** was prepared in 79% yield on a 0.9 mmol scale by the method of Bergmeier and co-workers[90] and gave mp 108-109 °C (lit.[90] 110-111 °C). δ_H(400 MHz; d_6-DMSO) 0.86 (3 H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.89 (3 H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.86-1.94 (1 H, m, CH$_3$C*H*CH$_3$), 2.31 (ABX system, 1 H, dd, *J* 3.0 and 15.8, COCH*H*CH) and 2.42-2.54 (ABX system, 2 H, m, COCH*H*CH and COCH$_2$C*H*).

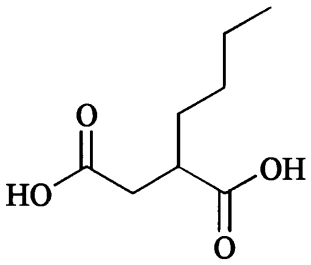
8.2.3.3 (±)-2-Propylsuccinic acid 140



140

Compound **140** was prepared in 74% yield on a 1.2 mmol scale by the method of Bergmeier and co-workers[90] and gave white plates from water. mp 95-98 °C; (Found: C, 52.45 H, 7.5%; $C_7H_{12}O_4$ requires C, 52.5 H, 7.55%); υ_{max}(KBr)/cm^{-1} 3433 (OH), 1625 (C=O); δ_H(400 MHz; d_6-DMSO) 0.86 (3 H, t, *J* 7.3, C*H*$_3$CH$_2$), 1.22-1.34 (2 H, m, CH$_3$C*H*$_2$), 1.40-1.55 (2 H, m, CH$_3$CH$_2$C*H*$_2$), 2.32 (ABX system, 1 H, dd, *J* 5.0 and 16.6, COC*H*$_2$CH), 2.44-2.51 (ABX system, 1 H, m, COCH*H*CH), 2.57-2.64 (ABX system, 1 H, m, COCH$_2$C*H*) and 12.18 (2 H, br s, COO*H*); δ_C(100 MHz; d_6-DMSO) 14.2 (*C*H$_3$), 20.0 (*C*H$_2$), 33.9 (*C*H$_2$), 36.0 (*C*H$_2$), 40.8 (*C*H), 173.5 (*C*=O) and 176.3 (*C*=O); *m/z* (FAB+) 161 [(M+H)$^+$, 100%] and 143 (70); [Found (FAB+): (M+H)$^+$ 161.0813; $C_7H_{12}O_4$ requires 161.0814].

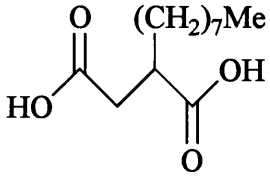
8.2.3.4 (±)-2-Butylsuccinic acid 141[90]



141

Compound **141** was prepared in 81% yield on a 1.5 mmol scale by the method of Bergmeier and co-workers[90] and gave mp 82-84 °C (lit.[90] 83 °C). δ_H(400 MHz; d_6-DMSO) 0.86 (3 H, t, *J* 6.5, CH_3CH_2), 1.25-1.56 (6 H, m, alkyl-H), 2.32 (ABX system, 1 H, dd, *J* 5.0 and 16.5, $COCH_2CH$) and 2.42-2.62 (ABX system, 2 H, m, $COCHHCH$ and $COCH_2CH$).

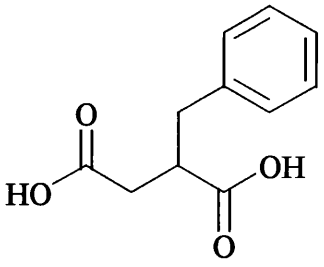
8.2.3.5 (±)-2-Octylsuccinic acid 142[90]



142

Compound **142** was prepared in 83% yield on a 1.5 mmol scale by the method of Bergmeier and co-workers[90] and gave mp 88-91 °C (lit.[90] 89-90 °C). δ_H(400 MHz; d_6-DMSO) 0.86 (3 H, t, *J* 7.0, CH_3CH_2), 1.24 (12 H, s, alkyl-H), 1.36-1.50 (2 H, m, alkyl-H), 2.32 (ABX system, 1 H, dd, *J* 5.0 and 16.0, $COCHHCH$), 2.45 (ABX system, 1 H, dd, *J* 6.3 and 16.0, $COCHHCH$), 2.56-2.63 (ABX system, 1 H, m, $COCH_2CH$) and 12.18 (2 H, br s, $COOH$).

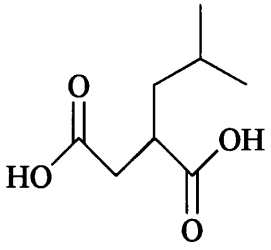
8.2.3.6 (±)-2-Benzylsuccinic acid 143[90]



143

Compound **143** was prepared in 81% yield on a 1.5 mmol scale by the method of Bergmeier and co-workers[90] and gave mp 164-166 °C (lit.[129] 165-166 °C). δ_H(400 MHz; d_6-DMSO) 2.25 (ABX system, 1 H, dd, *J* 4.4 and 16.8, COCH*H*CH), 2.43 (ABX system, 1 H, dd, *J* 8.8 and 16.8, COCH*H*CH), 2.70-2.77 (ABX system, 1 H, m, $COCH_2CH$), 2.87-2.94 (2 H, m, $ArCCH_2$), 7.13-7.39 (5 H, m, aromatic H) and 12.25 (2 H, br s, COO*H*).

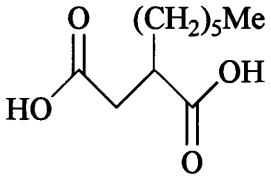
8.2.3.7 (±)-2-Isobutylsuccinic acid 144[130]



144

Compound **144** was prepared in 52% yield on a 0.8 mmol scale by the method of Bergmeier and co-workers[90] and gave mp 97-98 °C (lit.[131] 95-96 °C). δ_H(400 MHz; d_6-DMSO) 0.85 (3 H, d, *J* 7.3, CH_3CHCH_3), 0.88 (3 H, d, *J* 6.5, CH_3CHCH_3) 1.18-1.27 (1 H, m, alkyl-H), 1.38-1.47 (1 H, m, alkyl-H), 1.53-1.61 (1 H, m, alkyl-H), 2.32 (ABX system, 1 H, dd, *J* 5.1 and 16.6, COCH*H*CH), 2.42-2.51 (ABX system, 1 H, m, COCH*H*CH), 2.61-2.68 (ABX system, 1 H, m, $COCH_2CH$) and 12.20 (2 H, br s, COO*H*).

8.2.3.8 (±)-2-Hexylsuccinic acid 145[132]

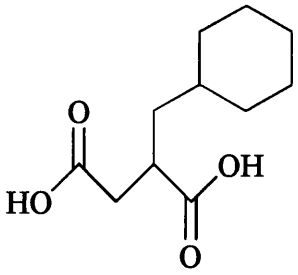


145

Compound **145** was prepared in 87% yield on a 1.2 mmol scale by the method of Bergmeier and co-workers[90] and gave mp 77-79 °C (lit.[132] 78-80 °C). (Found: C, 59.5 H, 9.1%; $C_{10}H_{18}O_4$ requires C, 59.4 H, 9.0%); υ_{max}(KBr)/cm^{-1} 2956 (CH_3), 2856 (CH) and 1695 (C=O); δ_H(400 MHz; d_6-DMSO) 0.86 (3 H, t, *J* 7.0, CH_3CH_2), 1.24 (8 H, s, alkyl-H), 1.38-1.49 (2 H, m, alkyl-H), 2.32 (ABX system, 1 H, dd, *J* 5.0 and 16.5, COCH*H*CH), 2.47 (ABX system, 1 H, dd, *J* 9.3 and 16.5, COCH*H*CH), 2.55-2.62 (ABX system, 1 H, m, $COCH_2CH$) and 12.18 (2 H, br s, 2 x COO*H*); δ_C(100 MHz; d_6-DMSO) 14.3 (CH_3), 22.4 (CH_2), 26.7 (CH_2), 28.9 (CH_2), 31.4 (CH_2), 36.0 (CH_2), 41.0 (*C*H), 173.5 (*C*=O) and 176.4

(*C*=O); *m/z* (CI^+ mode, isobutane) 203 [$(M+H)^+$, 5%] and 85 (100); [Found $(M+H)^+$ 203.1285; $C_{10}H_{18}O_4$ requires 203.1283].

8.2.3.9 (±)-2-Cyclohexylmethylsuccinic acid 146



146

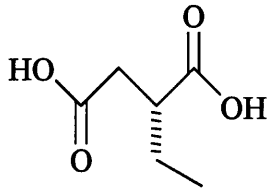
Compound **146** was prepared in 94% yield on a 0.8 mmol scale by the method of Bergmeier and co-workers[90] and gave mp 118-120 °C. υ_{max}(KBr)/cm^{-1} 3419 (OH), 2924 (CH_2) and 1699 (C=O); δ_H(400 MHz; d_6-DMSO) 0.82-0.85 (2 H, m, alkyl-H), 1.09-1.27 (5 H, m, alkyl-H), 1.39-1.45 (1 H, m, alkyl-H), 1.62-1.75 (5 H, m, alkyl-H), 2.31 (ABX system, 1 H, dd, *J* 5.0 and 16.6, COCH*H*CH), 2.41-2.47 (ABX system, 1 H, m, COCH*H*CH), 2.58-2.67 (ABX system, 1 H, m, $COCH_2CH$) and 12.19 (2 H, br s, 2 x COO*H*); δ_C(100 MHz; d_6-DMSO) 26.0 (2 x CH_2), 26.4 (CH_2), 32.9 (CH_2), 33.1 (CH_2), 35.0 (*C*H), 36.6 (CH_2), 38.6 (*C*H), 39.5 (CH_2), 173.5 (*C*=O) and 176.7 (*C*=O); *m/z* (CI^+ mode, isobutane) 215 [$(M+H)^+$, 44%] and 197 (100); [Found $(M+H)^+$ 215.1282; $C_{11}H_{18}O_4$ requires 215.1283].

8.2.4 Synthesis of enantiomerically enriched 2-substituted succinic acids

General procedure 1 for the saponification of succinamides.

Aqueous (30%) H_2O_2 (4.8 equiv.) and $LiOH.H_2O$ (2.4 equiv.) were added at 0 °C to a solution of substituted succinamide (1 mol equiv.) in THF/H_2O (4:1, 0.15 mmol/cm^3). The mixture was stirred at 0 °C for 7 h, saturated aqueous Na_2SO_3 was added and the mixture was extracted with ethyl acetate (2 x 10 cm^3). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give recovered auxiliary. The aqueous layer was then acidified with 1 M HCl to pH 1 and extracted with ethyl acetate (2 x 10 cm^3). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to produce the diacid.

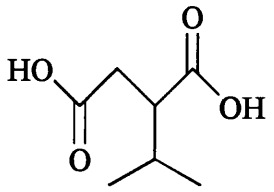
8.2.4.1 (2*R*)-Ethylsuccinic acid 167[93]



167

Using the mixture of **186** and **187** (0.7 g, 1.29 mmol) in General procedure 1 gave (2*R*)-ethylsuccinic acid **167** (0.12 g, 65%) as white needles. mp 95-97 °C (lit.[93] 96 °C); $[\alpha]_D$ +34 (*c* 1.01, acetone) [lit.[93] +24, (*c* 1.01, acetone)]; δ_H(400 MHz; d_6-DMSO) 0.86 (3 H, t, *J* 7.4, CH_3CH_2), 1.45-1.60 (2 H, m, CH_3CH_2), 2.31 (1 H, dd, *J* 4.7 and 16.2, COC*H*) and 2.42-2.60 (2H, m, COCH*HCH*).

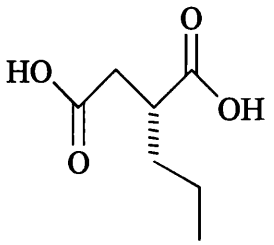
8.2.4.2 2-Isopropylsuccinic acid 168[94]



168

Using the mixture of **188** and **189** (0.7 g, 1.26 mmol) in General procedure 1 gave 2-isopropylsuccinic acid **168** (0.13 g, 67%) as white needles. mp 110-112 °C (lit.[94] 95 °C); υ_{max}(KBr)/cm^{-1} 2967 (OH), 2926 (OH) and 1698 (C=O); δ_H(400 MHz; d_6-DMSO) 0.86 (3 H, d, *J* 6.8, CH_3CHCH_3), 0.89 (3 H, d, *J* 6.8, CH_3CHCH_3), 1.86-1.94 (1 H, m, CH_3CHCH_3), 2.31 (1 H, dd, *J* 2.8 and 16.0, COCH*H*), 2.42-2.51 (2H, m, COCH*HCH*) and 12.18 (2 H, br s, 2 x COO*H*); δ_C(100 MHz; d_6-DMSO) 19.6 (CH_3), 20.3 (CH_3), 29.7 (*C*H), 32.8 (CH_2), 47.2 (*C*H), 173.9 (C=O) and 175.7 (C=O); *m/z* (CI^+ mode, isobutane) 161 [$(M+H)^+$, 78%] and 143 (100); [Found $(M+H)^+$ 161.0816; $C_7H_{12}O_4$ requires 161.0814].

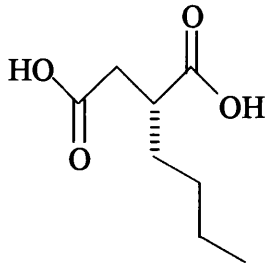
8.2.4.3 (2*R*)-Propylsuccinic acid 169[95]



169

Using the mixtures of **190** and **191** (0.6 g, 1.08 mmol) in General procedure 1 gave (2*R*)-propylsuccinic acid **169** (0.12 g, 71%) as white needles. mp 98-100 °C (lit.[95] 96 °C); $[\alpha]_D$ +14 (*c* 1.0, EtOAc) [lit.[95] +26.8, (*c* 1.1, H_2O)]; (Found: C, 52.3 H, 7.5%; $C_7H_{12}O_4$ requires C, 52.5 H, 7.5%); υ_{max}(KBr)/cm^{-1} 2960 (OH) and 1700 (C=O); δ_H(400 MHz; d_6-DMSO) 0.86 (3 H, t, *J* 7.2, CH_3CH_2), 1.25-1.33 (2 H, m, alkyl-H), 1.42-1.51 (2 H, m, alkyl-H), 2.32 (1 H, dd, *J* 4.8 and 16.4, COCH*H*), 2.45 (1 H, dd, *J* 6.8 and 16.4, COCH*H*), 2.57-2.64 (1 H, m, $COCH_2CH$) and 12.18 (2 H, br s, 2 x COO*H*); δ_C(100 MHz; d_6-DMSO) 14.2 (CH_3), 20.0 (CH_2), 33.9 (CH_2), 36.0 (CH_2) 40.8 (*C*H), 173.5 (C=O) and 176.4 (C=O); *m/z* (CI/NH_3) 178 ($M+NH_4^+$), 100%).

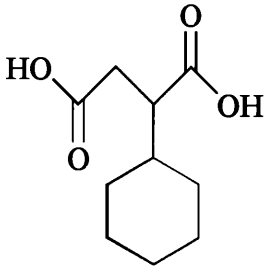
8.2.4.4 (2*R*)-Butylsuccinic acid 170[96]



170

Using the mixtures of **192** and **193** (0.7 g, 1.23 mmol) in General procedure 1 gave (2*R*)-butylsuccinic acid **170** (0.2 g, 67%) as white needles. 79-81 °C (lit.[96] 81-82 °C); $[\alpha]_D$ +12 (*c* 1.0, EtOAc) [lit.[96] +18.8, (*c* 4.16, H_2O)]; δ_H(400 MHz; d_6-DMSO) 0.86 (3 H, t, *J* 6.5, CH_3CH_2), 1.25-1.56 (6 H, m, alkyl-H), 2.32 (1 H, dd, *J* 5.0 and 16.5, COCH*H*CH) and 2.42-2.62 (2 H, m, COCH*H*CH and $COCH_2CH$).

8.2.4.5 2-Cyclohexylsuccinic acid 171[97]

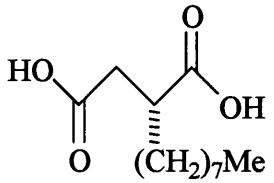


171

Using **194** and **195** (1.16 g, 1.95 mmol) in General procedure 1 gave 2-cyclohexylsuccinic acid **171** (0.26 g, 67%) as white needles. mp 94-96 °C (lit.[97] 91-92 °C);

δ_H(400 MHz; d_6-DMSO) 1.00-1.24 (5 H, m, alkyl-H), 1.50-1.70 (6 H, m, alkyl-H), 2.33 (1 H, dd, *J* 2.5 and 15.2, COCH*H*), 2.45-2.53 (2 H, m, COCH*HCH*).

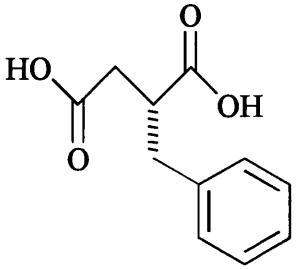
8.2.4.6 (2*R*)-Octylsuccinic acid 172



172

Using the mixture of **196** and **197** (0.5 g, 0.8 mmol) in General procedure 1 gave (2*R*)-octylsuccinic acid **172** (0.11 g, 61%) as white needles. mp 83-85 °C; $[\alpha]_D$ +14 (*c* 1.0, EtOAc); (Found: C, 62.8 H, 9.7%; $C_{12}H_{22}O_4$ requires C, 62.6 H, 9.6%); υ_{max}(KBr)/cm^{-1} 2917 (OH), 2853 (OH) and 1690 (C=O); δ_H(400 MHz; d_6-DMSO) 0.92 (3 H, t, *J* 6.4, C*H*$_3$CH$_2$), 1.30 (12 H, m, alkyl-H), 1.48-1.61 (2 H, m, alkyl-H), 2.38 (1 H, dd, *J* 5.0 and 16.5, COCH*H*), 2.48-2.56 (1 H, m, COCH*H*) and 2.62-2.69 (1 H, m, COCH$_2$C*H*); δ_C(100 MHz; d_6-DMSO) 14.3 (*C*H$_3$), 22.4 (*C*H$_2$), 26.7 (*C*H$_2$), 28.9 (*C*H$_2$), 29.1 (*C*H$_2$), 29.2 (*C*H$_2$), 31.6 (*C*H$_2$), 31.7 (*C*H$_2$), 36.0 (*C*H$_2$) 41.0 (*C*H), 173.5 (C=O) and 176.3 (C=O); *m/z* (CI^+ mode, isobutane) 231 [$(M+H)^+$, 93%] and 213 (100); [Found $(M+H)^+$ 231.1597; $C_{12}H_{22}O_4$ requires 231.1596].

8.2.4.7 (2*R*)-Benzylsuccinic acid 173[98]

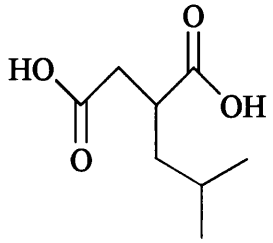


173

Using the mixture of **198** and other diastereomer (2.0 g, 3.32 mmol) in General procedure 1 gave (2*R*)-benzylsuccinic acid **173** (0.49 g, 71%) as white needles. mp 162-164 °C (lit.[98] 162-163 °C); $[\alpha]_D$ +17.7 (*c* 2.9, EtOAc) [lit.[98] +27, (*c* 1.5, EtOAc)]; (Found: C, 63.6 H, 5.8%; $C_{11}H_{12}O_4$ requires C, 63.5 H, 5.8%); υ_{max}(KBr)/cm^{-1} 2964 (OH), 2882 (OH) and 1694 (C=O); δ_H(400 MHz; d_6-DMSO) 2.25 (1 H, dd, *J* 4.3 and 16.8, COC*H*$_2$), 2.43 (1 H, dd, *J* 8.6 and 16.7, COC*H*$_2$), 2.74 (1 H, dd, *J* 10.0 and 15.6, PhCH*H*), 2.87-2.94 (2 H, m, PhCH*H* and COCH$_2$C*H*), 7.18-7.39 (5 H, m, Ar*H*) and 12.25 (2 H, br s, 2 x

COO*H*); δ_C(100 MHz; d_6-DMSO) 35.2 (*C*H_2), 37.3 (*C*H_2), 42.8 (*C*H), 126.7 (Ar*C*H), 128.7 (2 x Ar*C*H), 129.3 (2 x Ar*C*H), 139.1 (Ar*C*), 173.3 (C=O) and 175.5 (C=O); *m/z* (EI) 280 (M^+, 12%), 162 (62) and 91 (100); (Found M^+ 208.0736; $C_{11}H_{12}O_4$ requires M^+ 208.0736).

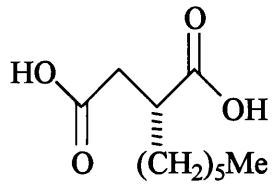
8.2.4.8 2-Isobutylsuccinic acid 174



174

Using the mixture of **199** and **200** (1.61 g, 2.8 mmol) in General procedure 1 gave 2-isobutylsuccinic acid **174** (0.37 g, 76%) as white needles. mp 96-97 °C; $[\alpha]_D$ 0 (*c* 0.1, EtOH); υ_{max}(KBr)/cm^{-1} 2960 (OH) and 1712 (C=O); δ_H(400 MHz; d_6-DMSO) 0.85 (3 H, d, *J* 7.3, C*H*$_3$CHCH$_3$), 0.88 (3 H, d, *J* 6.5, CH$_3$CHC*H*$_3$) 1.18-1.27 (1 H, m, alkyl-H), 1.38-1.47 (1 H, m, alkyl-H), 1.53-1.61 (1 H, m, alkyl-H), 2.32 (1 H, dd, *J* 5.1 and 16.6, COCH*H*CH), 2.42-2.51 (1 H, m, COCH*H*CH), 2.61-2.68 (1 H, m, COCH$_2$C*H*) and 12.20 (2 H, br s, COO*H*); δ_C(100 MHz; d_6-DMSO) 22.5 (*C*H$_3$), 22.8 (*C*H$_3$), 25.6 (*C*H), 36.5 (*C*H$_2$), 39.5 (*C*H), 41.1 (*C*H$_2$), 173.4 (*C*=O) and 176.6 (*C*=O); *m/z* (CI/NH_3) 192 ($M+NH_4^+$), 25%), 102 (88), 85 (100) and 79 (60).

8.2.4.9 (2*R*)-Hexylsuccinic acid 175[99]

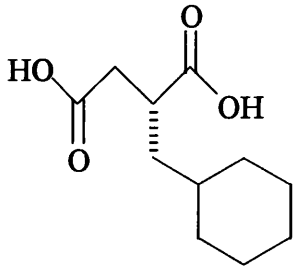


175

Using the mixture of **201** and **202** (2.1 g, 3.5 mmol) in General procedure 1 gave (2*R*)-hexylsuccinic acid **175** (0.49 g, 71%) as white needles. mp 77-79 °C (lit.[99] 83 °C); $[\alpha]_D$ +8 (*c* 1.5, EtOAc) (lit.[99] +14.3, (H_2O)]; υ_{max}(KBr)/cm^{-1} 2923 (OH), 2856 (OH) and 1693 (C=O); δ_H(400 MHz; d_6-DMSO) 0.88 (3 H, t, *J* 6.8, C*H*$_3$CH$_2$), 1.29-1.36 (9 H, m, alkyl-H), 1.50-1.57 (1 H, m, alkyl-H), 2.49-2.57 (1 H, m, alkyl-H), 2.69-2.77 (1 H, m, alkyl-H) and 2.81-2.88 (1 H, m, alkyl-H); δ_C(100 MHz; d_6-DMSO) 14.0 (*C*H$_3$), 22.5 (*C*H$_2$), 26.8 (*C*H$_2$), 29.0 (*C*H$_2$), 31.5 (*C*H$_2$), 31.6 (*C*H$_2$), 35.5 (*C*H$_2$), 41.1 (*C*H), 178.7

(C=O) and 181.6 (C=O); *m/z* (FAB+) 203 [$(M+H)^+$, 9%], 147 (25) and 74 (100); [Found (FAB+): $(M+H)^+$ 203.1285; $C_{10}H_{18}O_4$ requires 203.1283].

8.2.4.10 (2*R*)-Cyclohexylmethylsuccinic acid 176



176

Using the mixture of **203** and **204** (1.88 g, 3 mmol) in General procedure 1 gave (2*R*)-cyclohexylmethylsuccinic acid **176** (0.42 g, 66%) as white needles. mp 118-120 °C. $[\alpha]_D$ +6 (*c* 1.0, EtOH); υ_{max}(KBr)/cm^{-1} 3419 (OH), 2924 (CH_2) and 1699 (C=O); δ_H(400 MHz; d_6-DMSO) 0.82-0.85 (2 H, m, alkyl-H), 1.09-1.27 (5 H, m, alkyl-H), 1.39-1.45 (1 H, m, alkyl-H), 1.62-1.75 (5 H, m, alkyl-H), 2.31 (1 H, dd, *J* 5.0 and 16.6, COCH*H*CH), 2.41-2.47 (1 H, m, COCH*H*CH), 2.58-2.67 (1 H, m, $COCH_2CH$) and 12.19 (2 H, br s, COO*H*); δ_C(100 MHz; d_6-DMSO) 26.0 (2 x CH_2), 26.4 (CH_2), 32.9 (CH_2), 33.1 (CH_2), 35.0 (CH), 36.6 (CH_2), 38.6 (CH), 39.5 (CH_2), 173.5 (C=O) and 176.7 (C=O); *m/z* (CI^+ mode, isobutane) 215 [$(M+H)^+$, 44%] and 197 (100); [Found $(M+H)^+$ 215.1282; $C_{11}H_{18}O_4$ requires 215.1283].

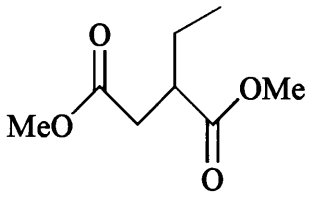
8.2.5 Conversion of diacids into dimethyl esters

General procedure 2 for the conversion of diacids into dimethyl esters using the Aldrich MNNG Diazomethane Generator.[91,133]

The sample (50 mg) was dissolved in diethyl ether (4 cm^3) and added to the outside tube of the diazomethane generator. The two parts were assembled and held together by tightening the 32 mm screw cap. Diethyl ether (1 cm^3) and carbitol (1 cm^3) were added to the inside tube. Diazald (0.6 g) was placed in the inside tube through the 8 mm open top screw cap. The lower part of the apparatus was immersed in ice water and about 1.5 cm^3 of KOH (37%) was injected dropwise through the silicone septum with a No. 23 needle to prevent back pressure. The apparatus was shaken by hand every 10 min to ensure

completion of reaction. After ~ 2 h the ether solution in the outside tube was shaken to remove ether in a warm water bath (60 °C) in a fume cupboard. Any unreacted diazomethane in the inside tube was destroyed by using silicic acid (0.2 g).

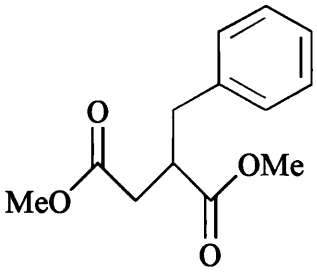
8.2.5.1 Dimethyl (±)-2-ethylsuccinate 331[134]



331

Using 2-ethylsuccinic acid **138** (50 mg, 0.34 mmol) in General procedure 2 gave dimethyl (±)-2-ethylsuccinate **331** as a colourless oil (43 mg, 86%); δ_H(400 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 7.4, CH_3CH_2), 1.54-1.73 (2 H, m, CH_3CH_2), 2.44 (ABX system, 1 H, dd, *J* 4.8 and 16.0, COCH*H*CH), 2.72 (ABX system, 1 H, *J* 9.3 and 16.0, COCH*H*CH), 2.77-2.84 (ABX system, 1 H, m, COCHHC*H*), 3.67 (3 H, s, OCH_3) and 3.70 (3 H, s, OCH_3).

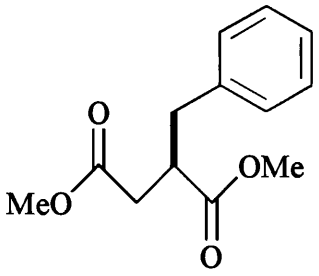
8.2.5.2 Dimethyl (±)-2-benzylsuccinate 152[135]



152

Using 2-benzylsuccinic acid **143** (50 mg, 0.24 mmol) in General procedure 2 gave a crude oil which was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give dimethyl (±)-2-benzylsuccinate **152** (31 mg, 54%). δ_H(400 MHz; $CDCl_3$) 2.40 (ABX system, 1 H, dd, *J* 5.0 and 16.8, ArC*H*$_2$CH), 2.68 (ABX system, 1 H, dd, *J* 9.0 and 16.8, ArCH*H*CH), 2.76 (ABX system, 1 H, dd, *J* 8.4 and 13.4, COCH*H*CH), 3.06 (ABX system, 1 H, dd, *J* 6.0 and 13.4, COCH*H*CH), 3.10-3.16 (ABX system, 1 H, m, $COCH_2CH$), 3.64 (3 H, s, OCH_3), 3.67 (3 H, s, OCH_3) and 7.07-7.30 (5 H, m, aromatic).

8.2.5.3 Dimethyl (2*R*)-benzylsuccinate 153[136]



153

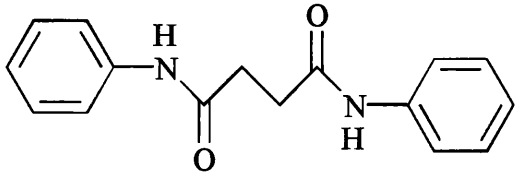
Using (2*R*)-benzylsuccinic acid **173** (50 mg, 0.24 mmol) in General procedure 2 gave dimethyl (2*R*)-benzylsuccinate **153** as a colourless oil (33 mg, 58%). $[\alpha]_D$ +20 (*c* 1.2, EtOAc); υ_{max}(NaCl)/cm^{-1} 3028 (aryl C-H), 2952 (CH_3) and 1737 (C=O); δ_H(400 MHz; $CDCl_3$) 2.41 (ABX system, 1 H, dd, *J* 5.0 and 16.8, ArCH*H*CH), 2.68 (ABX system, 1 H, dd, *J* 9.0 and 16.8, ArCH*H*CH), 2.76 (ABX system, 1 H, dd, *J* 8.3 and 13.4, COCH*H*CH), 3.06 (ABX system, 1 H, dd, *J* 6.3 and 13.4, COCH*H*CH), 3.11-3.17 (ABX system, 1 H, m, $COCH_2CH$), 3.62 (3 H, s, OCH_3), 3.67 (3 H, s, OCH_3) and 7.14-7.30 (5 H, m , aromatic); δ_C(100 MHz; $CDCl_3$) 35.3 (CH_2), 38.1 (CH_2), 43.4 (*C*H), 52.1 (OCH_3), 52.3 (OCH_3), 127.1 (Ar*C*H), 128.9 (2 x Ar*C*H), 129.4 (2 x Ar*C*H), 138.5 (Ar*C*), 172.7 (*C*=O) and 175.1 (*C*=O).

8.2.6 Conversion of diacids into dianilides

General procedure 3 for the coupling reaction of aniline to diacids.

The diacid was dissolved in dry DMF (10 cm^3) under N_2 and stirred at room temperature. Added to this was EDCI (2.2 equiv.) and aniline (4 equiv.). The mixture was stirred at room temperature for 24 h, quenched with H_2O (10 cm^3) and extracted with ethyl acetate (3 x 20 cm^3). The combined extracts were washed with 1M HCl (10 cm^3), sodium hydrogen carbonate (10 cm^3) and with brine (10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure.

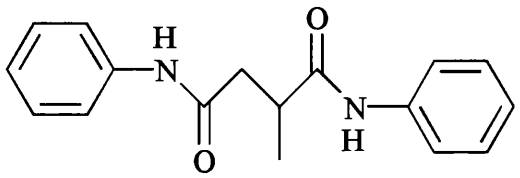
8.2.6.1 *N,N*-Diphenylsuccinamide 302[137]



302

Using succinic acid (0.5 g, 4.23 mmol) in General procedure 3 gave *N,N*-diphenylsuccinamide **302** as white needles from ethanol (0.32 g, 28%). mp 224-225 °C (lit.[137] mp 226 °C); (Found: C, 71.45 H, 6.0 N, 10.5%; $C_{16}H_{16}N_2O_2$ requires C, 71.6 H, 6.0 N, 10.4%); υ_{max}(KBr)/cm^{-1} 3316 (N-H), 3058 (aryl C-H), 1662 (C=O), 1596 (benzene ring) and 1527 (C=O); δ_H(400 MHz; d_6-DMSO) 2.50 (4 H, s, COC*H*$_2$C*H*$_2$), 7.02 (2 H, t, *J* 7.4, *para*-ArC*H*), 7.27 (4 H, t, *J* 7.9, *meta*-ArC*H*), 7.59 (4 H, d, *J* 7.8, *ortho*-ArC*H*), and 9.96 (2 H, s, N*H*); δ_C(100 MHz; d_6-DMSO) 31.6 (2 x *C*H$_2$), 119.3 (4 x ArCH), 123.2 (2 x ArCH), 129.0 (4 x ArCH), 139.7 (2 x Ar*C*) and 170.7 (2 x *C*=O); *m/z* (EI) 268 (M^+, 19%), 176 (M^+-$ArNH_2$, 36) and 93 ($ArNH_2$, 100); (Found M^+ 268.1210; $C_{16}H_{16}N_2O_2$ requires M^+ 268.1212).

8.2.6.2 (±)-*N,N*-Diphenyl-2-methylsuccinamide 158[138]

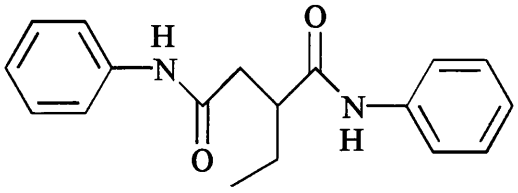


158

Using (±)-2-methylsuccinic acid (0.1 g, 0.76 mmol) in General procedure 3 gave (±)-*N,N*-diphenyl-2-methylsuccinamide **158** as white needles from ethyl acetate (0.12 g, 57%). mp 215-217 °C (lit.[138] mp 214-217 °C); (Found: C, 72.2 H, 6.4 N, 9.8%; $C_{17}H_{18}N_2O_2$ requires C, 72.4 H, 6.4 N, 9.9%); υ_{max}(KBr)/cm^{-1} 3282 (NH), 1649 (C=O), 1597 (benzene ring) and 1529 (C=O); δ_H(400 MHz; d_6-DMSO) 1.17 (3 H, d, *J* 7.0, C*H*$_3$CH), 2.43 (ABX system, 1 H, dd, *J* 6.6 and 15.0, COCH*H*CH), 2.74 (ABX system, 1 H, dd, *J* 7.8 and 15.0, COCH*H*CH), 3.02 (ABX system, 1 H, dd, *J* 7.1 and 14.0, COCH$_2$C*H*), 7.02 (2 H, t, *J* 7.2, *para*-ArC*H*), 7.28 (4 H, t, *J* 7.4, *meta*-ArC*H*), 7.58 (2 H, d, *J* 8.0, *ortho*-ArC*H*), 7.61 (2 H, d, *J* 8.0, *ortho*-ArC*H*), 9.96 (1 H, s, N*H*) and 9.97 (1H, s, N*H*); δ_C(100 MHz; d_6-DMSO) 18.3 (*C*H$_3$), 37.4 (*C*H), 40.5 (*C*H$_2$), 119.3 (2 x ArCH),

119.4 (2 x ArCH), 123.3 (2 x ArCH), 128.9 (2 x ArCH), 129.0 (2 x ArCH), 139.6 (ArC), 139.8 (ArC), 170.1 (C=O) and 174.4 (C=O); *m/z* (EI) 282 (M^+, 20%), 190 (M^+-$ArNH_2$, 50) and 93 ($ArNH_2$, 100); (Found M^+ 282.1367; $C_{17}H_{18}N_2O_2$ requires M^+ 282.1368).

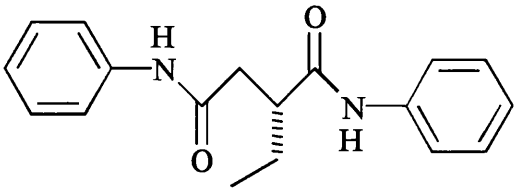
8.2.6.3 (±)-*N,N*-Diphenyl-2-ethylsuccinamide 159



159

Using (±)-2-ethylsuccinic acid **138** (67 mg, 0.45 mmol) in General procedure 3 gave (±)-*N,N*-diphenyl-2-ethylsuccinamide **159** (0.11 g, 85%) as white plates from ethyl acetate. mp 202-205 °C; (Found: C, 72.8 H, 6.8 N, 9.4%; $C_{18}H_{20}N_2O_2$ requires C, 72.95 H, 6.8 N, 9.45%); υ_{max}(KBr)/cm^{-1} 3436 (NH), 1655 (C=O) and 1598 (C=O); δ_H(400 MHz; d_6-DMSO) 0.90 (3 H, t, *J* 7.4, CH_3CH_2), 1.51-1.63 (2 H, m, CH_3CH_2), 2.47 (ABX system, 1 H, dd, *J* 6.0 and 15.6, COCHHCH), 2.72 (ABX system, 1 H, dd, *J* 8.4 and 15.2, COCHHCH), 2.86-2.93 (ABX system, 1 H, m, $COCH_2CH$), 7.01-7.04 (2 H, m, *para*-ArCH), 7.25-7.30 (4 H, m, *meta*-ArCH), 7.57 (2 H, d, *J* 8.0, *ortho*-ArCH), 7.62 (2 H, d, *J* 8.0, *ortho*-ArCH), 9.95 (1 H, s, NH) and 9.98 (1 H, s, NH); δ_C(100 MHz; d_6-DMSO) 11.8 (CH_3), 25.8 (CH_2), 38.6 (CH_2), 44.2 (CH), 119.3 (2 x ArCH), 119.5 (2 x ArCH), 123.3 (2 x ArCH), 128.9 (2 x ArCH), 129.0 (2 x ArCH), 139.6 (ArC), 139.7 (ArC), 170.2 (C=O) and 173.6 (C=O); *m/z* (EI) 296 (M^+, 10%), 204 (M^+-$ArNH_2$, 57) and 93 ($ArNH_2$, 100); (Found M^+ 296.1523; $C_{18}H_{20}N_2O_2$ requires M^+ 296.1525).

8.2.6.4 (2*R*)-*N,N*-Diphenyl-2-ethylsuccinamide 177

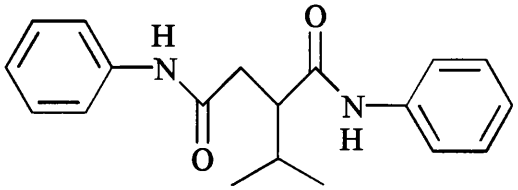


177

Using (2*R*)-ethylsuccinic acid **167** (70 mg, 0.05 mmol) in General procedure 3 gave (2*R*)-*N,N*-diphenyl-2-ethylsuccinamide **177** (80 mg, 57%) as white plates. Spectral data were identical to racemate **159**. mp 204-206 °C; $[\alpha]_D$ -28 (*c* 0.5, *i*PrOH); (Found: C, 72.6 H, 6.8 N, 9.35%; $C_{18}H_{20}N_2O_2$ requires C, 72.95 H, 6.8 N, 9.45%); *m/z* (EI) 296 (M^+, 10%),

204 (M^+-$ArNH_2$, 57) and 93 ($ArNH_2$, 100); (Found M^+ 296.1526; $C_{18}H_{20}N_2O_2$ requires M^+ 296.1525).

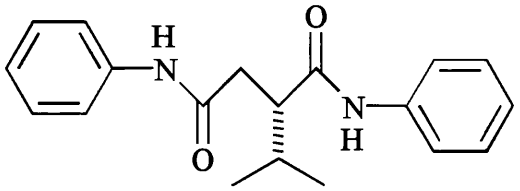
8.2.6.5 (±)-*N,N*-Diphenyl-2-isopropylsuccinamide 160



160

Using (±)-2-isopropylsuccinic acid **139** (0.22 g, 1.38 mmol) in General procedure 3 gave (±)-*N,N*-diphenyl-2-isopropylsuccinamide **160** (0.34 g, 79%) as white plates from ethyl acetate. mp 194-196 °C; (Found: C, 73.4 H, 7.1 N, 9.0%; $C_{19}H_{22}N_2O_2$ requires C, 73.5 H, 7.1 N, 9.0%); υ_{max}(KBr)/cm^{-1} 3316 (NH), 1657 (C=O) and 1527 (C=O); δ_H(400 MHz; d_6-DMSO) 0.94 (3 H, d, *J* 6.8, CH_3CHCH_3), 0.97 (3 H, d, *J* 6.8, CH_3CHCH_3), 1.88-1.96 (1 H, m, CH_3CHCH_3), 2.76-2.85 (3 H, m, $COCH_2CH$), 6.98-7.02 (2 H, m, *para*-ArCH), 7.25-7.29 (4 H, m, *meta*-ArCH), 7.56 (2 H, d, *J* 7.6, *ortho*-ArCH), 7.60 (2 H, d, *J* 7.6, *ortho*-ArCH), 9.95 (1 H, s, NH) and 9.97 (1 H, s, NH); δ_C(100 MHz; d_6-DMSO) 19.9 (CH_3), 20.7 (CH_3), 30.8 (CH), 35.5 (CH_2), 48.7 (CH), 119.2 (2 x ArCH), 119.4 (2 x ArCH), 123.2 (2 x ArCH), 128.9 (2 x ArCH), 129.0 (2 x ArCH), 139.6 (ArC), 139.7 (ArC), 170.6 (C=O) and 173.2 (C=O); *m/z* (EI) 310 (M^+, 7%), 218 (M^+-$ArNH_2$, 55) and 93 ($ArNH_2$, 100); (Found M^+ 310.1678; $C_{19}H_{22}N_2O_2$ requires M^+ 310.1681).

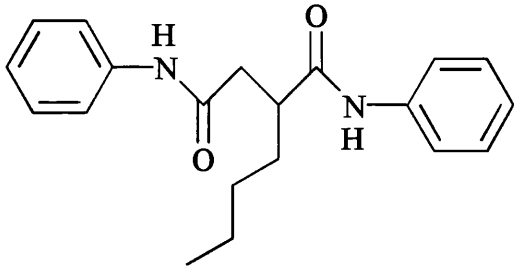
8.2.6.7 (2*R*)-*N,N*-Diphenyl-2-isopropylsuccinamide 178



178

Using (2*R*)-isopropylsuccinic acid **168** (0.16 g, 1.0 mmol) in General procedure 3 gave (2*R*)-*N,N*-diphenyl-2-isopropylsuccinamide **178** (0.23 g, 74%) as white plates. Spectral data were identical to racemate **160**. mp 193-195 °C; (Found: C, 73.1 H, 7.2 N, 9.1%; $C_{19}H_{22}N_2O_2$ requires C, 73.5 H, 7.1 N, 9.0%); $[\alpha]_D$ +4 (*c* 1.0, acetone); *m/z* (EI) 310 (M^+, 10%), 218 (M^+-$ArNH_2$, 74) and 93 ($ArNH_2$, 100); (Found M^+ 310.1682; $C_{19}H_{22}N_2O_2$ requires M^+ 310.1681).

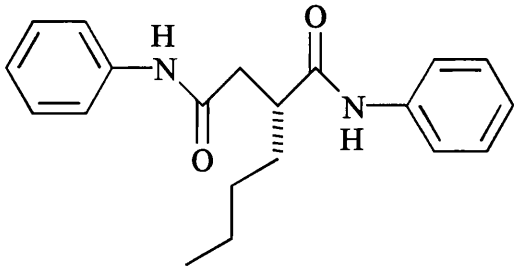
8.2.6.8 (±)-*N,N*-Diphenyl-2-butylsuccinamide 161



161

Using (±)-2-butylsuccinic acid **141** (0.20 g, 1.20 mmol) in General procedure 3 gave (±)-*N,N*-diphenyl-2-butylsuccinamide **161** (0.22 g, 56%) as white plates from ethyl acetate. mp 154-157 °C; υ_{max}(KBr)/cm^{-1} 3294 (NH), 1652 (C=O) and 1531 (C=O); δ_H(400 MHz; d_6-DMSO) 0.85 (3 H, t, *J* 6.9, C*H*$_3$CH$_2$), 1.28-1.58 (6 H, m, alkyl-H), 2.44-2.51 (ABX system, 1 H, m, COCH*H*CH), 2.70 (ABX system, 1 H, dd, *J* 8.3 and 15.4, COCH*H*CH), 2.92-2.95 (ABX system, 1 H, m, COCH$_2$C*H*), 6.99-7.03 (2 H, m, *para*-ArC*H*), 7.22-7.30 (4 H, m, *meta*-ArC*H*), 7.57 (2 H, d, *J* 7.9, *ortho*-ArC*H*), 7.62 (2 H, d, *J* 7.8, *ortho*-ArC*H*), 9.96 (1 H, s, N*H*) and 10.0 (1H, s, N*H*); δ_C(100 MHz; d_6-DMSO) 14.2 (*C*H$_3$), 22.5 (*C*H$_2$), 29.2 (*C*H$_2$), 32.4 (*C*H$_2$), 39.3 (*C*H$_2$), 43.0 (*C*H), 119.3 (2 x Ar*C*H), 119.5 (2 x Ar*C*H), 123.2 (2 x Ar*C*H), 128.9 (2 x Ar*C*H), 129.0 (2 x Ar*C*H), 139.5 (Ar*C*), 139.7 (Ar*C*), 170.2 (*C*=O) and 173.7 (*C*=O); *m/z* (EI) 324 (M^+, 5%), 232 (M^+-ArNH$_2$, 56) and 93 (ArNH$_2$, 100); (Found M^+ 324.1842; $C_{20}H_{24}N_2O_2$ requires M^+ 324.1838).

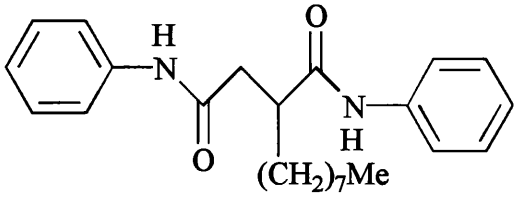
8.2.6.9 (2*R*)-*N,N*-Diphenyl-2-butylsuccinamide 179



179

Using (2*R*)-butylsuccinic acid **170** (78 mg, 0.33 mmol) in General procedure 3 gave (2*R*)-*N,N*-diphenyl-2-butylsuccinamide **179** (75 mg, 71%) as white plates. Spectral data were identical to racemate **161**. mp 153-156 °C; $[\alpha]_D$ -29 (*c* 0.6, iPrOH); (Found: C, 73.5 H, 7.5 N, 8.6%; $C_{20}H_{24}N_2O_2$ requires C, 74.0 H, 7.5 N, 8.6%); *m/z* (EI) 324 (M^+, 8%), 232 (M^+-ArNH$_2$, 59) and 93 (ArNH$_2$, 100); (Found M^+ 324.1837; $C_{20}H_{24}N_2O_2$ requires M^+ 324.1838).

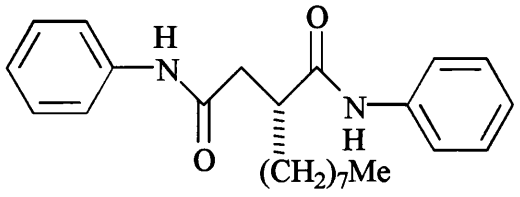
8.2.6.10 (±)-*N,N*-Diphenyl-2-octylsuccinamide 162



162

Using (±)-2-octylsuccinic acid **142** (0.20 g, 0.87 mmol) in General procedure 3 gave (±)-*N,N*-diphenyl-2-octylsuccinamide **162** (0.25 g, 67%) as white plates from ethanol. mp 175-178 °C; (Found: C, 75.8 H, 8.5 N, 7.4%; $C_{24}H_{32}N_2O_2$ requires C, 75.75 H, 8.5 N, 7.4%); υ_{max}(KBr)/cm^{-1} 3293 (NH), 1654 (C=O) and 1529 (C=O); δ_H(400 MHz; d_6-DMSO) 0.83 (3 H, t, *J* 6.8, C*H*$_3$CH$_2$), 1.22-1.60 (14 H, m, alkyl-H), 2.44-2.50 (ABX system, 1 H, m, COCH*H*CH), 2.70 (ABX system, 1 H, dd, *J* 8.0 and 15.2, COCH*H*CH), 2.92-2.95 (ABX system, 1 H, m, COCH$_2$C*H*), 7.00-7.03 (2 H, m, *para*-ArC*H*), 7.25-7.29 (4 H, m, *meta*-ArC*H*), 7.57 (2 H, d, *J* 7.6, *ortho*-ArC*H*), 7.61 (2 H, d, *J* 8.0, *para*-ArC*H*), 9.96 (1 H, s, N*H*) and 10.0 (1 H, s, N*H*); δ_C(100 MHz; d_6-DMSO) 14.3 (*C*H$_3$), 22.4 (*C*H$_2$), 26.9 (*C*H$_2$), 28.9 (*C*H$_2$), 29.2 (*C*H$_2$), 29.3 (*C*H$_2$), 31.5 (*C*H$_2$), 32.6 (*C*H$_2$), 39.5 (*C*H$_2$), 43.0 (*C*H), 119.3 (2 x Ar*C*H), 119.5 (2 x Ar*C*H), 123.3 (2 x Ar*C*H), 128.9 (2 x Ar*C*H), 129.0 (2 x Ar*C*H), 139.5 (Ar*C*), 139.7 (Ar*C*), 170.2 (*C*=O), and 173.8 (*C*=O); *m/z* (EI) 380 (M$^+$, 7%), 288 (M$^+$-ArNH$_2$, 52) and 93 (ArNH$_2$, 100); (Found M$^+$ 380.2463; $C_{24}H_{32}N_2O_2$ requires M$^+$ 380.2464).

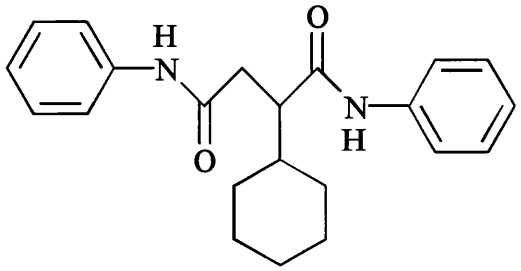
8.2.6.11 (2*R*)-*N,N*-Diphenyl-2-octylsuccinamide 181



181

Using (2*R*)-octylsuccinic acid **172** (0.25 g, 1.1 mmol) in General procedure 3 gave (2*R*)-*N,N*-diphenyl-2-octylsuccinamide **181** (0.26 g, 62%) as white plates. Spectral data were identical to racemate **162**. mp 174-177 °C; [α]$_D$ -40 (*c* 1.0, acetone); (Found: C, 75.7 H, 8.6 N, 7.4%; $C_{24}H_{32}N_2O_2$ requires C, 75.75 H, 8.5 N, 7.4%); *m/z* (EI) 380 (M$^+$, 20%), 288 (M$^+$-ArNH$_2$, 100) and 93 (ArNH$_2$, 100); (Found M$^+$ 380.2466; $C_{24}H_{32}N_2O_2$ requires M$^+$ 380.2464).

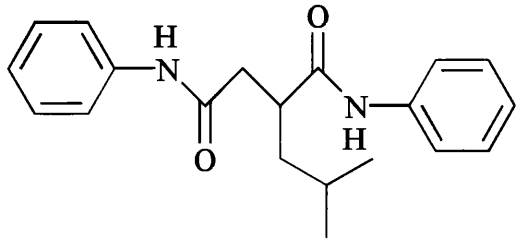
8.2.6.12 (±)-*N,N*-Diphenyl-2-cyclohexylsuccinamide 180



180

Using (±)-2-cyclohexylsuccinic acid **171** (0.2 g, 1.0 mmol) in General procedure 3 gave (±)-*N,N*-diphenyl-2-cyclohexylsuccinamide **180** (0.25 g, 63%) as white plates from ethanol. mp 245-247 °C; (Found: C, 75.25 H, 7.55 N, 8.0%; $C_{22}H_{26}N_2O_2$ requires C, 75.4 H, 7.5 N, 8.0%); υ_{max}(KBr)/cm^{-1} 3286 (NH), 1656 (C=O) and 1533 (C=O); δ_H(400 MHz; d_6-DMSO) 0.94-1.21 (5 H, m, alkyl-H), 1.56-1.80 (6 H, m, alkyl-H), 2.50-2.54 (ABX system, 1 H, m, COCH*H*CH), 2.74 (ABX system, 1 H, dd, *J* 9.9 and 15.0, COCH*H*CH), 2.81-2.85 (ABX system, 1 H, m, $COCH_2CH$), 6.98-7.02 (2 H, m, *para*-ArC*H*), 7.24-7.28 (4 H, m, *meta*-ArC*H*), 7.56 (2 H, d, *J* 8.0, *ortho*-ArC*H*), 7.61 (2 H, d, *J* 8.0, *ortho*-ArC*H*) and 9.86 (2 H, s, N*H*); δ_C(100 MHz; d_6-DMSO) 26.3 (3 x CH_2), 30.2 (CH_2), 30.7 (CH_2), 36.0 (CH_2), 40.6 (*C*H), 48.3 (*C*H), 119.2 (2 x Ar*C*H), 119.4 (2 x Ar*C*H), 123.2 (2 x Ar*C*H), 129.0 (2 x Ar*C*H), 139.0 (Ar*C*), 139.6 (Ar*C*), 170.6 (*C*=O) and 173.2 (*C*=O); *m/z* (EI) 350 (M^+, 12%), 258 (M^+-$ArNH_2$, 100) and 93 ($ArNH_2$, 100); (Found M^+ 350.1994; $C_{22}H_{26}N_2O_2$ requires M^+ 350.1994).

8.2.6.13 (±)-*N,N*-Diphenyl-2-isobutylsuccinamide 163

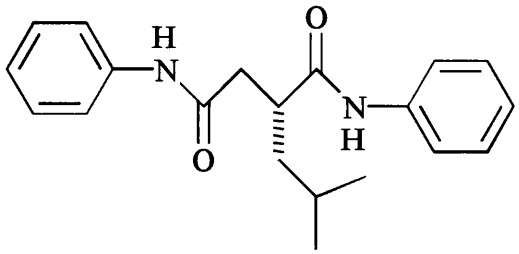


163

Using (±)-2-isobutylsuccinic acid **144** (50 mg, 0.28 mmol) in General procedure 3 gave (±)-*N,N*-diphenyl-2-isobutylsuccinamide **163** (52 mg, 58%) as white plates from ethanol. mp 196-198 °C; (Found: C, 74.0 H, 7.45 N, 8.6%; $C_{20}H_{24}N_2O_2$ requires C, 74.05 H, 7.5 N, 8.6%); υ_{max}(KBr)/cm^{-1} 3244 (NH), 1654 (C=O) and 1596 (C=O); δ_H(400 MHz; d_6-DMSO) 0.88 (3 H, d, *J* 6.3, CH_3CHCH_3), 0.94 (3 H, d, *J* 6.3, CH_3CHCH_3), 1.24-1.28 (1

H, m, 6-H), 1.52-1.62 (2 H, m, CH_3CHCH_2), 2.44-2.50 (ABX system, 1 H, m, $COCH_2CH$), 2.66 (ABX system, 1 H, dd, *J* 8.0, 15.1, $COCHHCH$), 2.98-3.03 (ABX system, 1 H, m, $COCH_2CH$), 7.02 (2 H, t, *J* 7.4, *para*-ArCH), 7.27 (4 H, t, *J* 7.8, *meta*-ArCH), 7.57 (2 H, d, *J* 7.8, *ortho*-ArCH), 7.63 (2 H, d, *J* 7.7, *ortho*-ArCH), 9.96 (1 H, s, NH) and 10.04 (1 H, s, NH); δ_C(100 MHz; d_6-DMSO) 22.6 (CH_3), 23.4 (CH_3), 26.0 (CH), 40.3 (CH_2), 41.4 (CH), 41.9 (CH_2), 119.4 (2 x ArCH), 119.6 (2 x ArCH), 123.3 (2 x ArCH), 128.9 (2 x ArCH), 129.0 (2 x ArCH), 139.5 (ArC), 139.7 (ArC), 170.0 (C=O) and 174.0 (C=O); *m/z* (EI) 324 (M^+, 15%), 268 (M^+-^{i}Bu, 42), 232 (M^+-$ArNH_2$, 100) and 93 ($ArNH_2$, 100); (Found M^+ 324.1839; $C_{20}H_{24}N_2O_2$ requires M^+ 324.1838).

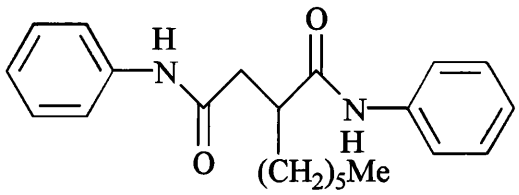
8.2.6.14 (2*R*)-*N,N*-Diphenyl-2-isobutylsuccinamide 183



183

Using (2*R*)-isobutylsuccinic acid **174** (0.2 g, 1.15 mmol) in General procedure 3 gave a crude mixture which was chromatographed (SiO_2, Et_2O) to give (2*R*)-*N,N*-diphenyl-2-isobutylsuccinamide **183** (0.16 g, 43%) as white plates. Spectral data were identical to racemate **163**. mp 193-195 °C; $[\alpha]_D$ -4 (*c* 0.5, iPrOH); (Found: C, 74.0 H, 7.45 N, 8.6%; $C_{20}H_{24}N_2O_2$ requires C, 74.05 H, 7.5 N, 8.6%); *m/z* (EI) 324 (M^+, 6%), 268 (M^+-^{i}Bu, 16), 232 (M^+-$ArNH_2$, 48) and 93 ($ArNH_2$, 100); (Found M^+ 324.1839; $C_{20}H_{24}N_2O_2$ requires M^+ 324.1838).

8.2.6.15 (±)-*N,N*-Diphenyl-2-hexylsuccinamide 165

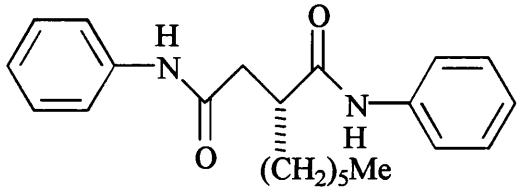


165

Using (±)-2-hexylsuccinic acid **145** (0.2 g, 1.0 mmol) in General procedure 3 gave (±)-*N,N*-diphenyl-2-hexylsuccinamide **165** (0.18 g, 51%) as white plates after recrystallisation from ethanol. mp 167-169 °C; (Found: C, 75.1 H, 8.0 N, 8.0%;

$C_{22}H_{28}N_2O_2$ requires C, 75.0 H, 8.0 N, 7.95%); υ_{max}(KBr)/cm^{-1} 3294 (NH), 1651 (C=O) and 1531 (C=O); δ_H(400 MHz; d_6-DMSO) 0.84 (3 H, t, *J* 6.8, C*H*$_3$CH$_2$), 1.24-1.27 (8 H, m, alkyl-H), 1.44-1.63 (2 H, m, alkyl-H), 2.44-2.50 (ABX system, 1 H, m, COCH*H*CH), 2.70 (ABX system, 1 H, dd, *J* 8.4, 15.2, COCH*H*CH), 2.88-2.97 (ABX system, 1 H, m, COCH$_2$C*H*), 7.02-7.06 (2 H, m, *para*-ArC*H*), 7.25-7.32 (4 H, m, *meta*-ArC*H*), 7.54 (2 H, d, *J* 7.6, *ortho*-ArC*H*), 7.62 (2 H, d, *J* 8.0, *ortho*-ArC*H*), 9.96 (1 H, s, N*H*), and 10.0 (1 H, s, N*H*); δ_C(100 MHz; d_6-DMSO) 14.3 (*C*H$_3$), 22.3 (*C*H$_2$), 27.0 (*C*H$_2$), 29.0 (*C*H$_2$), 31.5 (*C*H$_2$), 32.7 (*C*H$_2$), 39.1 (*C*H$_2$), 43.0 (*C*H), 119.3 (2 x Ar*C*H), 119.5 (2 x Ar*C*H), 123.3 (2 x Ar*C*H), 128.9 (2 x Ar*C*H), 129.0 (2 x Ar*C*H), 139.5 (Ar*C*), 139.7 (Ar*C*), 170.2 (*C*=O) and 173.8 (*C*=O); *m/z* (EI) 352 (M$^+$, 6%), 260 (M$^+$-ArNH$_2$, 44) and 93 (ArNH$_2$, 100); (Found M$^+$ 352.2150; $C_{22}H_{28}N_2O_2$ requires M$^+$ 352.2151).

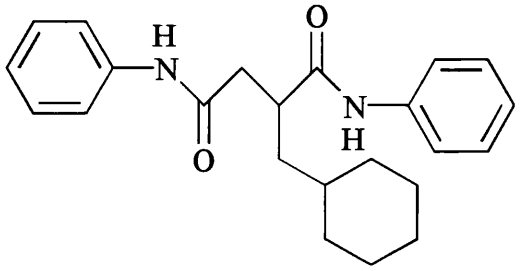
8.2.6.16 (2*R*)-N,N-Diphenyl-2-hexylsuccinamide 184



184

Using (2*R*)-hexylsuccinic acid **175** (0.23 g, 1.14 mmol) in General procedure 3 gave a crude mixture which was chromatographed (SiO_2, Et_2O) to give (2*R*)-*N,N*-diphenyl-2-hexylsuccinamide **184** (0.18 g, 45%) as white plates. Spectral data were identical to racemate **165**. mp 167-169 °C; $[\alpha]_D$ -10 (*c* 1.0, iPrOH); *m/z* (EI) 352 (M$^+$, 8%), 260 (M$^+$-ArNH$_2$, 48) and 93 (ArNH$_2$, 100); (Found M$^+$ 352.2151; $C_{22}H_{28}N_2O_2$ requires M$^+$ 352.2151).

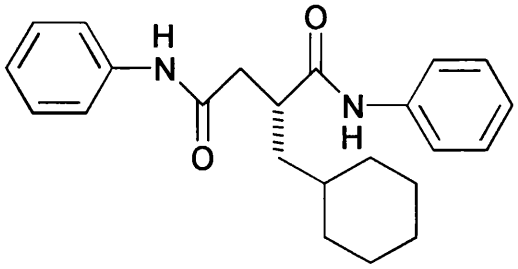
8.2.6.17 (±)-*N,N*-Diphenyl-2-cyclohexylmethylsuccinamide 166



166

Using (±)-2-cyclohexylmethylsuccinic acid **146** (0.1 g, 0.47 mmol) in General procedure 3 gave (±)-*N,N*-diphenyl-2-cyclohexylmethylsuccinamide **166** (90 mg, 53%) as white plates from ethanol. mp 172-174 °C; (Found: C, 75.7 H, 7.7 N, 7.8%; $C_{23}H_{28}N_2O_2$ requires C, 75.8 H, 7.7 N, 7.7%); υ_{max}(KBr)/cm^{-1} 3265 (NH), 1655 (C=O) and 1534 (C=O); δ_H(400 MHz; d_6-DMSO) 0.88-0.94 (2 H, m, alkyl-H), 1.09-1.32 (5 H, m, alkyl-H), 1.54-1.90 (6 H, m, alkyl-H), 2.45 (ABX system, 1 H, dd, *J* 6.5, 15.2, COCH*H*CH), 2.66 (ABX system, 1 H, dd, *J* 8.0, 15.2, COCH*H*CH), 3.02-3.05 (ABX system, 1 H, m, $COCH_2CH$), 7.02-7.04 (2 H, m, *para*-ArC*H*), 7.26-7.30 (4 H, m, *meta*-ArC*H*), 7.57 (2 H, d, *J* 7.6, *ortho*-ArC*H*), 7.62 (2 H, d, *J* 7.6, *ortho*-ArC*H*), 9.96 (1 H, s, N*H*) and 10.0 (1 H, s, N*H*); δ_C(100 MHz; d_6-DMSO) 26.0 (CH_2), 26.4 (CH_2), 33.0 (CH_2), 33.6 (CH_2), 35.3 (*C*H), 39.5 (2 x CH_2), 39.9 (CH_2), 40.7 (*C*H), 119.4 (2 x Ar*C*H), 119.6 (2 x Ar*C*H), 123.3 (2 x Ar*C*H), 128.9 (2 x Ar*C*H), 129.0 (2 x Ar*C*H), 139.5 (Ar*C*), 139.7 (Ar*C*), 170.0 (*C*=O), and 174.0 (*C*=O); *m/z* (EI) 364 (M^+, 7%), 272 (M^+-$ArNH_2$, 54) and 93 ($ArNH_2$, 100); (Found M^+ 364.2148; $C_{23}H_{28}N_2O_2$ requires M^+ 364.2151).

8.2.6.18 (2*R*)-*N,N*-Diphenyl-2-cyclohexylmethylsuccinamide 185

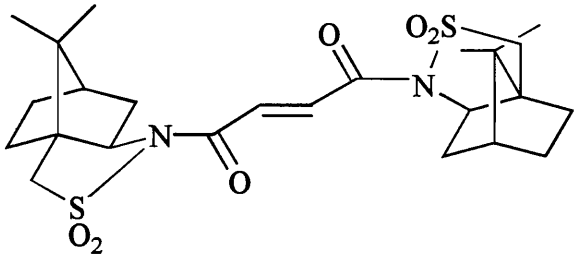


185

Using (2*R*)-cyclohexylmethylsuccinic acid **176** (0.42 g, 1.96 mmol) in General procedure 3 gave a crude mixture which was chromatographed (SiO_2, Et_2O) to give (2*R*)-*N,N*-diphenyl-2-cyclohexylmethylsuccinamide **185** (0.57 g, 80%) as white plates. Spectral data were identical to racemate **166**. mp 171-173 °C; $[\alpha]_D$ -12 (*c* 1.0, iPrOH); *m/z* (EI) 364 (M^+, 7%), 272 (M^+-$ArNH_2$, 72) and 93 ($ArNH_2$, 100); (Found M^+ 364.2152; $C_{23}H_{28}N_2O_2$ requires M^+ 364.2151).

8.2.7 Synthesis of 2-substituted succinamides

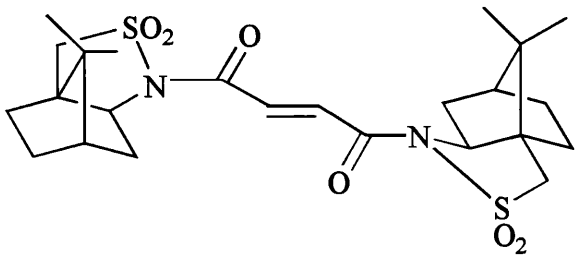
8.2.7.1 *N,N'*-Bis[(2*R*)-bornane-10,2-sultam]fumaramide 100[80]



100

Compound **100** was prepared in 81% yield on a 3.34 mmol scale by the method of Bauer and co-workers[80] and gave mp 245-247 °C (lit.[80] 247-248 °C); $[\alpha]_D$ -133 (*c* 1.0, $CHCl_3$) [lit.[80] –135.6, (*c* 1.18, $CHCl_3$)]; δ_H(400 MHz, $CDCl_3$) 0.99 (6 H, s, CH_3CCH_3), 1.16 (6 H, s, CH_3CCH_3), 1.32-1.47 (4 H, m, alkyl-H), 1.90-1.99 (6 H, m, alkyl-H), 2.09-2.20 (4 H, m, alkyl-H), 3.48 (AB system, 2 H, d, *J* 13.8, CH_2SO_2), 3.55 (AB system, 2 H, d, *J* 13.8, CH_2SO_2), 3.95-3.98 (2 H, m, CHN) and 7.64 (2 H, s, CH=CH).

8.2.7.2 *N,N'*-Bis[(2*S*)-bornane-10,2-sultam]fumaramide

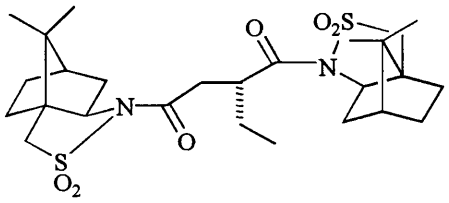


The above compound was prepared in 68% yield on a 11.6 mmol scale by the method of Bauer and co-workers[80] and gave mp 236-238 °C. Spectral data were identical to enantiomer **100**. $[\alpha]_D$ +145 (*c* 1.2, $CHCl_3$); (Found: C, 56.4 H, 6.7 N, 5.5%; $C_{24}H_{34}N_2O_6S_2$ requires C, 56.45 H, 6.7 N, 5.5%); *m/z* (EI) 510 (M^+, 4%), 382 (17), 296 (76) and 135 (100); (Found M^+ 510.1859; $C_{24}H_{34}N_2O_6S_2$ requires M^+ 510.1858).

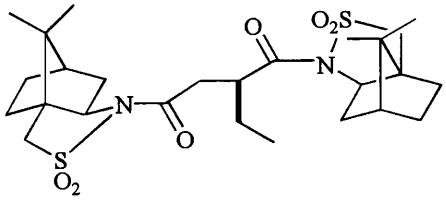
General procedure 4 for the 1,4-addition of Grignard reagents to *N,N'*-bis[(2*R*)-bornane-10,2-sultam]fumaramide 100.

The Grignard reagent (3.5 equiv.) in diethyl ether was added dropwise to a stirred solution of *N,N'*-bis[(2*R*)-bornane-10,2-sultam]fumaramide **100** (1 equiv.) in dry THF under N_2 at –78 °C. After 3 h at –78 °C the reaction mixture was quenched with sat. aq. NH_4Cl soln. and then poured onto sat. aq. NH_4Cl soln. The product was extracted with ethyl acetate (2 x 20 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

8.2.7.3 (2*R*)- 186 and (2*S*)-*N,N'*-Bis[(2*R*)-bornane-10,2-sultam]-2-ethylsuccinamide 187



186



187

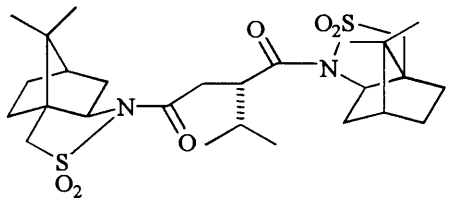
Using ethyl magnesium bromide (7.0 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **100** on a 4.0 mmol scale following General procedure 4 produced a residue which was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-*N,N'*-bis[(2*R*)-bornane-10,2-sultam]-2-ethylsuccinamide **186** (1.0 g, 56%) and (2*S*)-*N,N'*-bis[(2*R*)-bornane-10,2-sultam]-2-ethylsuccinamide **187** (0.35 g, 17%) as white plates.

186 (Major): mp 196-199 °C; $[\alpha]_D$ -98 (*c* 1.2, EtOAc); (Found: C, 57.5 H, 7.4 N, 5.1%; $C_{26}H_{40}N_2O_6S_2$ requires C, 57.75 H, 7.5 N, 5.2%); υ_{max}(KBr)/cm^{-1} 2965 (CH), 1687 (amide), 1330 and 1164 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.93-0.96 (9 H, m, 6H from C*C*H_3 and 3H from C*H*$_3$CH$_2$), 1.13 (3 H, s, CC*H*$_3$), 1.15 (3 H, s, CC*H*$_3$), 1.24-1.42 (4 H, m, alkyl-H), 1.61-1.70 (1 H, m, alkyl-H), 1.78-1.98 (8 H, m, alkyl-H), 2.05-2.18 (3 H, m, alkyl-H) 2.85 (1 H, dd, *J* 4.4 and 17.0, CH*H*CHC(O)N), 3.31 (1 H, dd, *J* 9.0 and 17.0, CH*H*CHC(O)N), 3.40-3.49 (5 H, m, 2 x C*H*$_2$SO$_2$ and CH$_2$C*H*C(O)N), 3.86 (1 H, t, *J* 8.0, C*H*N) and 3.95 (1 H, t, *J* 6.3, C*H*N); δ_C(100 MHz; $CDCl_3$) 11.4 (*C*H$_3$), 20.3 (2 x *C*H$_3$), 21.2 (*C*H$_3$), 21.3 (*C*H$_3$), 26.0 (*C*H$_2$), 26.8 (2 x *C*H$_2$), 33.2 (*C*H$_2$), 33.3 (*C*H$_2$), 36.0 (*C*H$_2$), 38.8 (*C*H$_2$), 39.0 (*C*H$_2$), 42.7 (*C*H), 45.0 (*C*H), 45.1 (*C*H), 48.1 (2 x *C*), 48.7 (*C*), 48.9 (*C*), 53.3 (*C*H$_2$), 53.4 (*C*H$_2$), 65.6 (*C*H), 65.7 (*C*H), 170.0 (*C*=O) and 174.0 (*C*=O); *m/z* (EI) 540

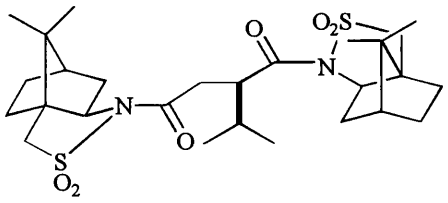
(M^+), 326 (M^+-camphorsultam, 100) and 135 (34); (Found M^+ 540.2329; $C_{26}H_{40}N_2O_6S_2$ requires M^+ 540.2328).

187 (Minor): mp 115-117 °C; $[\alpha]_D$ -104 (*c* 1.2, EtOAc); (Found: C, 57.6 H, 7.45 N, 5.2%; $C_{26}H_{40}N_2O_6S_2$ requires C, 57.75 H, 7.5 N, 5.2%); υ_{max}(KBr)/cm^{-1} 2962 (CH), 1693 (amide), 1333 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.94-0.98 (12 H, m, 9H from CC*H*$_3$ and 3H from C*H*$_3$CH$_2$), 1.15 (3 H, s, CC*H*$_3$), 1.31-1.44 (4 H, m, alkyl-H), 1.51-1.58 (1 H, m, alkyl-H), 1.84-2.16 (11 H, m, alkyl-H), 3.00 (1 H, dd, *J* 5.0 and 17.0, CH*H*CHC(O)N), 3.14 (1 H, dd, *J* 8.7 and 17.0, CH*H*CHC(O)N), 3.35-3.51 (5 H, m, 2 x C*H*$_2$SO$_2$ and CH$_2$C*H*C(O)N), 3.82-3.92 (2 H, m, 2 x C*H*N); δ_C(100 MHz; $CDCl_3$) 11.8 (*C*H$_3$), 20.3 (*C*H$_3$), 20.4 (*C*H$_3$), 21.0 (*C*H$_3$), 21.2 (*C*H$_3$), 24.5 (*C*H$_2$), 26.8 (*C*H$_2$), 26.9 (*C*H$_2$), 33.2 (*C*H$_2$), 33.3 (*C*H$_2$), 38.2 (*C*H$_2$), 38.4 (*C*H$_2$), 38.7 (*C*H$_2$), 42.8 (*C*H), 45.0 (2 x *C*H), 48.1 (*C*), 48.2 (*C*), 48.8 (*C*), 48.9 (*C*), 53.2 (*C*H$_2$), 53.5 (*C*H$_2$), 65.5 (*C*H), 65.7 (*C*H), 170.2 (*C*=O) and 174.2 (*C*=O); *m/z* (FAB+) 541 [$(M+H)^+$, 8%], 326 (M^+-camphorsultam, 100) and 135 (24); [Found (FAB+): $(M+H)^+$ 541.2405; $C_{26}H_{40}N_2O_6S_2$ requires 541.2406].

8.2.7.4 (2*R*)- 188 and (2*S*)-*N*,*N*'-Bis[(2*R*)-bornane-10,2-sultam]-2-isopropylsuccinamide 189



188



189

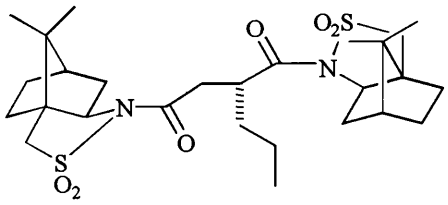
Using isopropyl magnesium chloride (2.7 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **100** on a 1.6 mmol scale following General procedure 4 gave a residue, 0.83 g. A portion of the residue (0.14 g) was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-*N*,*N*'-bis[(2*R*)-bornane-10,2-sultam]-2-isopropylsuccinamide **188** (81 mg, 58%) and (2*S*)-*N*,*N*'-bis[(2*R*)-bornane-10,2-sultam]-2-isopropylsuccinamide **189** (43 mg, 31%) as white plates.

188 (Major): mp 74-78 °C; $[\alpha]_D$ -142 (*c* 0.7, EtOAc); υ_{max}(KBr)/cm^{-1} 2962 (CH), 1691 (amide), 1330 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.86 (3 H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 0.92 (3 H, s, CC*H*$_3$), 0.96 (3 H, s, CC*H*$_3$), 1.02 (3 H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 1.15 (6 H, s, CC*H*$_3$), 1.24-1.42 (4 H, m, alkyl-H), 1.83-1.89 (6 H, m, alkyl-H), 2.00-2.18 (4 H, m, alkyl-H), 2.27-2.31 (1 H, m, CH$_2$C*H*C(O)N), 2.80 (1 H, dd, *J* 3.7 and 17.0, CH*H*CHC(O)N), 3.26 (1 H, dd, *J* 9.6 and 17.0, CH*H*CHC(O)N), 3.40-3.49 (4 H, m, 2 x

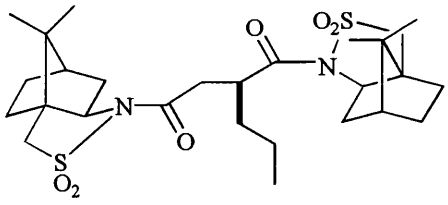
CH_2SO$_2$), 3.86 (1 H, t, *J* 5.0, C*H*N) and 3.95 (1 H, t, *J* 5.4, C*H*N); δ_C(100 MHz; $CDCl_3$) 17.9 (*C*H$_3$), 20.3 (2 x *C*H$_3$), 21.2 (2 x *C*H$_3$), 21.3 (*C*H$_3$), 26.9 (2 x *C*H$_2$), 30.6 (*C*H), 32.1 (*C*H$_2$), 33.2 (*C*H$_2$), 33.3 (*C*H$_2$), 38.7 (*C*H$_2$), 39.1 (*C*H$_2$), 45.0 (2 x *C*H), 47.1 (*C*H), 48.1 (2 x *C*), 48.6 (*C*), 48.9 (*C*), 53.3 (*C*H$_2$), 53.5 (*C*H$_2$), 65.7 (2 x *C*H), 170.3 (*C*=O) and 173.8 (*C*=O); *m/z* (FAB+) 555 [(M+H)$^+$, 10%], 340 (M$^+$-camphorsultam, 100) and 135 (20); [Found (M+H)$^+$ 555.2565; $C_{27}H_{42}N_2O_6S_2$ requires 555.2563].

189 (Minor): mp 256-258 °C; $[\alpha]_D$ -83 (*c* 0.7, EtOAc); (Found: C, 58.45 H, 7.5 N, 5.0%; $C_{27}H_{42}N_2O_6S_2$ requires C, 58.5 H, 7.6 N, 5.05%); υ_{max}(KBr)/cm^{-1} 2965 (CH), 1693 (amide), 1324 and 1137 (-SO$_2$-N); δ_H(400 MHz; $CDCl_3$) 0.92-0.96 (9 H, m, 3H from CC*H*$_3$ and 6H from CH$_3$CHC*H*$_3$), 1.00-1.02 (3 H, m, CC*H*$_3$), 1.15 (3 H, s, CC*H*$_3$), 1.26 (3 H, s, CC*H*$_3$), 1.28-1.44 (4 H, m, alkyl-H), 1.83-1.89 (6 H, m, alkyl-H), 1.95-2.05 (3 H, m, alkyl-H), 2.15-2.20 (1 H, m, alkyl-H), 2.29-2.33 (1 H, m, CH$_2$C*H*C(O)N), 2.95 (1 H, dd, *J* 3.9 and 17.0, CH*H*CHC(O)N), 3.12 (1 H, dd, *J* 10.0 and 17.0, CH*H*CHC(O)N), 3.31-3.36 (1 H, m, CH$_2$C*H*C(O)N), 3.39-3.50 (4 H, m, 2 x C*H*$_2$SO$_2$), 3.82-3.86 (1 H, app t, *J* 6.3, C*H*N) and 3.90-3.92 (1 H, app t, *J* 6.3, C*H*N); δ_C(100 MHz; $CDCl_3$) 17.9 (*C*H$_3$), 18.8 (*C*H$_3$), 20.3 (*C*H$_3$), 20.5 (*C*H$_3$), 21.0 (*C*H$_3$), 21.3 (*C*H$_3$), 21.7 (*C*H$_3$), 26.8 (*C*H$_2$), 26.9 (*C*H$_2$), 28.7 (*C*H), 33.2 (*C*H$_2$), 33.3 (*C*H$_2$), 34.3 (*C*H$_2$), 38.5 (*C*H$_2$), 38.7 (*C*H$_2$), 45.0 (*C*H), 46.4 (*C*H), 48.1 (*C*), 48.2 (*C*), 48.8 (*C*), 48.9 (*C*), 53.2 (*C*H$_2$), 53.5 (*C*H$_2$), 65.6 (*C*H), 65.7 (*C*H), 170.5 (*C*=O) and 173.8 (*C*=O); *m/z* (CI$^+$ mode, isobutane) 555 [(M+H)$^+$, 14%], 340 (M$^+$-camphorsultam, 100) and 216 (49); [Found (M+H)$^+$ 555.2563; $C_{27}H_{42}N_2O_6S_2$ requires 555.2563].

8.2.7.5 (2*R*)- 190 and (2*S*)-*N,N'*-Bis[(2*R*)-bornane-10,2-sultam]-2-propylsuccinamide 191



190



191

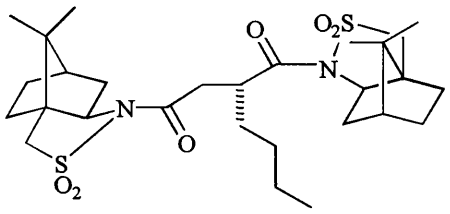
Using propyl magnesium bromide (3.5 cm^3 of a 1 mol dm^{-3} solution in Et_2O) and **100** on a 1.0 mmol scale following General procedure 4 produced a residue which was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-*N,N'*-bis[(2*R*)-bornane-10,2-

sultam]-2-propylsuccinamide **190** (0.23 g, 43%) and (2*S*)-*N*,*N*'-bis[(2*R*)-bornane-10,2-sultam]-2-propylsuccinamide **191** (0.14 g, 26%) as white plates.

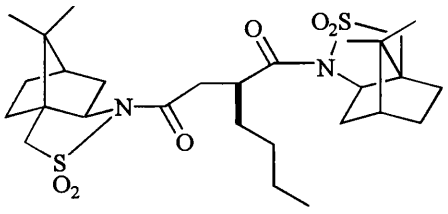
190 (Major): mp 198-200 °C; $[\alpha]_D$ -90 (*c* 1.0, EtOAc); (Found: C, 58.2 H, 7.6 N, 5.0%; $C_{27}H_{42}N_2O_6S_2$ requires C, 58.5 H, 7.6 N, 5.05%); υ_{max}(KBr)/cm^{-1} 2960 (CH), 1685 (amide), 1335 and 1133 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7.2, CH_2CH_3), 0.96 (3 H, s, CCH_3), 0.98 (3 H, s, CCH_3), 1.16 (3 H, s, CCH_3), 1.17 (3 H, s, CCH_3), 1.31-1.43 (6 H, m, alkyl-H), 1.55-1.60 (3 H, m, alkyl-H), 1.73-1.77 (1 H, m, alkyl-H), 1.86-1.89 (5 H, m, alkyl-H), 2.07-2.19 (3 H, m, alkyl-H), 2.86 (1 H, dd, *J* 4.5 and 17.2, $CHHCHC(O)N$), 3.32 (1 H, dd, *J* 8.9 and 17.2, $CHHCHC(O)N$), 3.41-3.51 (5 H, m, 2 x CH_2SO_2 and $CH_2CHC(O)N$), 3.87 (1 H, t, *J* 7.4, CHN) and 3.95 (1 H, t, *J* 6.2, CHN); δ_C(100 MHz; $CDCl_3$) 13.9 (CH_3), 19.9 (2 x CH_3), 19.9 (CH_2), 20.8 (CH_3), 20.9 (CH_3), 26.4 (2 x CH_2), 32.8 (CH_2), 32.9 (CH_2), 34.5 (CH_2), 36.0 (CH_2), 38.4 (CH_2), 38.6 (CH_2), 41.1 (CH), 44.7 (2 x CH), 47.7 (2 x C), 48.3 (C), 48.5 (C), 52.9 (CH_2), 53.0 (CH_2), 65.2 (2 x CH), 169.6 (C=O) and 173.8 (C=O); *m/z* (FAB+) 577 [$(M+Na)^+$, 100%] and 340 (MH^+-camphorsultam, 33); [Found $(M+Na)^+$ 577.2380; $C_{27}H_{42}N_2O_6S_2$ requires 577.2382].

191 (Minor): mp 187-189 °C; $[\alpha]_D$ -88 (*c* 1.0, EtOAc); (Found: C, 58.2 H, 7.7 N, 5.0%; $C_{27}H_{42}N_2O_6S_2$ requires C, 58.5 H, 7.6 N, 5.05%); υ_{max}(KBr)/cm^{-1} 2960 (CH), 1687 (amide), 1336 and 1136 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7.2, CH_2CH_3), 0.95-0.97 (6 H, m, CCH_3), 1.15 (3 H, s, CCH_3), 1.25 (3 H, s, CCH_3), 1.31-1.51 (7 H, m, alkyl-H), 1.78-1.93 (7 H, m, alkyl-H), 1.96-2.16 (4 H, m, alkyl-H), 3.00 (1 H, dd, *J* 5.2 and 17.0, $CHHCHC(O)N$), 3.13 (1 H, dd, *J* 8.6 and 17.0, $CHHCHC(O)N$), 3.39-3.51 (5 H, m, 2 x CH_2SO_2 and $CH_2CHC(O)N$), 3.83-3.86 (1 H, app t, *J* 6.3, CHN) and 3.88-3.91 (1 H, app t, *J* 6.3, CHN); δ_C(100 MHz; $CDCl_3$) 14.3 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 20.5 (CH_2), 21.0 (CH_3), 21.2 (CH_3), 26.8 (CH_2), 26.9 (CH_2), 33.2 (2 x CH_2), 33.3 (CH_2), 33.4 (CH_2), 38.5 (CH_2), 38.7 (CH_2), 41.2 (CH), 45.0 (2 x CH), 48.1 (C), 48.2 (C), 48.8 (C), 48.9 (C), 53.2 (CH_2), 53.5 (CH_2), 65.5 (CH), 65.7 (CH), 170.1 (C=O) and 174.4 (C=O); *m/z* (FAB+) 555 [$(M+H)^+$, 6%] and 340 (MH^+-camphorsultam, 100); [Found $(M+H)^+$ 555.2563; $C_{27}H_{42}N_2O_6S_2$ requires 555.2563].

8.2.7.6 (2*R*)- 192 and (2*S*)-*N,N'*-Bis[(2*R*)-bornane-10,2-sultam]-2-butylsuccinamide 193



192



193

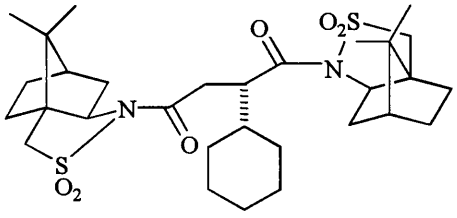
Using butyl magnesium chloride (1.7 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **100** on a 1 mmol scale following General procedure 4 produced a residue which was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-*N,N'*-bis[(2*R*)-bornane-10,2-sultam]-2-butylsuccinamide **192** (0.28 g, 56%) and (2*S*)-*N,N'*-bis[(2*R*)-bornane-10,2-sultam]-2-butylsuccinamide **193** (0.1 g, 20%) as white plates.

192 (Major): mp 73-75 °C; $[\alpha]_D$ -75 (*c* 0.88, EtOAc); (Found: C, 59.0 H, 7.7 N, 4.95%; $C_{28}H_{44}N_2O_6S_2$ requires C, 59.1 H, 7.5 N, 4.9%); υ_{max}(KBr)/cm^{-1} 2960 (CH), 1690 (amide), 1333 and 1135 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 7.2, CH_2CH_3), 0.95 (3 H, s, CCH_3), 0.96 (3 H, s, CCH_3), 1.15 (3 H, s, CCH_3), 1.16 (3 H, s, CCH_3), 1.23-1.42 (8 H, m, alkyl-H), 1.52-1.62 (1 H, m, alkyl-H), 1.72-1.76 (1 H, m, alkyl-H), 1.85-1.88 (6 H, m, alkyl-H), 2.05-2.18 (4 H, m, alkyl-H), 2.85 (1 H, dd, *J* 2.3 and 17.2, $CHHCHC(O)N$), 3.31 (1 H, dd, *J* 9.0 and 17.2, $CHHCHC(O)N$), 3.40-3.50 (5 H, m, 2 x CH_2SO_2 and $CH_2CHC(O)N$), 3.84-3.88 (1 H, app t, *J* 6.3, CHN) and 3.94 (1 H, t, *J* 6.3, CHN); δ_C(100 MHz; $CDCl_3$) 14.2 (CH_3), 20.3 (2 x CH_3), 21.2 (CH_3), 21.3 (CH_3), 22.9 (CH_2), 26.8 (2 x CH_2), 29.1 (CH_2), 32.5 (CH_2), 33.2 (2 x CH_2), 36.4 (CH_2), 38.8 (CH_2), 39.0 (CH_2), 41.6 (CH), 45.0 (2 x CH), 48.1 (2 x C), 48.7 (C), 48.8 (C), 53.3 (2 x CH_2), 65.6 (2 x CH), 170.0 (C=O) and 174.2 (C=O); *m/z* (FAB+) 591 [$(M+Na)^+$, 100%] and 354 (MH^+-camphorsultam, 33); [Found $(M+Na)^+$ 591.2535; $C_{28}H_{44}N_2O_6S_2$ requires 591.2539].

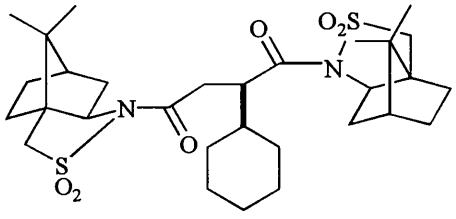
193 (Minor): mp 131-133 °C; $[\alpha]_D$ -82 (*c* 1.0, EtOAc); (Found: C, 58.9 H, 8.0 N, 4.75%; $C_{28}H_{44}N_2O_6S_2$ requires C, 59.1 H, 7.8 N, 4.9%); υ_{max}(KBr)/cm^{-1} 2960 (CH), 1695 (amide), 1331 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 6.6, CH_2CH_3), 0.97 (3 H, s, CCH_3), 0.98 (3 H, s, CCH_3), 1.17 (3 H, s, CCH_3), 1.24-1.50 (13 H, m, alkyl-H), 1.86-1.90 (6 H, m, alkyl-H), 1.98-2.18 (4 H, m, alkyl-H), 3.01 (1 H, dd, *J* 5.0 and 17.0, $CHHCHC(O)N$), 3.15 (1 H, dd, *J* 8.5 and 17.0, $CHHCHC(O)N$), 3.41-3.53 (5 H, m, 2 x CH_2SO_2 and $CH_2CHC(O)N$), 3.86 (1 H, t, *J* 7.1, CHN) and 3.91 (1 H, t, *J* 7.3, CHN); δ_C(100 MHz; $CDCl_3$) 14.2 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 20.9 (CH_3), 21.2 (CH_3), 23.0

(CH_2), 26.8 (CH_2), 26.9 (CH_2), 29.4 (CH_2), 31.0 (CH_2), 33.2 (CH_2), 33.3 (CH_2), 38.4 (CH_2), 38.5 (CH_2), 38.7 (CH_2), 41.5 (*C*H), 45.0 (2 x *C*H), 48.1 (*C*), 48.2 (*C*), 48.8 (*C*), 48.9 (*C*), 53.3 (CH_2), 53.5 (CH_2), 65.5 (*C*H), 65.7 (*C*H), 170.1 (*C*=O) and 174.4 (*C*=O); *m/z* (FAB+) 569 [$(M+H)^+$, 4%] and 354 (MH^+-camphorsultam, 100); [Found $(M+H)^+$ 569.2717; $C_{28}H_{44}N_2O_6S_2$ requires 569.2719].

8.2.7.7 (2*R*)- 194 and (2*S*)-*N,N'*-Bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylsuccinamide 195



194



195

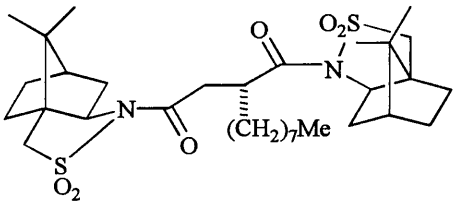
Using cyclohexyl magnesium chloride (6.8 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **100** on a 3.9 mmol scale following General procedure 4 afforded a mixture of diastereoisomers 2.52 g. A portion (0.5 g) was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-*N,N'*-bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylsuccinamide **194** (0.28g, 56%) and (2*S*)-*N,N'*-bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylsuccinamide **195** (0.11g, 22%) as white plates.

194 (Major): mp 180-183 °C; $[\alpha]_D$ -80 (*c* 1.0, EtOAc); (Found: C, 60.4 H, 7.9 N, 4.7%; $C_{30}H_{46}N_2O_6S_2$ requires C, 60.6 H, 7.8 N, 4.7%); υ_{max}(KBr)/cm^{-1} 2927 (CH), 1686 (amide), 1333 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.86-1.42 (20 H, m, alkyl-H), 1.60-1.73 (6 H, m, alkyl-H), 1.84-1.89 (7 H, m, alkyl-H), 2.00-2.18 (4 H, m, alkyl-H), 2.83 (1 H, dd, *J* 4.0 and 17.0, CH*H*CHC(O)N), 3.25 (1 H, dd, *J* 9.3 and 17.0, CH*H*CHC(O)N), 3.39-3.55 (5 H, m, 2 x CH_2SO_2 and $CH_2CHC(O)N$), 3.86 (1 H, app t, *J* 6.3, C*H*N) and 3.94 (1 H, t, *J* 6.2, C*H*N); δ_C(100 MHz; $CDCl_3$) 20.3 (2 x CH_3), 21.0 (CH_3), 21.2 (CH_3), 26.4 (CH_2), 26.8 (2 x CH_2), 27.0 (CH_2), 28.7 (CH_2), 31.4 (CH_2), 33.1 (CH_2), 33.3 (CH_2), 38.8 (CH_2), 39.0 (2 x CH_2), 40.8 (*C*H), 45.0 (*C*H), 48.1 (*C*H), 48.6 (2 x *C*), 48.8 (2 x *C*), 53.3 (CH_2), 53.4 (CH_2), 65.6 (*C*H), 65.7 (*C*H), 170.2 (*C*=O) and 173.6 (*C*=O); *m/z* (CI/NH_3) 612 ($M+NH_4^+$), 42%), 595 (MH^+, 38), 380 (MH^+-camphorsultam, 63) and 233 (100).

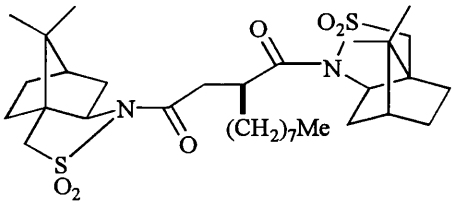
195 (Minor): mp 244-246 °C; $[\alpha]_D$ -84 (*c* 1.0, EtOAc); (Found: C, 60.65 H, 7.9 N, 4.8%; $C_{30}H_{46}N_2O_6S_2$ requires C, 60.6 H, 7.8 N, 4.7%); υ_{max}(KBr)/cm^{-1} 2929 (CH), 1684 (amide), 1327 and 1136 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.96-1.43 (21 H, m, alkyl-H),

1.56-2.19 (16 H, m, alkyl-H), 2.97 (1 H, dd, *J* 4.1 and 17.0, CH*H*CHC(O)N), 3.11 (1 H, dd, *J* 9.7 and 16.8, CH*H*CHC(O)N), 3.29-3.31 (1 H, m, $CH_2CHC(O)N$), 3.39-3.51 (4 H, m, 2 x CH_2SO_2), 3.84 (1 H, app t, *J* 6.2, C*H*N) and 3.92 (1 H, app t, *J* 6.2, C*H*N); δ_C(100 MHz; $CDCl_3$) 20.3 (CH_3), 20.5 (CH_3), 21.0 (CH_3), 21.3 (CH_3), 26.6 (CH_2), 26.7 (CH_2), 26.8 (2 x CH_2), 27.1 (CH_2), 28.7 (CH_2), 32.1 (CH_2), 33.2 (CH_2), 33.4 (CH_2), 35.2 (CH_2), 38.6 (CH_2), 38.7 (CH_2), 38.9 (CH), 45.0 (CH), 45.1 (CH), 46.4 (CH_2), 48.1 (2 x C), 48.7 (C), 48.9 (C), 53.2 (CH_2), 53.5 (CH_2), 65.6 (CH), 65.8 (CH), 170.4 (C=O) and 173.6 (C=O); *m/z* (FAB+) 595 [$(M+H)^+$, 4%] and 380 (MH^+-camphorsultam, 100); [Found $(M+H)^+$ 595.2878; $C_{30}H_{46}N_2O_6S_2$ requires 595.2876].

8.2.7.8 (2*R*)- 196 and (2*S*)-*N*,*N*'-Bis[(2*R*)-bornane-10,2-sultam]-2-octylsuccinamide 197



196



197

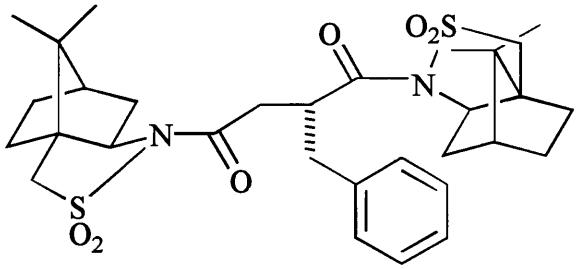
Using octyl magnesium bromide (6.8 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **100** on a 3.9 mmol scale following General procedure 4 produced a mixture of diastereoisomers 2.76 g. A portion (0.5 g) was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-*N*,*N*'-bis[(2*R*)-bornane-10,2-sultam]-2-octylsuccinamide **196** (0.39 g, 78%) as white plates and (2*S*)-*N*,*N*'-bis[(2*R*)-bornane-10,2-sultam]-2-octylsuccinamide **197** (93 mg, 19%) as a colourless oil.

196 (Major): mp 160-163 °C; $[\alpha]_D$ -76 (*c* 1.2, EtOAc); (Found: C, 61.5 H, 8.3 N, 4.5%; $C_{33}H_{52}N_2O_6S_2$ requires C, 61.5 H, 8.4 N, 4.5%); υ_{max}(KBr)/cm^{-1} 2923 (CH), 1683 (amide), 1331 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 7.1, CH_2CH_3), 0.95 (3 H, s, CCH_3), 0.96 (3 H, s, CCH_3), 1.15 (3 H, s, CCH_3), 1.16 (3 H, s, CCH_3), 1.23-1.42 (19 H, m, alkyl-H), 1.73-1.79 (1 H, m, alkyl-H), 1.85-1.88 (5 H, m, alkyl-H), 2.05-2.15 (3 H, m, alkyl-H), 2.85 (1 H, dd, *J* 4.6 and 17.1, CH*H*CHC(O)N), 3.30 (1 H, dd, *J* 9.0 and 17.1, CH*H*CHC(O)N), 3.44-3.50 (5 H, m, 2 x CH_2SO_2 and $CH_2CHC(O)N$), 3.84-3.87 (1 H, app t, *J* 6.3, C*H*N) and 3.94 (1 H, t, *J* 6.3, C*H*N); δ_C(100 MHz; $CDCl_3$) 14.5 (CH_3), 20.3 (2 x CH_3), 21.2 (CH_3), 21.3 (CH_3), 23.0 (CH_2), 26.8 (2 x CH_2), 26.9 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.9 (CH_2), 32.2 (CH_2), 32.9 (CH_2), 33.2 (CH_2), 33.3 (CH_2), 36.4 (CH_2), 38.8

(CH_2), 38.9 (CH_2), 41.7 (2 x *C*H), 45.1 (*C*H), 48.1 (2 x *C*), 48.7 (*C*), 48.8 (*C*), 53.3 (CH_2), 53.4 (CH_2), 65.6 (*C*H), 65.7 (*C*H), 170.0 (*C*=O) and 174.2 (*C*=O); *m/z* (EI) 624 (M+), 410 (M^+-camphorsultam, 100%) and 135 (30); [Found M^+ 624.3260; $C_{32}H_{52}N_2O_6S_2$ requires M^+ 624.3267].

197 (Minor): $[\alpha]_D$ -83 (*c* 1.2, EtOAc); υ_{max}(KBr)/cm^{-1} 2932 (CH), 1678 (amide), 1332 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 7.0, CH_2CH_3), 0.96 (3 H, s, CCH_3), 0.97 (3 H, s, CCH_3), 1.16 (3 H, s, CCH_3), 1.26-1.49 (21 H, m, alkyl-H), 1.85-2.18 (10 H, m, alkyl-H), 3.00 (1 H, dd, *J* 5.1 and 17.0, CH*H*CHC(O)N), 3.14 (1 H, dd, *J* 8.5 and 17.0, CH*H*CHC(O)N), 3.40-3.52 (5 H, m, 2 x CH_2SO_2 and $CH_2CHC(O)N$), 3.85 (1 H, app t, *J* 6.2, C*H*N) and 3.90 (1 H, app t, *J* 6.2, C*H*N); δ_C(100 MHz; $CDCl_3$) 14.1 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 20.5 (CH_3), 20.8 (CH_3), 22.6 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 26.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 30.9 (CH_2), 31.8 (CH_2), 32.8 (CH_2), 32.9 (CH_2), 38.0 (CH_2), 38.1 (CH_2), 38.3 (CH_2), 41.1 (*C*H), 44.6 (2 x *C*H), 47.7 (*C*), 47.8 (*C*), 48.4 (*C*), 48.5 (*C*), 52.9 (CH_2), 53.1 (CH_2), 65.1 (*C*H), 65.3 (*C*H), 169.8 (*C*=O) and 174.0 (*C*=O); *m/z* (FAB+) 647 [$(M+Na)^+$, 5%], 147 (42) and 73 (100); [Found $(M+Na)^+$ 647.3166; $C_{32}H_{52}N_2O_6S_2$ requires 647.3165].

8.2.7.9 (2*R*)-*N,N'*-Bis[(2*R*)-bornane-10,2-sultam]-2-benzylsuccinamide 198

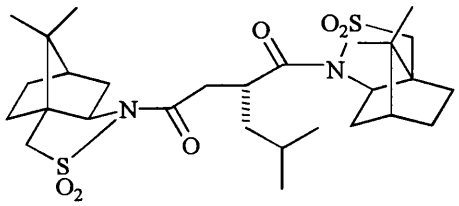


198

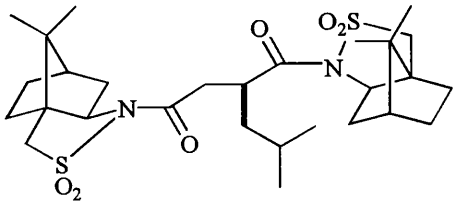
Using benzyl magnesium chloride (7.0 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **100** on a 4.0 mmol scale following General procedure 4 produced a mixture which was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-*N,N'*-bis[(2*R*)-bornane-10,2-sultam]-2-benzylsuccinamide **198** (1.7 g, 71 %) as white plates. mp 191-193 °C; $[\alpha]_D$ -70 (*c* 1.0, EtOAc); (Found: C, 61.6 H, 7.1 N, 4.6%; $C_{31}H_{42}N_2O_6S_2$ requires C, 61.8 H, 7.0 N, 4.65%); υ_{max}(KBr)/cm^{-1} 2958 (CH), 1685 (amide), 1333 and 1135 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.92 (3 H, s, CCH_3), 0.93 (3 H, s, CCH_3), 0.98 (3 H, s, CCH_3), 1.07 (3 H, s, CCH_3), 1.22-1.37 (4 H, m, alkyl-H), 1.80-1.86 (6 H, m, alkyl-H), 2.00-2.06 (4 H, m, alkyl-H), 2.67 (1 H, dd, *J* 9.4 and 13, ArCCH*H*), 2.74 (1 H, dd, *J* 5.2 and 17.5 CH*H*CHC(O)N),

3.22 (1 H, dd, *J* 7.5 and 13, ArCCH*H*), 3.32 (1 H, dd, *J* 8.3 and 17.4, CH*H*CHC(O)N), 3.42-3.51 (4 H, m, 2 x CH_2SO$_2$), 3.82-3.87 (3 H, m) and 7.17-7.37 (5 H, m, Ar-C*H*); δ_C(100 MHz; $CDCl_3$) 20.3 (2 x *C*H$_3$), 21.2 (*C*H$_3$), 21.3 (*C*H$_3$), 26.8 (2 x *C*H$_2$), 33.2 (*C*H$_2$), 33.3 (*C*H$_2$), 36.3 (*C*H$_2$), 38.8 (2 x *C*H$_2$), 43.6 (*C*H), 45.0 (2 x *C*H), 48.1 (2 x *C*), 48.7 (*C*), 48.8 (*C*), 53.2 (2 x *C*H$_2$), 53.4 (*C*H$_2$), 65.5 (*C*H), 65.6 (*C*H), 127.1 (Ar*C*H), 128.9 (2 x Ar*C*H), 129.8 (2 x Ar*C*H), 138.2 (Ar*C*), 169.9 (*C*=O) and 173.5 (*C*=O); *m/z* (EI) 602 (M+, 8%), 346 (100) and 135 (76); [Found M^+ 602.2487; $C_{31}H_{42}N_2O_6S_2$ requires 602.2484].

8.2.7.10 (2*R*)- 199 and (2*S*)-*N*,*N*'-Bis[(2*R*)-bornane-10,2-sultam]-2-isobutylsuccinamide 200



199



200

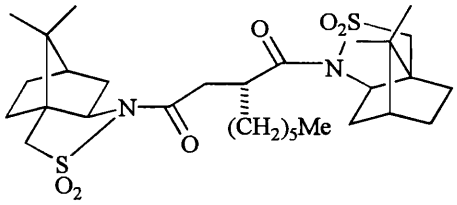
Using isobutyl magnesium bromide (6.8 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **100** on a 3.9 mmol scale following general procedure 4 produced a mixture of diastereoisomers 2.26 g. A portion (0.5 g) was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-*N*,*N*'-bis[(2*R*)-bornane-10,2-sultam]-2-isobutylsuccinamide **199** (0.16 g, 32%) and (2*S*)-*N*,*N*'-bis[(2*R*)-bornane-10,2-sultam]-2-isobutylsuccinamide **200** (96 mg, 19%) as white plates.

199 (Major): mp 239-241 °C; $[\alpha]_D$ -76 (*c* 1.0, EtOAc); (Found: C, 59.1 H, 7.75 N, 4.9%; $C_{28}H_{44}N_2O_6S_2$ requires C, 59.1 H, 7.8 N, 4.9%); υ_{max}(KBr)/cm^{-1} 2958 (CH), 1685 (amide), 1333 and 1164 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.90-0.96 (12 H, m), 1.15 (3 H, s, CC*H*$_3$), 1.16 (3 H, s, CC*H*$_3$), 1.20-1.46 (5 H, m, alkyl-H), 1.59-1.69 (2 H, m, alkyl-H), 1.84-1.92 (6 H, m, alkyl-H), 2.05-2.19 (4 H, m, alkyl-H), 2.86 (1 H, dd, *J* 5.2 and 17.2, CH*H*CHC(O)N), 3.26 (1 H, dd, *J* 8.4 and 17.2, CH*H*CHC(O)N), 3.40-3.57 (5 H, m, 2 x CH_2SO$_2$ and CH$_2$C*H*C(O)N), 3.84-3.88 (1 H, app t, *J* 6.3, C*H*N) and 3.94 (1 H, t, *J* 6.3, C*H*N); δ_C(100 MHz; $CDCl_3$) 20.3 (2 x *C*H$_3$), 21.2 (*C*H$_3$), 21.3 (*C*H$_3$), 21.9 (*C*H$_3$), 23.6 (*C*H$_3$), 26.1 (*C*H), 26.8 (2 x *C*H$_2$), 33.2 (*C*H$_2$), 33.3 (*C*H$_2$), 36.5 (*C*H$_2$), 38.8 (*C*H$_2$), 38.9 (*C*H$_2$), 40.0 (*C*H), 41.6 (*C*H$_2$), 45.1 (2 x *C*H), 48.1 (2 x *C*), 48.7 (*C*), 48.8 (*C*), 53.3 (*C*H$_2$), 53.4 (*C*H$_2$), 65.7 (2 x *C*H), 170.0 (*C*=O) and 174.6 (*C*=O); *m/z* (FAB+) 591 [(M+Na)$^+$,

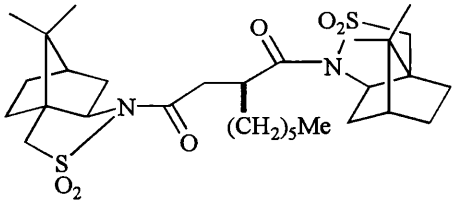
100%] and 354 (MH^+-camphorsultam, 15); [Found $(M+Na)^+$ 591.2536; $C_{28}H_{44}N_2O_6S_2$ requires 591.2539].

200 (Minor): mp 208-210 °C; $[\alpha]_D$ -80 (*c* 1.0, EtOAc); (Found: C, 59.05 H, 7.9 N, 4.9%; $C_{28}H_{44}N_2O_6S_2$ requires C, 59.1 H, 7.8 N, 4.9%); υ_{max}(KBr)/cm^{-1} 2960 (CH), 1685 (amide), 1336 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.89-0.97 (12 H, m, alkyl-H), 1.15 (3 H, s, CC*H*$_3$), 1.25 (3 H, s, CC*H*$_3$), 1.29-1.43 (5 H, m, alkyl-H), 1.61-1.68 (2 H, m, alkyl-H), 1.73-1.80 (1 H, m, alkyl-H), 1.84-1.89 (6 H, m, alkyl-H), 1.94-2.16 (4 H, m, alkyl-H), 3.00 (1 H, dd, *J* 5.5 and 17.0, CH*H*CHC(O)N), 3.09 (1 H, dd, *J* 7.9 and 17.0, CH*H*CHC(O)N), 3.39-3.54 (5 H, m, 2 x C*H*$_2$SO$_2$ and CH$_2$C*H*C(O)N), 3.84 (1 H, app t, *J* 6.2 C*H*N) and 3.88 (1 H, app t, *J* 6.2, C*H*N); δ_C(100 MHz; $CDCl_3$) 20.3 (*C*H$_3$), 20.4 (*C*H$_3$), 20.9 (*C*H$_3$), 21.2 (*C*H$_3$), 22.0 (*C*H$_3$), 23.5 (*C*H$_3$), 26.0 (*C*H), 26.8 (*C*H$_2$), 26.9 (*C*H$_2$), 33.2 (*C*H$_2$), 33.3 (*C*H$_2$), 38.4 (*C*H$_2$), 38.5 (*C*H$_2$), 38.7 (*C*H$_2$), 39.7 (*C*H), 40.0 (*C*H$_2$), 45.0 (2 x *C*H), 48.1 (*C*), 48.2 (*C*), 48.8 (*C*), 48.9 (*C*), 53.3 (*C*H$_2$), 53.5 (*C*H$_2$), 65.6 (*C*H), 65.7 (*C*H), 170.1 (*C*=O) and 174.5 (*C*=O); *m/z* (FAB+) 591 [$(M+Na)^+$, 38%] and 354 (MH^+-camphorsultam, 100); [Found $(M+Na)^+$ 591.2540; $C_{28}H_{44}N_2O_6S_2$ requires 591.2539].

8.2.7.11 (2*R*)- 201 and (2*S*)-*N,N'*-Bis[(2*R*)-bornane-10,2-sultam]-2-hexylsuccinamide 202



201



202

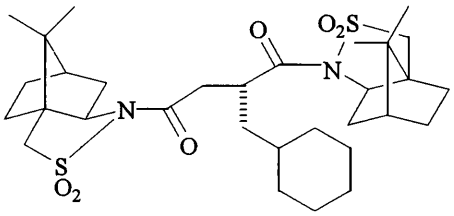
Using hexyl magnesium bromide (6.8 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **100** on a 3.9 mmol scale following General procedure 4 produced a mixture of diastereoisomers 2.58 g. A portion (0.5 g) was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-*N,N'*-bis[(2*R*)-bornane-10,2-sultam]-2-hexylsuccinamide **201** (0.31 g, 62%) and (2*S*)-*N,N'*-bis[(2*R*)-bornane-10,2-sultam]-2-hexylsuccinamide **202** (89 mg, 18%) as white plates.

201 (Major): mp 164-166 °C; $[\alpha]_D$ -60 (*c* 1.0, EtOAc); (Found: C, 60.2 H, 8.1 N, 4.7%; $C_{30}H_{48}N_2O_6S_2$ requires C, 60.4 H, 8.1 N, 4.7%); υ_{max}(KBr)/cm^{-1} 2960 (CH), 1685 (amide), 1330 and 1164 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 7.0, CH$_2$C*H*$_3$), 0.96 (3 H, s, CC*H*$_3$), 0.97 (3 H, m, CC*H*$_3$), 1.16 (3 H, s, CC*H*$_3$), 1.17 (3 H, s, CC*H*$_3$), 1.24-

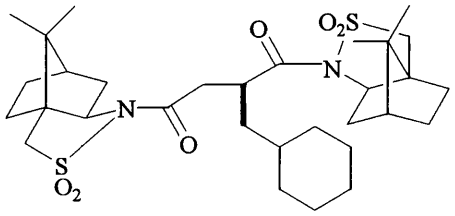
1.48 (11 H, m, alkyl-H), 1.54-1.62 (4 H, m, alkyl-H), 1.71-1.78 (1 H, m, alkyl-H), 1.85-1.92 (5 H, m, alkyl-H), 2.06-2.18 (4 H, m, alkyl-H), 2.86 (1 H, dd, *J* 4.6 and 17.1, CH*H*CHC(O)N), 3.31 (1 H, dd, *J* 9 and 17.1, CH*H*CHC(O)N), 3.45-3.55 (4 H, m, 2 x C*H*$_2$SO$_2$), 3.86 (1 H, app t, *J* 6.3, C*H*N) and 3.95 (1 H, t, *J* 6.3, C*H*N); δ_C(100 MHz; $CDCl_3$) 13.8 (*C*H$_3$), 19.7 (2 x *C*H$_3$), 20.6 (*C*H$_3$), 20.7 (*C*H$_3$), 22.3 (*C*H$_2$), 26.2 (*C*H$_2$), 26.3 (*C*H$_2$), 28.9 (*C*H$_2$), 31.4 (2 x *C*H$_2$), 32.3 (*C*H$_2$), 32.6 (*C*H$_2$), 32.7 (*C*H$_2$), 35.8 (*C*H$_2$), 38.2 (*C*H$_2$), 38.3 (*C*H$_2$), 41.1 (*C*H), 44.5 (2 x *C*H$_2$), 47.5 (2 x *C*), 48.1 (*C*), 48.2 (*C*), 52.7 (*C*H$_2$), 52.8 (*C*H$_2$), 65.0 (*C*H), 65.1 (*C*H), 169.4 (*C*=O) and 173.6(*C*=O); *m/z* (FAB+) 597 [$(M+H)^+$, 10%] and 382 (MH^+-camphorsultam, 100); [Found $(M+H)^+$ 597.3033; $C_{30}H_{48}N_2O_6S_2$ requires 597.3032].

202 (Minor): mp 76-78 °C; $[\alpha]_D$ -66 (*c* 1.0, EtOAc); (Found: C, 60.55 H, 8.3 N, 4.6%; $C_{30}H_{48}N_2O_6S_2$ requires C, 60.4 H, 8.1 N, 4.7%); υ_{max}(KBr)/cm^{-1} 2958 (CH), 1693 (amide), 1333 and 1134 (-SO$_2$-N); δ_H(400 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 6.9, CH$_2$C*H*$_3$), 0.95 (3 H, s, CC*H*$_3$), 0.97 (3 H, s, CC*H*$_3$), 1.16 (3 H, s, CC*H*$_3$), 1.20-1.48 (14 H, m, alkyl-H), 1.58 (4 H, s, alkyl-H), 1.85-1.94 (6 H, m, alkyl-H), 1.98-2.16 (4 H, m, alkyl-H), 3.00 (1 H, dd, *J* 5.1 and 17.0, CH*H*CHC(O)N), 3.14 (1 H, dd, *J* 8.5 and 17.0, CH*H*CHC(O)N), 3.39-3.52 (4 H, m, 2 x C*H*$_2$SO$_2$), 3.85 (1 H, t, *J* 6.2, C*H*N) and 3.90 (1 H, t, *J* 6.2, C*H*N); δ_C(100 MHz; $CDCl_3$) 14.0 (*C*H$_3$), 19.8 (*C*H$_3$), 20.0 (*C*H$_3$), 20.5 (*C*H$_3$), 20.8 (*C*H$_3$), 22.5 (*C*H$_2$), 26.4 (2 x *C*H$_2$), 26.8 (*C*H$_2$), 29.1 (*C*H$_2$), 30.9 (*C*H$_2$), 31.5 (*C*H$_2$), 32.7 (*C*H$_2$), 32.8 (*C*H$_2$), 37.9 (*C*H$_2$), 38.0 (*C*H$_2$), 38.2 (*C*H$_2$), 41.1 (*C*H), 44.6 (2 x *C*H), 47.7 (2 x *C*), 48.4 (*C*), 48.5 (*C*), 52.8 (*C*H$_2$), 53.0 (*C*H$_2$), 65.1 (*C*H), 65.2 (*C*H), 169.7 (*C*=O) and 173.9 (*C*=O); *m/z* (FAB+) 619 [$(M+Na)^+$, 100%] and 382 (MH^+-camphorsultam, 25); [Found $(M+Na)^+$ 619.2855; $C_{30}H_{48}N_2O_6S_2$ requires 619.2852].

8.2.7.12 (2*R*)- 203 and (2*S*)-*N*,*N*'-Bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylhexylmethylsuccinamide 204



203



204

Using cyclohexylmethyl magnesium bromide (6.8 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **100** on a 3.9 mmol scale following General procedure 4 produced a mixture of

diastereoisomers 2.37 g. A portion (0.5 g) was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-*N*,*N*'-bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylmethylsuccinamide **203** (0.28 g, 56%) and (2*S*)-*N*,*N*'-bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylmethylsuccinamide **204** (94 mg, 19%) as white plates.

203 (Major): mp 214-216 °C; $[\alpha]_D$ -60 (*c* 1.0, EtOAc); (Found: C, 61.0 H, 8.2 N, 4.7%; $C_{31}H_{48}N_2O_6S_2$ requires C, 61.15 H, 7.95 N, 4.6%); υ_{max}(KBr)/cm^{-1} 2924 (CH), 1685 (amide), 1334 and 1164 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.87-0.96 (8 H, m, alkyl-H), 1.07-1.18 (8 H, m, alkyl-H) 1.24-1.42 (6 H, m, alkyl-H), 1.60-1.76 (7 H, m, alkyl-H), 1.84-1.93 (5 H, m, alkyl-H), 2.05-2.19 (5 H, m, alkyl-H), 2.85 (1 H, dd, *J* 5.3 and 17.2, CH*H*CHC(O)N), 3.25 (1 H, dd, *J* 8.2 and 17.2, CH*H*CHC(O)N), 3.41-3.50 (4 H, m, 2 x C*H*$_2$$SO_2$), 3.71 (1 H, m, CH_2C*H*C(O)N), 3.87 (1 H, app t, *J* 6.4, C*H*N) and 3.93 (1 H, t, *J* 6.3, C*H*N); δ_C(100 MHz; $CDCl_3$) 20.3 (2 x *C*H_3), 21.3 (2 x *C*H_3), 26.4 (*C*H_2), 26.6 (*C*H_2), 26.8 (*C*H_2), 26.9 (2 x *C*H_2), 32.6 (*C*H_2), 33.2 (*C*H_2), 33.3 (*C*H_2), 34.1 (*C*H_2), 35.5 (*C*H), 36.7 (*C*H_2), 38.8 (*C*H_2), 38.9 (*C*H_2), 39.2 (*C*H), 40.4 (*C*H_2), 45.1 (2 x *C*H), 48.1 (2 x *C*), 48.7 (*C*), 48.8 (*C*), 53.3 (*C*H_2), 53.4 (*C*H_2), 65.7 (2 x *C*H), 170.0 (*C*=O) and 174.8 (*C*=O); *m/z* (FAB+) 609 [$(M+H)^+$, 20%] and 394 (MH^+-camphorsultam, 100); [Found $(M+H)^+$ 609.3032; $C_{31}H_{48}N_2O_6S_2$ requires 609.3032].

204 (Minor): mp 101-103 °C; $[\alpha]_D$ -86 (*c* 1.0, EtOAc); (Found: C, 61.3 H, 8.0 N, 4.7%; $C_{31}H_{48}N_2O_6S_2$ requires C, 61.15 H, 7.95 N, 4.6%); υ_{max}(KBr)/cm^{-1} 2935 (CH), 1687 (amide), 1328 and 1136 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.89 (8 H, m, alkyl-H), 1.11-1.44 (14 H, m, alkyl-H) 1.58-1.89 (12 H, m, alkyl-H), 1.98-2.18 (5 H, m, alkyl-H), 2.99 (1 H, dd, *J* 5.4 and 17.0, C*H*$_2$CHC(O)N), 3.10 (1 H, dd, *J* 7.8 and 17.0, CH*H*CHC(O)N), 3.39-3.55 (5 H, m, 2 x C*H*$_2$$SO_2$ and CH_2C*H*C(O)N), 3.85 (1 H, t, *J* 6.2, C*H*N) and 3.90 (1 H, t, *J* 6.1, C*H*N); δ_C(100 MHz; $CDCl_3$) 19.8 (*C*H_3), 20.0 (*C*H_3), 20.5 (*C*H_3), 20.7 (*C*H_3), 26.0 (*C*H_2), 26.1 (*C*H_2), 26.4 (2 x *C*H_2), 26.5 (2 x *C*H_2) 32.3 (*C*H_2), 32.7 (*C*H_2), 32.8 (*C*H_2), 33.7 (*C*H_2), 34.9 (*C*H), 38.0 (*C*H_2), 38.1 (*C*H_2), 38.3 (2 x *C*H_2), 38.5 (*C*H), 44.5 (*C*H), 44.6 (*C*H), 47.7 (*C*), 48.4 (2 x *C*), 52.8 (*C*H_2), 53.0 (*C*H_2), 65.1 (*C*H), 65.2 (*C*H), 169.6 (*C*=O) and 174.2 (*C*=O). *m/z* (FAB+) 609 [$(M+H)^+$, 38%] and 394 (MH^+-camphorsultam, 100); [Found $(M+H)^+$ 609.3031; $C_{31}H_{48}N_2O_6S_2$ requires 609.3032].

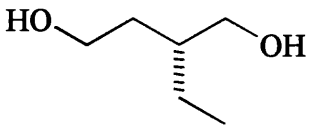
8.3 Experimental for Chapter 5

8.3.1 Synthesis of enantiomerically enriched 2-substituted butane-1,4-diols

General procedure 5 for the reduction of 2-substituted succinamides into 2-substituted butane-1,4-diols.

The 2-substituted succinamide mixtures (0.5 g) in dry THF (10 cm^3) was added dropwise to a stirred solution of lithium aluminium hydride (5 equiv.) in dry THF (50 cm^3) under N_2 at 0 °C. After 3 h at 0 °C the reaction mixture was quenched with sat. aq. NH_4Cl soln. (2 cm^3). The mixture was filtered and concentrated under reduced pressure.

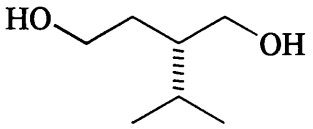
8.3.1.1 (2*R*)-2-Ethylbutane-1,4-diol 229[89]



229

Using the mixture of **186** and **187** (0.8 g, 1.5 mmol) in General procedure 5 gave a mixture of diol and chiral sultam (0.72 g) which was chromatographed [SiO_2, acetone-hexane (1:1)] to give (2*R*)-2-ethylbutane-1,4-diol **229** (80 mg, 39%) as a colourless oil. $[\alpha]_D$ +12 (*c* 1.5, $CHCl_3$) [lit.[89] +14.3, (*c* 1.5, $CHCl_3$)]; δ_H(400 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 7.4, CH_2CH_3), 1.25-1.43 (2 H, m, CH_2CH_3), 1.55-1.62 (2 H, m, CH_2CH_2OH), 1.67-1.76 (1 H, m, C*H*), 3.00 (2 H, br s, OH), 3.49 (ABX system, 1 H, dd, *J* 6.7 and 10.8 Hz, CHCH*H*OH), 3.63-3.68 (2 H, m, CH_2CH_2OH) and 3.76-3.81 (1 H, m, CHCH*H*OH).

8.3.1.2 (2*R*)-2-Isopropylbutane-1,4-diol 230[109]

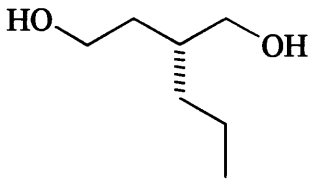


230

Using the mixture of **188** and **189** (0.5 g, 0.9 mmol) in General procedure 5 gave a mixture (0.24 g) which was chromatographed [SiO_2, acetone-hexane (2:3)] to give (2*R*)-2-isopropylbutane-1,4-diol **230** (0.05 g, 43 %) as a colourless oil. $[\alpha]_D$ -3.3 (*c* 1.0, MeOH) [lit.[109] -10, (*c* 1.0, MeOH)]; δ_H(400 MHz; $CDCl_3$) 0.88 (3 H, d, *J* 7.2, $CHCH_3$), 0.89 (3 H,

d, *J* 7.2, CHC*H*$_3$), 1.44-1.61 (2 H, m, C*H*$_2$CH$_2$OH), 1.68-1.79 (2 H, m, CH$_3$C*H*C*H*), 3.20 (2 H, br s, OH), 3.54 (ABX system, 1 H, dd, *J* 7.8 and 10.6, CHCH*H*OH), 3.60-3.70 (2 H, m, CH$_2$C*H*$_2$OH), 3.77-3.82 (ABX system, 1 H, m, CHCH*H*OH).

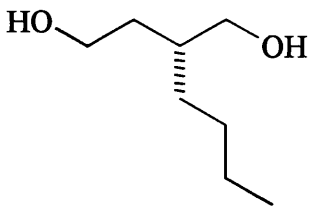
8.3.1.3 (2*R*)-2-Propylbutane-1,4-diol 231[109]



231

Using the mixture of **190** and **191** (0.5 g, 0.9 mmol) in General procedure 5 gave a mixture (0.18 g) which was chromatographed [SiO_2, acetone-hexane (1:1)] to give (2*R*)-2-propylbutane-1,4-diol **231** (0.06 g, 46%) as a colourless oil. $[\alpha]_D$ -1 (*c* 1.1, MeOH) (lit.[109] -3.6, [*c* 2.12, MeOH]); δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 6.9, CH$_2$C*H*$_3$), 1.21-1.37 (4 H, m, CH$_3$C*H*$_2$C*H*$_2$), 1.55-1.75 (3 H, m, C*H*C*H*$_2$CH$_2$OH), 2.63 (2 H, br s, OH), 3.49 (ABX system, 1 H, dd, *J* 7.0 and 10.8, CHCH*H*OH), 3.64-3.71 (2 H, m, CH$_2$C*H*$_2$OH) and 3.76-3.81 (ABX system, 1 H, m, CHCH*H*OH).

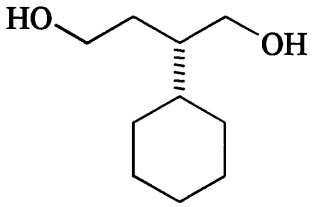
8.3.1.4 (2*R*)-2-Butylbutane-1,4-diol 232



232

Using the mixture of **192** and **193** (0.5 g, 0.9 mmol) in General procedure 5 gave a mixture (0.17 g) which was chromatographed [SiO_2, acetone-hexane (2:3)] to give (2*R*)-2-butylbutane-1,4-diol **232** (73 mg, 56%) as a colourless oil. $[\alpha]_D$ -1 (*c* 1.5, EtOH); υ_{max}(NaCl)/cm^{-1} 3410 (OH), 2946 (CH), 1466 (OH), and 1041 (C-O); δ_H(400 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.8, CH$_2$C*H*$_3$), 1.21-1.34 (6 H, m, alkyl-H), 1.52-1.73 (3 H, m, C*H*C*H*$_2$CH$_2$OH), 3.39 (2 H, br s, OH), 3.45 (ABX system, 1 H, dd, *J* 6.8 and 10.4, CHCH*H*OH), 3.60-3.65 (2 H, m, CH$_2$C*H*$_2$OH) and 3.73-3.78 (ABX system, 1 H, m, CHCH*H*OH); δ_C(100 MHz; $CDCl_3$) 14.2 (*C*H$_3$), 23.1 (*C*H$_2$), 29.5 (*C*H$_2$), 31.6 (*C*H$_2$), 36.0 (*C*H$_2$), 39.6 (*C*H), 61.2 (*C*H$_2$), 66.5 (*C*H$_2$); *m/z* (CI$^+$ mode, isobutane) 147 (MH$^+$, 21%) and 57 (100); (Found MH$^+$ 147.1384; $C_8H_{18}O_2$ requires 147.1385).

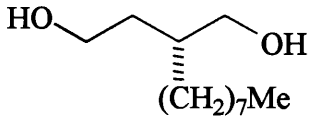
8.3.1.5 (2*R*)-2-Cyclohexylbutane-1,4-diol 233



233

Using the mixture of **194** and **195** (0.5 g, 0.8 mmol) in General procedure 5 gave a mixture (0.44 g) which was chromatographed [SiO_2, acetone-hexane (2:3)] to give (2*R*)-2-cyclohexylbutane-1,4-diol **233** (53 mg, 38%) as a colourless oil. $[\alpha]_D$ -7.6 (*c* 0.5, EtOH); υ_{max}(NaCl)/cm^{-1} 3336 (OH), 2921, 1448 (OH), and 1041 (C-O); δ_H(400 MHz; $CDCl_3$) 0.95-1.74 (14 H, m, alkyl-H), 3.52 (ABX system, 1 H, dd, *J* 6.8 and 17.6, CHCH*H*OH), 3.56-3.62 (1 H, m, CH_2CH*H*OH), 3.66 (ABX system, 1 H, dd, *J* 4.0 and 10.8, CHCH*H*OH), 3.73-3.78 (1 H, m, CH_2CH*H*OH); δ_C(100 MHz; $CDCl_3$) 26.6 (*C*H_2), 26.7 (2 x *C*H_2), 30.0 (*C*H_2), 30.1 (*C*H_2), 33.4 (*C*H_2), 40.1 (*C*H), 45.0 (*C*H), 61.7 (*C*H_2), 64.8 (*C*H_2); *m/z* (FAB+) 173 (MH^+, 100%) and 155 (27); (Found MH^+ 173.1541; $C_{10}H_{20}O_2$ requires 173.1542).

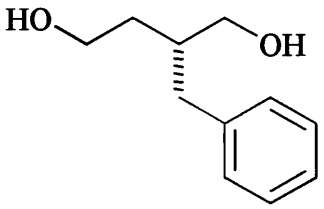
8.3.1.6 (2*R*)-2-Octylbutane-1,4-diol 234



234

Using the mixture of **196** and **197** (0.6 g, 1.0 mmol) in General procedure 5 gave a mixture (0.45 g) which was chromatographed [SiO_2, acetone-hexane (2:3)] to give (2*R*)-2-octylhexylbutane-1,4-diol **234** (0.15 g, 79%) as a colourless oil. $[\alpha]_D$ +0.5 (*c* 0.2, EtOH); υ_{max}(NaCl)/cm^{-1} 3328 (OH), 2924 (CH), 1465 (OH), and 1041 (C-O); δ_H(400 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.0, CH_2CH_3), 1.26-1.33 (15 H, m, alkyl-H), 1.57-1.77 (2 H, m, CH_2CH_2OH), 2.62 (2 H, br s, OH), 3.52 (ABX system, 1 H, dd, *J* 6.8 and 10.7, CHCH*H*OH), 3.68-3.73 (2 H, m, CH_2CH_2OH), 3.79-3.85 (ABX system, 1 H, m, CHCH*H*OH); δ_C(100 MHz; $CDCl_3$) 14.1 (*C*H_3), 22.6 (*C*H_2), 27.1 (*C*H_2), 29.3 (*C*H_2), 29.5 (*C*H_2), 29.9 (*C*H_2), 31.7 (*C*H_2), 31.9 (*C*H_2), 35.8 (*C*H_2), 39.3 (*C*H), 61.3 (*C*H_2) and 66.4 (*C*H_2); *m/z* (EI) 202 (M^+, 3%), and 154 (100); (Found M^+ 202.1934; $C_{12}H_{26}O_2$ requires 202.1933).

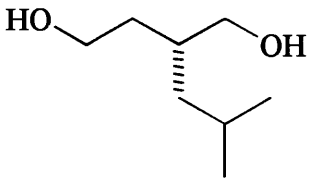
8.3.1.7 (2*R*)-2-Benzylbutane-1,4-diol 235



235

Using the mixture of **198** and other diastereomer (0.6 g, 1.0 mmol) in General procedure 5 gave a mixture (0.60 g) which was chromatographed [SiO_2, acetone-hexane (2:3)] to give (2*R*)-2-benzylbutane-1,4-diol **235** (0.15 g, 75%) as a colourless oil. $[\alpha]_D$ +6.6 (*c* 1.5, EtOAc); υ_{max}(NaCl)/cm^{-1} 3348 (OH), 2927 (CH), 1603 (Aromatic ring), 1454 (OH), and 1043 (C-O); δ_H(400 MHz; $CDCl_3$) 1.56-1.75 (2 H, m, ArC*H*$_2$CH), 1.97-2.01 (1 H, m, ArCH$_2$C*H*), 2.40 (2 H, br s, OH), 2.53-2.74 (2 H, m C*H*$_2$CH$_2$OH), 3.47-3.52 (1 H, m, CHCH*H*OH), 3.62-3.68 (2 H, m, CH$_2$C*H*$_2$OH), 3.75-3.80 (1 H, m, CHCH*H*OH) and 7.16-7.30 (5 H, m, Ar-C*H*); δ_C(100 MHz; $CDCl_3$) 35.6 (*C*H$_2$), 38.6 (*C*H$_2$), 41.6 (*C*H), 61.5 (*C*H$_2$), 66.0 (*C*H$_2$), 126.4 (Ar*C*H), 128.8 (Ar*C*H), 129.5 (Ar*C*H) and 140.7 (Ar*C*); *m/z* (EI) 162 (M-H_2O, 37%), 91 (M-benzyl, 100) and 84 (90); (Found M^+ 162.1046; $C_{11}H_{16}O_2$ requires 162.1045).

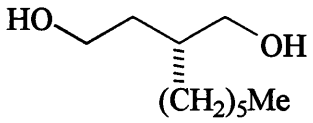
8.3.1.8 (2*R*)-2-Isobutylbutane-1,4-diol 236



236

Using the mixture of **199** and **200** (0.5 g, 0.9 mmol) in General procedure 5 gave a mixture (0.45 g) which was chromatographed [SiO_2, acetone-hexane (2:3)] to give (2*R*)-2-isobutylbutane-1,4-diol **236** (0.11 g, 85%) as a colourless oil. $[\alpha]_D$ +2.4 (*c* 4.2, EtOAc); υ_{max}(NaCl)/cm^{-1} 3334 (OH), 2954 (CH), 1468 (OH), and 1039 (C-O); δ_H(400 MHz; $CDCl_3$) 0.88 (6 H, t, *J* 6.4, C*H*$_3$CHC*H*$_3$), 1.04-1.25 (2 H, m, CH$_3$CHC*H*$_2$), 1.50-1.75 (4 H, m, alkyl-H), 3.42 (ABX system, 1 H, dd, *J* 7.2 and 10.8, CHCH*H*OH), 3.56 (2 H, br s, OH), 3.61-3.66 (2 H, m, CH$_2$C*H*$_2$OH) and 3.74-3.79 (1 H, m, CHCH*H*OH); δ_C(100 MHz; $CDCl_3$) 22.7 (*C*H$_3$), 22.8 (*C*H$_3$), 25.2 (*C*H), 30.1 (*C*H$_2$), 37.1 (*C*H), 41.1 (*C*H$_2$), 61.0 (*C*H$_2$), 66.5 (*C*H$_2$); *m/z* (CI^+ mode, isobutane) 147 (MH^+, 10%) and 57 (100); (Found MH^+ 147.1386; $C_8H_{18}O_2$ requires 147.1385).

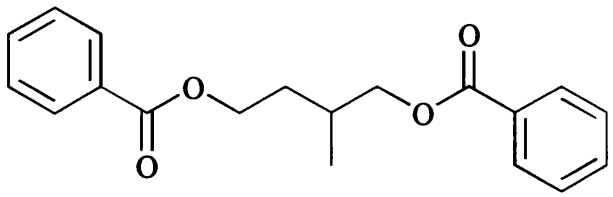
8.3.1.10 (2*R*)-2-Hexylbutane-1,4-diol 237



237

Using the mixture of **201** and **202** (0.54 g, 0.9 mmol) in General procedure 5 gave a mixture (0.38 g) which was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-2-hexylbutane-1,4-diol **237** (0.12 g, 75%) as a colourless oil. $[\alpha]_D$ +2 (*c* 1.0, EtOAc); υ_{max}(NaCl)/cm^{-1} 3320 (OH), 2925 (CH), 1466 (OH), and 1043 (C-O); δ_H(400 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 7.0, CH_2CH_3), 1.27 (10 H, br s, alkyl-H), 1.52-1.73 (3 H, m, $CHCH_2CH_2OH$), 3.27 (2 H, br s, OH), 3.46 (ABX system, 1 H, dd, *J* 7.0 and 10.7, $CHCHHOH$), 3.61-3.67 (2 H, m, CH_2CH_2OH) and 3.74-3.80 (1 H, m, $CHCHHOH$); δ_C(100 MHz; $CDCl_3$) 14.5 (CH_3), 23.0 (CH_2), 27.4 (CH_2), 30.0 (CH_2), 32.2 (2 x CH_2), 36.2 (CH_2), 39.8 (*C*H), 61.5 (CH_2) and 66.7 (CH_2); *m/z* (FAB+) 175 (MH^+, 100%), 137 (30), 83 (16) and 73 (15); (Found MH^+ 175.1697; $C_{10}H_{22}O_2$ requires 175.1698).

8.3.1.11 2-Methylbutane-1,4-diol dibenzoate 238[107]



238

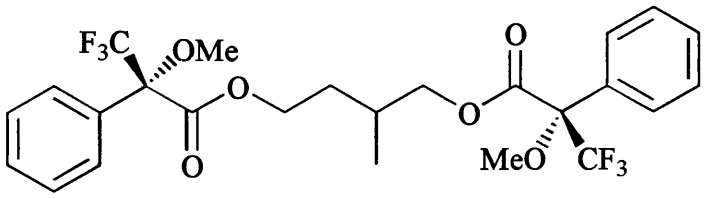
Compound **238** was prepared in 70% yield on a 3.3 mmol scale by the method of Feringa and co-workers.[107] υ_{max}(NaCl)/cm^{-1} 3064 (alkyl), 2962 (alkyl), 1736 (C=O), 1603 (aromatic ring) and 1531 (aromatic ring); δ_H(400 MHz; $CDCl_3$) 1.14 (3 H, d, *J* 6.8, CH_3CH), 1.61-1.80 (1 H, m, alkyl-H), 1.96-2.08 (1 H, m, alkyl-H), 2.18-2.26 (1 H, m, alkyl-H), 4.27 (2 H, d, *J* 6.1, $CHCH_2CO$), 4.41-4.51 (2 H, m, $COCH_2CH_2$), 7.42-7.47 (4 H, m, ArC*H*), 7.54-7.59 (2 H, m, ArC*H*) and 8.03-8.05 (4 H, m, ArC*H*); *m/z* (EI) 312 (M^+, 2%), 207 (20) 190 (40), 105 (100), 77 (100) and 68 ($ArNH_2$, 100); (Found M^+ 312.1362; $C_{19}H_{20}O_4$ requires M^+ 312.1362).

8.3.2 Synthesis of Mosher ester derivatives of enantiomerically enriched 2-substituted butane-1,4-diols

General procedure 6 for the conversion of 2-substituted butane-1,4-diols into Mosher diesters.

EDCI (5 equiv.) was added to a mixture of diol (~20 mg), (*R*)- or (*S*)-Mosher acid [methoxytrifluorophenylacetic acid (MTPA)] (2.5 equiv.) and DMAP (1 equiv.) in dry DCM (2 cm^3) under N_2. The mixture was stirred at room temperature for 24 h, then quenched with 5% citric acid (2 cm^3) and extracted with dichloromethane (3 x 5 cm^3). The combined extracts were washed with sodium hydrogen carbonate (10 cm^3) followed by water (10 cm^3) and brine (10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure.

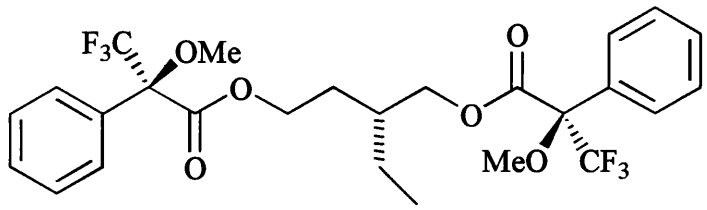
8.3.2.1 (*S*)-MTPA Diester of (±)-2-methylbutane-1,4-diol 239[139]



239

Using (±)-2-methylbutane-1,4-diol (30 mg, 0.29 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:1)] gave (*S*)-MTPA diester **239** (0.12 g, 75%) as a colourless oil. $[\alpha]_D$ -65 (*c* 1.0, EtOAc); υ_{max}(NaCl)/cm^{-1} 2964 (alkyl) and 1747 (C=O); δ_H(400 MHz; $CDCl_3$) 0.93 (1.5 H, d, *J* 6.8, C*H*$_3$CH), 0.95 (1.5 H, d, *J* 6.8, C*H*$_3$CH), 1.44-1.95 (3 H, m, OCH$_2$C*H*$_2$C*H*), 3.53 (6 H, s, OC*H*$_3$), 4.10 (ABX system, 1 H, dd, *J* 5.6 and 8.0, OCH*H*CH), 4.19 (ABX system, 1 H, dd, *J* 8.0 and 10.8, OCH*H*CH), 4.27-4.41 (2 H, m, OC*H*$_2$CH$_2$), 7.37-7.43 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 16.2 (*C*H$_3$), 29.4 (*C*H), 31.6 (*C*H$_2$), 55.4 (2 x OCH$_3$), 63.9 (*C*H$_2$), 70.4 (*C*H$_2$), 121.9 (2 x *C*), 124.7 (2 x *C*), 127.3 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 x Ar*C*) and 166.5 (2 x *C*=O); δ_F(200 MHz; $CDCl_3$) –72.01 and –71.96; *m/z* (FAB+) 559 [$(M+Na)^+$, 8%] 303 (14) and 189 (100); [Found $(M+Na)^+$ 559.1526; $C_{25}H_{26}F_6O_6$ requires 559.1531].

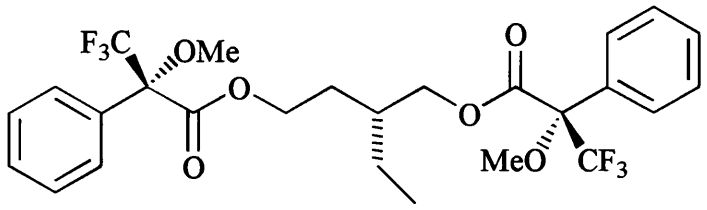
8.3.2.2 (*R*)-MTPA Diester of (2*R*)-2-ethylbutane-1,4-diol 238



238

Using (2*R*)-2-ethylbutane-1,4-diol **229** (22 mg, 0.19 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:1)] gave (*R*)-MTPA diester **238** (87 mg, 87%) as a colourless oil. $[\alpha]_D$ +50 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2964 (alkyl) and 1747 (C=O); δ_H(400 MHz; $CDCl_3$) 0.85 (3 H, t, *J* 7.5, CH_3CH_2), 1.27-1.36 (2 H, m, CH_3CH_2), 1.67-1.72 (3 H, m, OCH_2CH_2CH), 3.53 (6 H, s, OCH_3), 4.18 (ABX system, 1 H, dd, *J* 4.4 and 10.8, OCH*H*CH), 4.25-4.40 (3 H, m, OCH_2CH_2 and OCH*H*CH), 7.37-7.41 (6 H, m, ArC*H*) and 7.48-7.50 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 10.8 (CH_3), 23.3 (CH_2), 29.6 (CH_2), 35.7 (*C*H), 55.4 (2 x OCH_3), 64.0 (CH_2), 67.8 (CH_2), 124.8 (2 x *C*), 125.8 (2 x *C*), 127.3 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (2 x Ar*C*H), 132.2 (2 x Ar*C*) and 166.5 (2 x *C*=O); δ_F(200 MHz; $CDCl_3$) –71.95, -71.93 and –71.91; *m/z* (CI^+ mode, isobutane) 551 (MH^+, 10%) 317 (45) and 189 (100); (Found MH^+ 551.1870; $C_{26}H_{28}F_6O_6$ requires 551.1868).

8.3.2.3 (*S*)-MTPA Diester of (2*R*)-2-ethylbutane-1,4-diol 239

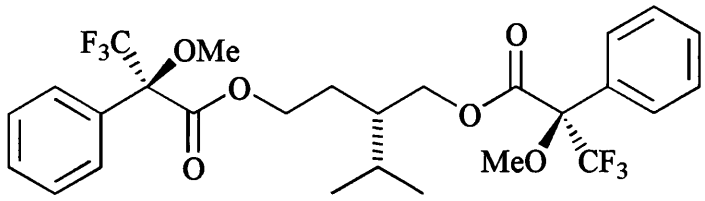


239

Using (2*R*)-2-ethylbutane-1,4-diol **229** (23 mg, 0.19 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:1)] gave (*S*)-MTPA diester **239** (85 mg, 77%) as a colourless oil. $[\alpha]_D$ -42 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2964 (alkyl) and 1745 (C=O); δ_H(400 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 7.5, CH_3CH_2), 1.29-1.37 (2 H, m, CH_3CH_2), 1.66-1.93 (3 H, m, OCH_2CH_2CH), 3.53 (6 H, s, OCH_3), 4.17 (ABX system, 1 H, dd, *J* 5.0 and 11.1, OCH*H*CH), 4.25-4.39 (3 H, m, OCH_2CH_2 and OCH*H*CH), 7.37-7.41 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 10.8 (CH_3), 23.4 (CH_2), 29.6 (CH_2), 35.6 (*C*H), 55.4 (2 x OCH_3), 64.0 (CH_2), 67.8 (CH_2), 121.9 (2 x *C*), 124.7 (2 x

C), 127.3 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 x Ar*C*) and 166.5 (2 x *C*=O); δ_F(200 MHz; $CDCl_3$) –71.95, -71.93 and –71.91; *m/z* (CI^+ mode, isobutane) 551 (MH^+, 11%) 317 (36) and 189 (27); (Found MH^+ 551.1866; $C_{26}H_{28}F_6O_6$ requires 551.1868).

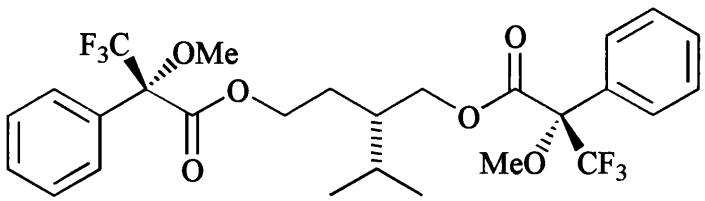
8.3.2.4 (*R*)-MTPA Diester of (2*R*)-2-isopropylbutane-1,4-diol 240



240

Using (2*R*)-2-isopropylbutane-1,4-diol **230** (20 mg, 0.15 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:1)] gave (*R*)-MTPA diester **240** (40 mg, 47%) as a colourless oil. $[\alpha]_D$ +60 (*c* 0.4, EtOAc); υ_{max}(NaCl)/cm^{-1} 2964 (alkyl) and 1747 (C=O); δ_H(400 MHz; $CDCl_3$) 0.85 (6 H, m, C*H*$_3$CHC*H*$_3$), 1.57-1.82 (4 H, m), 3.53 (6 H, s, OC*H*$_3$), 4.17 (ABX system, 1 H, dd, *J* 5.6 and 11.6, OCH*H*CH), 4.22-4.39 (3 H, m, OC*H*$_2$CH$_2$ and OCH*H*CH), 7.37-7.41 (6 H, m, ArC*H*) and 7.49-7.50 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 19.1 (*C*H$_3$), 19.2 (*C*H$_3$), 27.2 (*C*H$_2$), 28.3 (*C*H), 39.9 (*C*H), 55.4 (2 x OCH$_3$), 64.5 (*C*H$_2$), 66.8 (*C*H$_2$), 121.9 (2 x *C*), 124.7 (2 x *C*), 127.2 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 x Ar*C*) and 166.5 (2 x *C*=O); δ_F(200 MHz; $CDCl_3$) –71.96, -71.95 –71.84 and –71.81; *m/z* (CI^+ mode, isobutane) 565 (MH^+, 17%) 331 (69) and 189 (54); (Found MH^+ 565.2022; $C_{27}H_{30}F_6O_6$ requires 565.2025).

8.3.2.5 (*S*)-MTPA Diester of (2*R*)-2-isopropylbutane-1,4-diol 241

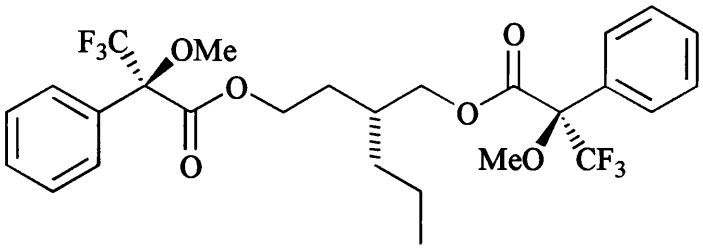


241

Using (2*R*)-2-isopropylbutane-1,4-diol **230** (20 mg, 0.15 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:1)] gave (*S*)-MTPA diester **241** (66 mg, 78%) as a colourless oil. $[\alpha]_D$ -59 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2964 (alkyl) and 1747 (C=O); δ_H(400 MHz; $CDCl_3$) 0.85 (6 H, m, C*H*$_3$CHC*H*$_3$), 1.52-1.82

(4 H, m), 3.53 (6 H, s, OCH_3), 4.17 (ABX system, 1 H, dd, *J* 5.6 and 11.6, OCH*H*CH), 4.25-4.39 (3 H, m, OCH_2CH$_2$ and OCH*H*CH), 7.37-7.42 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 19.1 (*C*H$_3$), 19.2 (*C*H$_3$), 27.2 (*C*H$_2$), 28.3 (*C*H), 39.9 (*C*H), 55.4 (2 x O*C*H$_3$), 64.5 (*C*H$_2$), 66.8 (*C*H$_2$), 121.9 (2 x *C*), 124.8 (2 x *C*), 127.2 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 Ar*C*) and 166.5 (2 x *C*=O); δ_F(200 MHz; $CDCl_3$) –71.96, -71.94 –71.84 and –71.81; *m/z* (CI^+ mode, isobutane) 565 (MH^+, 27%) 331 (72) and 189 (50); (Found MH^+ 565.2026; $C_{27}H_{30}F_6O_6$ requires 565.2025).

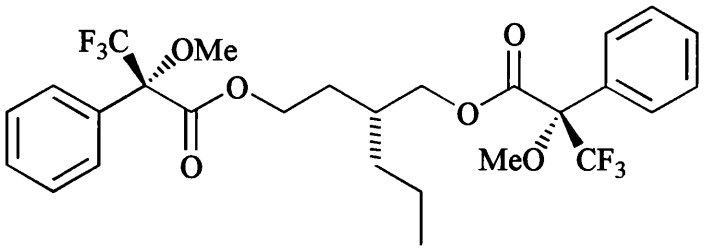
8.3.2.6 (*R*)-MTPA Diester of (2*R*)-2-propylbutane-1,4-diol 242



242

Using (2*R*)-2-propylbutane-1,4-diol **231** (25 mg, 0.19 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*R*)-MTPA diester **242** (85 mg, 77%) as a colourless oil. $[\alpha]_D$ +70 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2958 (alkyl) and 1749 (C=O); δ_H(400 MHz; $CDCl_3$) 0.79-0.91 (3 H, m, C*H*$_3$CH$_2$), 1.23-1.29 (4 H, m, CH$_3$C*H*$_2$C*H*$_2$), 1.62-1.79 (3 H, m, OCH$_2$C*H*CH$_2$), 3.53 (6 H, s, OC*H*$_3$), 4.11-4.19 (1 H, m, OCH*H*CH), 4.24-4.39 (3 H, m, OC*H*$_2$CH$_2$ and OCH*H*CH), 7.37-7.42 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 14.4 (*C*H$_3$), 19.6 (*C*H$_2$), 30.0 (*C*H$_2$), 32.8 (*C*H$_2$), 33.9 (*C*H), 55.4 (2 x O*C*H$_3$), 64.0 (*C*H$_2$), 68.1 (*C*H$_2$), 121.9 (2 x *C*), 124.7 (2 x *C*), 127.6 (2 x Ar*C*H), 128.3 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.5 (2 x Ar*C*) and 166.5 (2 x *C*=O); δ_F(200 MHz; $CDCl_3$) –71.94, -71.92 and –71.88; *m/z* (CI^+ mode, isobutane) 565 (MH^+, 33%) 331 (95) and 189 (73); (Found MH^+ 565.2023; $C_{27}H_{30}F_6O_6$ requires 565.2025).

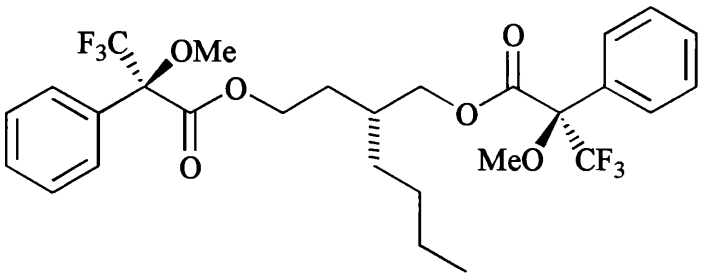
8.3.2.7 (*S*)-MTPA Diester of (2*R*)-2-propylbutane-1,4-diol 243



243

Using (2*R*)-2-propylbutane-1,4-diol **231** (25 mg, 0.19 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*S*)-MTPA diester **243** (90 mg, 82%) as a colourless oil. $[\alpha]_D$ -58 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2958 (alkyl) and 1749 (C=O); δ_H(400 MHz; $CDCl_3$) 0.80-0.87 (3 H, m, C*H*$_3$CH$_2$), 1.23-1.31 (4 H, m, CH$_3$C*H*$_2$C*H*$_2$), 1.64-1.79 (3 H, m, OCH$_2$C*H*CH$_2$), 3.53 (6 H, s, OC*H*$_3$), 4.16 (ABX system, 1 H, dd, *J* 5.2 and 11.2, OCH*H*CH), 4.24-4.39 (3 H, m, OC*H*$_2$CH$_2$ and OCH*H*CH), 7.37-7.41 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 14.0 (*C*H$_3$), 19.6 (*C*H$_2$), 30.0 (*C*H$_2$), 32.8 (*C*H$_2$), 33.9 (*C*H), 55.4 (2 x OCH$_3$), 64.0 (*C*H$_2$), 68.1 (*C*H$_2$), 121.9 (2 x *C*), 124.7 (2 x *C*), 127.2 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.5 (2 x Ar*C*) and 166.5 (2 x *C*=O); δ_F(200 MHz; $CDCl_3$) –71.94, -71.91 and –71.87; *m/z* (CI$^+$ mode, isobutane) 565 (MH$^+$, 10%) 331 (55) and 189 (28); (Found MH$^+$ 565.2023; $C_{27}H_{30}F_6O_6$ requires 565.2025).

8.3.2.8 (*R*)-MTPA Diester of (2*R*)-2-butylbutane-1,4-diol 244

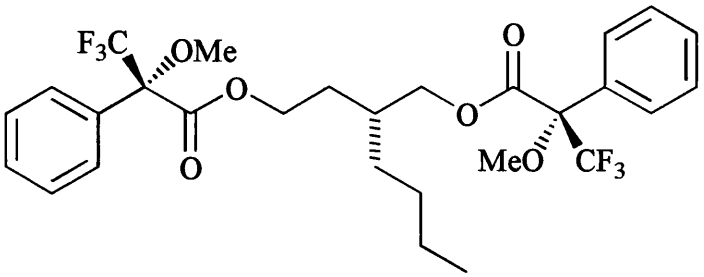


244

Using (2*R*)-butylbutane-1,4-diol **232** (25 mg, 0.17 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*R*)-MTPA diester **244** (89 mg, 91%) as a colourless oil. $[\alpha]_D$ +53 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2956 (alkyl) and 1749 (C=O); δ_H(400 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 6.9, C*H*$_3$CH$_2$), 1.16-1.31 (6 H, m, alkyl-H), 1.62-1.77 (3 H, m, OCH$_2$C*H*CH$_2$), 3.52 (6 H, s, OC*H*$_3$), 4.14-4.19 (1 H, m, OCH*H*CH), 4.24-4.39 (3 H, m, OC*H*$_2$CH$_2$ and OCH*H*CH), 7.36-7.41 (6 H, m, ArC*H*) and 7.49-7.51 (4

H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 13.9 (*C*H_3), 22.7 (*C*H_2), 30.0 (*C*H_2), 30.2 (*C*H_2), 30.3 (*C*H_2), 34.2 (*C*H), 55.4 (2 x O*C*H_3), 64.0 (*C*H_2), 68.1 (*C*H_2), 121.9 (2 x *C*), 124.7 (2 x *C*), 127.2 (2 Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 x Ar*C*), 166.5 (*C*=O) and 166.6 (*C*=O); δ_F(200 MHz; $CDCl_3$) –71.96, -71.95, -71.91 and –71.88; *m/z* (EI) 578 (M^+, 1%), 345 (16) and 189 (100); (Found M^+ 578.2105; $C_{28}H_{32}F_6O_6$ requires M^+ 578.2103).

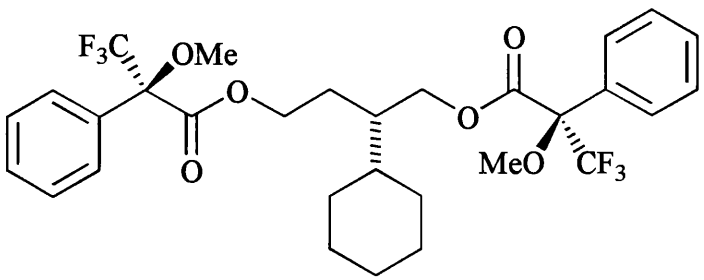
8.3.2.9 (*S*)-MTPA Diester of (2*R*)-2-butylbutane-1,4-diol 245



245

Using (2*R*)-butylbutane-1,4-diol **232** (25 mg, 0.17 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*S*)-MTPA diester **245** (75 mg, 77%) as a colourless oil. $[\alpha]_D$ -45 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2956 (alkyl) and 1749 (C=O); δ_H(400 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 6.9, C*H*$_3$CH$_2$), 1.16-1.31 (6 H, m, alkyl-H), 1.62-1.77 (3 H, m, OCH$_2$C*H*C*H*$_2$), 3.52 (6 H, s, OC*H*$_3$), 4.14-4.19 (1 H, m, OCH*H*CH), 4.24-4.39 (3 H, m, OC*H*$_2$CH$_2$ and OCH*H*CH), 7.36-7.41 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 13.9 (*C*H_3), 22.7 (*C*H_2), 30.0 (*C*H_2), 30.2 (*C*H_2), 30.3 (*C*H_2), 34.2 (*C*H), 55.4 (2 x O*C*H_3), 64.0 (*C*H_2), 68.1 (*C*H_2), 121.9 (2 x *C*), 124.7 (2 x *C*), 127.2 (2 Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 x Ar*C*), 166.5 (*C*=O) and 166.6 (*C*=O); δ_F(200 MHz; $CDCl_3$) –71.96, -71.95, -71.91 and –71.88; *m/z* (EI) 578 (M^+, 1%), 345 (19) and 189 (100); (Found M^+ 578.2104; $C_{28}H_{32}F_6O_6$ requires M^+ 578.2103).

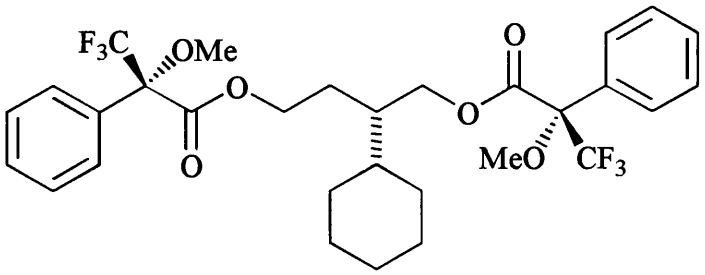
8.3.2.10 (*R*)-MTPA Diester of (2*R*)-cyclohexylbutane-1,4-diol 246



246

Using (2*R*)-cyclohexylbutane-1,4-diol **233** (22 mg, 0.13 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*R*)-MTPA diester **246** (65 mg, 84%) as a colourless oil. $[\alpha]_D$ +52 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2927 (alkyl) and 1748 (C=O); δ_H(400 MHz; $CDCl_3$) 0.84-0.99 (2 H, m, alkyl-H), 1.01-1.16 (3 H, m, alkyl-H), 1.24-1.35 (1 H, m, alkyl-H), 1.50-1.83 (8 H, m, alkyl-H), 3.52 (6 H, s, OC*H*$_3$), 4.18 (ABX system, 1 H, dd, *J* 5.2 and 11.2, OCH*H*CH), 4.22-4.38 (3 H, m, OC*H*$_2$CH$_2$ and OCH*H*CH), 7.37-7.44 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 26.3 (*C*H$_2$), 26.4 (*C*H$_2$), 27.4 (*C*H$_2$), 27.5 (*C*H$_2$), 29.6 (*C*H$_2$), 29.8 (*C*H$_2$), 38.6 (*C*H), 39.4 (*C*H), 55.4 (O*C*H$_3$), 64.6 (*C*H$_2$), 67.2 (*C*H$_2$), 121.9 (2 x *C*), 124.7 (2 x *C*), 127.6 (2 Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 x Ar*C*), 166.5 (*C*=O) and 166.6 (*C*=O); δ_F(200 MHz; $CDCl_3$) –71.95, -71.85 and –71.76; *m/z* (EI) 604 (M^+, 0.3%), 189 (100) and 137 (42); (Found M^+ 604.2261; $C_{30}H_{34}F_6O_6$ requires M^+ 604.2260).

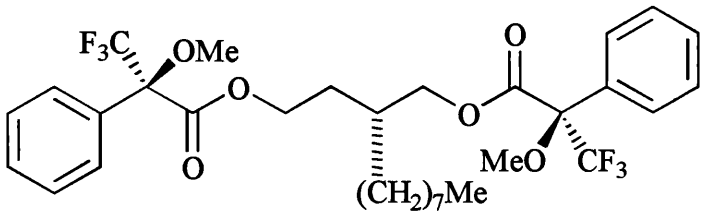
8.3.2.11 (*S*)-MTPA Diester of (2*R*)-2-cyclohexylbutane-1,4-diol 247



247

Using (2*R*)-2-cyclohexylbutane-1,4-diol **233** (22 mg, 0.13 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*S*)-MTPA diester **247** (71 mg, 92%) as a colourless oil. $[\alpha]_D$ -63 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2927 (alkyl) and 1748 (C=O); δ_H(400 MHz; $CDCl_3$) 0.87-0.99 (2 H, m, alkyl-H), 1.05-1.18 (3 H, m, alkyl-H), 1.25-1.38 (1 H, m, alkyl-H), 1.53-1.85 (8 H, m, alkyl-H), 3.53 (6 H, s, OC*H*$_3$), 4.18 (ABX system, 1 H, dd, *J* 5.2 and 11.2, OCH*H*CH), 4.22-4.43 (3 H, m, OC*H*$_2$CH$_2$ and OC*H*$_2$CH), 7.37-7.44 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 26.4 (*C*H$_2$), 26.5 (*C*H$_2$), 27.4 (*C*H$_2$), 27.5 (*C*H$_2$), 29.6 (*C*H$_2$), 29.9 (*C*H$_2$), 38.6 (*C*H), 39.3 (*C*H), 55.4 (2 x O*C*H$_3$), 64.6 (*C*H$_2$), 66.8 (*C*H$_2$), 121.9 (2 x *C*), 124.8 (2 x *C*), 127.2 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 x Ar*C*), 166.5 (*C*=O) and 166.6 (*C*=O); δ_F(200 MHz; $CDCl_3$) –71.96, -71.85 and –71.76; *m/z* (EI) 604 (M^+, 1%), 371 (15) 189 (100) and 137 (42); (Found M^+ 604.2257; $C_{30}H_{34}F_6O_6$ requires M^+ 604.2260).

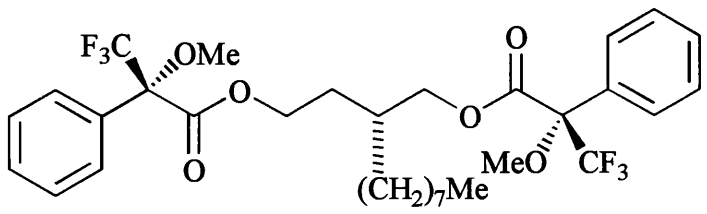
8.3.2.12 (*R*)-MTPA Diester of (2*R*)-2-octylbutane-1,4-diol 248



248

Using (2*R*)-2-octylbutane-1,4-diol **234** (30 mg, 0.15 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*R*)-MTPA diester **248** (76 mg, 80%) as a colourless oil. $[\alpha]_D$ +58 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2929 (alkyl) and 1749 (C=O); δ_H(400 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.14-1.33 (14 H, m, alkyl-H), 1.62-1.77 (3 H, m, OCH$_2$C*H*CH$_2$), 3.53 (6 H, s, OC*H*$_3$), 4.14-4.19 (1 H, m, OCH*H*CH), 4.25-4.39 (3 H, m, OC*H*$_2$CH$_2$ and OCH*H*CH), 7.38-7.43 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 14.1 (*C*H$_3$), 22.6 (*C*H$_2$), 26.5 (*C*H$_2$), 29.2 (*C*H$_2$), 30.0 (*C*H$_2$), 30.3 (*C*H$_2$), 30.9 (*C*H$_2$), 31.0 (*C*H$_2$), 31.8 (*C*H$_2$), 34.2 (*C*H), 55.4 (O*C*H$_3$), 64.0 (*C*H$_2$), 68.1 (*C*H$_2$), 121.9 (2 x *C*), 124.7 (2 x *C*), 127.2 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 x Ar*C*), 166.5 (*C*=O) and 166.6 (*C*=O); δ_F(200 MHz; $CDCl_3$) 37.56, 37.57, 37.60 and 37.63; *m/z* (EI) 634 (M^+, 0.5%), 401 (8) and 189 (100); (Found M^+ 634.2728; $C_{32}H_{40}F_6O_6$ requires M^+ 634.2729).

8.3.2.13 (*S*)-MTPA Diester of (2*R*)-2-octylbutane-1,4-diol 249

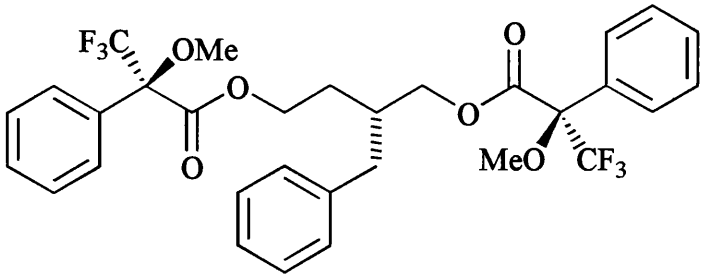


249

Using (2*R*)-2-octylbutane-1,4-diol **234** (30 mg, 0.15 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*S*)-MTPA diester **249** (78 mg, 82%) as a colourless oil. $[\alpha]_D$ -62 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2929 (alkyl) and 1749 (C=O); δ_H(400 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.14-1.35 (14 H, m, alkyl-H), 1.65-1.77 (3 H, m, OCH$_2$C*H*CH$_2$), 3.53 (6 H, s, OC*H*$_3$), 4.12-4.19 (1 H, m, OCH*H*CH), 4.24-4.39 (3 H, m, OC*H*$_2$CH$_2$ and OCH*H*CH), 7.37-7.41 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 14.1 (*C*H$_3$), 22.6 (*C*H$_2$), 26.5 (*C*H$_2$), 29.2 (*C*H$_2$), 30.0 (*C*H$_2$), 30.3 (*C*H$_2$), 30.9 (*C*H$_2$), 31.0 (*C*H$_2$), 31.8 (*C*H$_2$), 34.2 (*C*H), 55.4 (2 x O*C*H$_3$), 64.0

(CH_2), 68.1 (CH_2), 121.9 (2 x *C*), 124.7 (2 x *C*), 127.2 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 x Ar*C*), 166.5 (*C*=O) and 166.6 (*C*=O); δ_F(200 MHz; $CDCl_3$) 37.56, 37.57, 37.60 and 37.63; *m/z* (EI) 634 (M^+, 1%), 401 (15) and 189 (100); (Found M^+ 634.2729; $C_{32}H_{40}F_6O_6$ requires M^+ 634.2729).

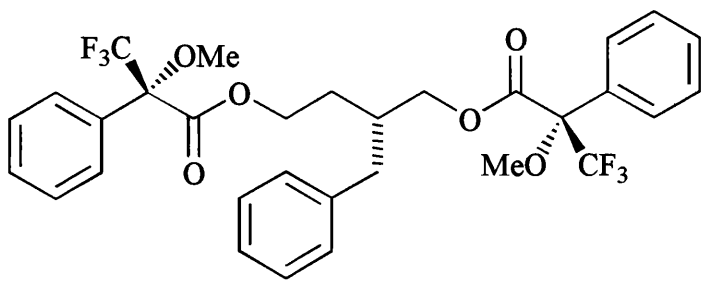
8.3.2.14 (*R*)-MTPA Diester of (2*R*)-2-benzylbutane-1,4-diol 250



250

Using (2*R*)-2-benzylbutane-1,4-diol **235** (30 mg, 0.15 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*R*)-MTPA diester **250** (87 mg, 92%) as a colourless oil. $[\alpha]_D$ +70 (*c* 0.4, EtOAc); υ_{max}(NaCl)/cm^{-1} 2951 (alkyl) and 1750 (C=O); δ_H(400 MHz; $CDCl_3$) 1.76-1.78 (2 H, m, alkyl-H), 2.06-2.19 (1 H, m, OCH_2CHCH_2), 2.52 -2.60 (2 H, m, alkyl-H), 3.52 (3 H, s, OCH_3), 3.53 (3 H, s, OCH_3), 4.13 (2 H, d, *J* 4.5, OCH_2CH), 4.25-4.43 (2 H, m, OCH_2CH_2), 6.95-6.97 (2 H, m, Ar*C*H), 7.19-7.27 (3 H, m, Ar*C*H), 7.39-7.44 (6 H, m, Ar*C*H) and 7.50-7.52 (4 H, m, Ar*C*H); δ_C(100 MHz; $CDCl_3$) 29.9 (CH_2), 36.2 (*C*H), 36.9 (CH_2), 55.4 (2 x OCH_3), 63.8 (CH_2), 67.1 (CH_2), 121.9 (2 x *C*), 124.8 (2 x *C*), 126.4 (2 x Ar*C*H), 127.2 (Ar*C*H), 127.3 (Ar*C*H), 128.5 (4 x Ar*C*H), 128.9 (3 x Ar*C*H), 129.7 (4 x Ar*C*H), 132.2 (2 x Ar*C*), 138.6 (2 Ar*C*) and 166.5 (2 x *C*=O); δ_F(200 MHz; $CDCl_3$) –71.93, -71.85, -71.70 and –71.66; *m/z* (FAB+) 613 (MH^+, 4%), 379 (15) and 189 (100); (Found MH^+ 613.2020; $C_{31}H_{30}F_6O_6$ requires 613.2025).

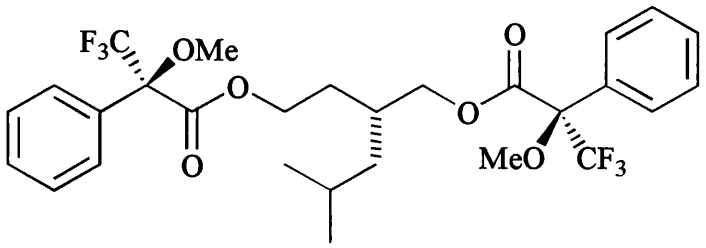
8.3.2.15 (*S*)-MTPA Diester of (2*R*)-2-benzylbutane-1,4-diol 251



251

Using (2*R*)-2-benzylbutane-1,4-diol **235** (30 mg, 0.15 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*S*)-MTPA diester **251** (75 mg, 79%) as a colourless oil. $[\alpha]_D$ -69 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2951 (alkyl) and 1748 (C=O); δ_H(400 MHz; $CDCl_3$) 1.70-1.73 (2 H, m, alkyl-H), 2.01-2.10 (1 H, m, OCH_2CHCH_2), 2.51-2.64 (2 H, m, alkyl-H), 3.50 (3 H, s, OCH_3), 3.52 (3 H, s, OCH_3), 4.02 (1 H, dd, *J* 4.4 and 11.2, OCH*H*CH), 4.24 (1 H, dd, *J* 4.8 and 11.2, OCH*H*CH), 4.28-4.40 (2 H, m, OCH_2CH_2), 6.98 (2 H, d, *J* 6.6, ArC*H*), 7.18-7.27 (3 H, m, ArC*H*), 7.34-7.44 (6 H, m, ArC*H*) and 7.48-7.52 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 29.6 (CH_2), 36.0 (*C*H), 37.1 (CH_2), 55.4 (2 x OCH_3), 63.7 (CH_2), 66.9 (CH_2), 121.9 (2 x *C*), 124.8 (2 x *C*), 126.5 (2 x ArCH), 127.2 (Ar*C*H), 127.4 (Ar*C*H), 128.5 (4 x Ar*C*H), 128.9 (2 x Ar*C*H), 129.7 (4 x Ar*C*H), 132.2 (2 x Ar*C*), 138.5 (2 x Ar*C*), 166.4 (C=O) and 166.5 (C=O); δ_F(200 MHz; $CDCl_3$) –71.92, -71.84, -71.70 and –71.65; *m/z* (FAB+) 613 (MH^+, 6%), 379 (16) and 189 (100); (Found MH^+ 613.2024; $C_{31}H_{30}F_6O_6$ requires 613.2025).

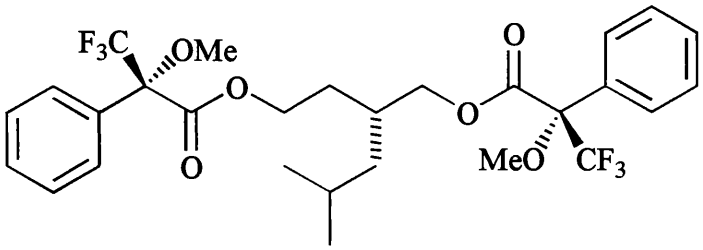
8.3.2.16 (*R*)-MTPA Diester of (2*R*)-2-isobutylbutane-1,4-diol 252



252

Using (2*R*)-2-isobutylbutane-1,4-diol **236** (8 mg, 0.05 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*R*)-MTPA diester **252** (19 mg, 66%) as a colourless oil. $[\alpha]_D$ +60 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2956 (alkyl) and 1749 (C=O); δ_H(400 MHz; $CDCl_3$) 0.79 (3 H, d, *J* 6.8, CH_3CHCH_3), 0.81 (3 H, d, *J* 6.8, CH_3CHCH_3), 1.03-1.20 (2 H, m, CH_3CHCH_2), 1.51-1.75 (3 H, m, alkyl-H), 1.83-1.89 (1 H, m, CH_2CHCH_2O), 3.53 (6 H, s, OCH_3), 4.13-4.19 (1 H, m, OCH*H*CH), 4.24-4.38 (3 H, m, OCH_2CH_2 and OCH*H*CH), 7.36-7.44 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 22.1 (CH_3), 22.8 (CH_3), 25.0 (*C*H), 29.5 (CH_2), 30.8 (*C*H), 39.1 (CH_2), 55.4 (2 x OCH_3), 64.0 (CH_2), 68.1 (CH_2), 121.9 (2 x *C*), 124.7 (2 x *C*), 127.3 (2 x ArCH), 128.4 (4 x ArCH), 129.6 (4 x Ar*C*H), 132.1 (2 x Ar*C*) and 166.5 (2 x *C*=O); δ_F(200 MHz; $CDCl_3$) –71.97, -71.91, -71.90 and –71.86; *m/z* (EI) 578 (M^+, 3%), 345 (30) and 189 (100); (Found M^+ 578.2104; $C_{28}H_{32}F_6O_6$ requires M^+ 578.2103).

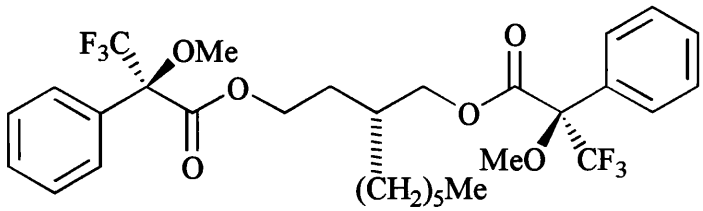
8.3.2.17 (S)-MTPA Diester of (2*R*)-2-isobutylbutane-1,4-diol 253



253

Using (2*R*)-2-isobutylbutane-1,4-diol **236** (8 mg, 0.05 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*S*)-MTPA diester **253** (23 mg, 66%) as a colourless oil. $[\alpha]_D$ -62 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2956 (alkyl) and 1749 (C=O); δ_H(400 MHz; $CDCl_3$) 0.79 (3 H, d, *J* 6.8, CH_3CHCH_3), 0.81 (3 H, d, *J* 6.8, CH_3CHCH_3), 1.03-1.20 (2 H, m, CH_3CHCH_2), 1.51-1.75 (3 H, m, alkyl-H), 1.83-1.89 (1 H, m, CH_2CHCH_2O), 3.53 (6 H, s, OCH_3), 4.13-4.19 (1 H, m, OCHHCH), 4.24-4.38 (3 H, m, OCH_2CH_2 and OCHHCH), 7.36-7.44 (6 H, m, ArCH) and 7.49-7.51 (4 H, m, ArCH); δ_C(100 MHz; $CDCl_3$) 22.1 (CH_3), 22.8 (CH_3), 25.0 (CH), 29.5 (CH_2), 30.8 (CH), 39.1 (CH_2), 55.4 (2 x OCH_3), 64.0 (CH_2), 68.1 (CH_2), 121.9 (2 x C), 124.7 (2 x C), 127.3 (2 x ArCH), 128.4 (4 x ArCH), 129.6 (4 x ArCH), 132.1 (2 x ArC) and 166.5 (2 x C=O); δ_F(200 MHz; $CDCl_3$) –71.97, -71.91, -71.90 and –71.86; *m/z* (EI) 578 (M^+, 0.5%), 345 (5) and 189 (100); (Found M^+ 578.2101; $C_{28}H_{32}F_6O_6$ requires M^+ 578.2103).

8.3.2.18 (*R*)-MTPA Diester of (2*R*)-2-hexylbutane-1,4-diol 254

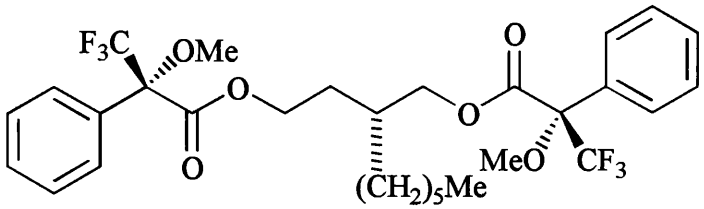


254

Using (2*R*)-2-hexylbutane-1,4-diol **237** (19 mg, 0.11 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*R*)-MTPA diester **254** (32 mg, 48%) as a colourless oil. $[\alpha]_D$ +74 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2929 (alkyl) and 1749 (C=O); δ_H(400 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 7.1, CH_3CH_2), 1.21-1.29 (10 H, m, alkyl-H), 1.64-1.77 (3 H, m, OCH_2CHCH_2), 3.52 (6 H, s, OCH_3), 4.14-4.19 (1 H, m, OCHHCH), 4.24-4.39 (3 H, m, OCH_2CH_2 and OCHHCH), 7.36-7.43 (6 H, m, ArCH) and 7.49-7.51 (4 H, m, ArCH); δ_C(100 MHz) 14.0 (CH_3), 22.5 (CH_2), 26.4 (CH_2), 29.3 (CH_2), 30.1 (CH_2),

30.7 (*C*H_2), 31.6 (*C*H_2), 34.2 (*C*H), 55.4 (2 x O*C*H_3), 64.0 (*C*H_2), 68.1 (*C*H_2), 121.9 (2 x *C*), 124.7 (2 x *C*), 127.2 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 x Ar*C*), 166.5 (*C*=O) and 166.6 (*C*=O); δ_F(200 MHz; $CDCl_3$) –71.95, -71.94, -71.90 and –71.87; *m/z* (EI) 606 (M^+, 3%), 373 (58) and 189 (100); (Found M^+ 606.2418; $C_{30}H_{36}F_6O_6$ requires M^+ 606.2416).

8.3.2.19 (*S*)-MTPA Diester of (2*R*)-2-hexylbutane-1,4-diol 255

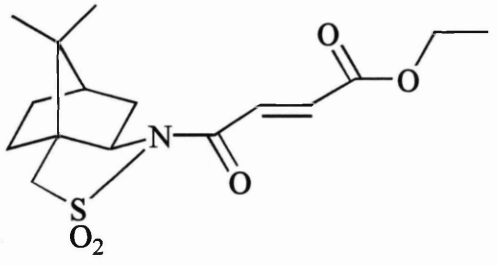


255

Using (2*R*)-2-hexylbutane-1,4-diol **237** (19 mg, 0.11 mmol) in General procedure 6 followed by chromatography [SiO_2, EtOAc-hexane (1:4)] gave (*S*)-MTPA diester **255** (55 mg, 82%) as a colourless oil. $[\alpha]_D$ -68 (*c* 0.8, EtOAc); υ_{max}(NaCl)/cm^{-1} 2929 (alkyl) and 1749 (C=O); δ_H(400 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.1, C*H*$_3$CH$_2$), 1.22-1.29 (10 H, m), 1.64-1.67 (2 H, m, OCH$_2$CHC*H*$_2$), 1.74-1.77 (1 H, m, OCH$_2$C*H*CH$_2$), 3.53 (6 H, s, OC*H*$_3$), 4.16 (ABX system, 1 H, dd, *J* 5.2 and 11.2, OCH*H*CH), 4.24-4.37 (3 H, m, OC*H*$_2$CH$_2$ and OCH*H*CH), 7.37-7.41 (6 H, m, ArC*H*) and 7.49-7.51 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 14.0 (*C*H_3), 22.6 (*C*H_2), 26.4 (*C*H_2), 29.3 (*C*H_2), 30.1 (*C*H_2), 30.7 (*C*H_2), 31.6 (*C*H_2), 34.2 (*C*H), 55.4 (2 x O*C*H_3), 64.0 (*C*H_2), 68.1 (*C*H_2), 121.8 (2 x *C*), 124.7 (2 x *C*), 127.2 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 129.6 (4 x Ar*C*H), 132.2 (2 x Ar*C*), 166.5 (*C*=O) and 166.6 (*C*=O); δ_F(200 MHz; $CDCl_3$) –71.95, -71.93, -71.90 and –71.87; *m/z* (EI) 606 (M^+, 1.6%), 373 (29) and 189 (100); (Found M^+ 606.2415; $C_{30}H_{36}F_6O_6$ requires M^+ 606.2416).

8.4.1 Synthesis of 2-substituted succinamides

8.4.1.1 (-)-(2*R*)-*N*-[(*E*)-3-(Ethoxycarbonyl)prop-2-enoyl]bornane-10,2-sultam 264[116]



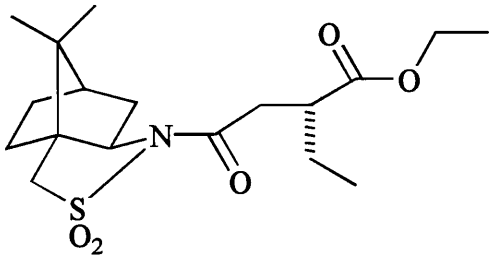
264

Compound **264** was prepared in 77% yield on a 69 mmol scale by the method of Curran and co-workers[116] and gave mp 118-120 °C (lit.[116] 119-121 °C); $[\alpha]_D$ –90 (*c* 1.2, $CHCl_3$) [lit.[116] –93.5, (*c* 1.2, $CHCl_3$)]; δ_H(400 MHz, $CDCl_3$) 0.99 (3 H, s, CH_3CCH_3), 1.17 (3 H, s, CH_3CCH_3), 1.32 (3 H, t, *J* 7.1, CH_3CH_2O), 1.36-1.47 (2 H, m, alkyl-H), 1.90-1.99 (3 H, m, alkyl-H), 2.09-2.17 (2 H, m, alkyl-H), (2 H, AB system, *J* 13.8, CH_2SO_2), 3.95-3.98 (1 H, m, CHN), 4.22-4.30 (2 H, m, OCH_2CH_3), 6.93 (1 H, d, *J* 15.3, CH=CH) and 7.54 (1 H, d, *J* 15.3, CH=CH).

General procedure 7 for the 1,4-addition of Grignard reagents to (-)-(2*R*)-*N*-[(*E*)-3-(ethoxycarbonyl)prop-2-enoyl]bornane-10,2-sultam 264.

The Grignard reagent (2.2 equiv.) in diethyl ether was added dropwise to a stirred solution of (-)-(2*R*)-*N*-[(*E*)-3-(ethoxycarbonyl)prop-2-enoyl]bornane-10,2-sultam **264** (1 equiv.) in dry THF (20 cm^3) under N_2 at –78 °C. After 3 h at –78 °C the reaction mixture was quenched with sat. aq. NH_4Cl soln. (15 cm^3) and then poured onto sat. aq. NH_4Cl soln (15 cm^3). The product was extracted with ethyl acetate (2 x 20 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

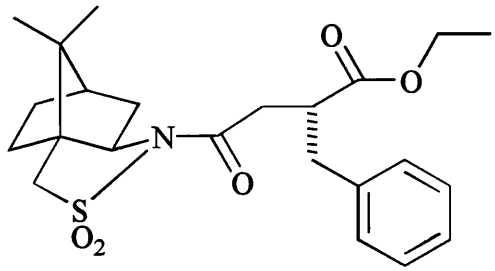
8.4.1.2 (-)-(2*R*)-*N*-[(3*R*)-3-(Ethoxycarbonyl)-3-ethylpropanoyl]bornane-10,2-sultam 271



271

Using ethyl magnesium chloride (1.1 cm^3 of a 3 mol dm^{-3} solution in Et_2O) and **264** on a 1.46 mmol scale following General procedure 7 gave a mixture of diastereoisomers **271** (0.23 g, 43%) as a colourless oil. $[\alpha]_D$ –94.6 (*c* 1.2, $CHCl_3$); υ_{max}(NaCl)/cm^{-1} 2932 (CH), 1686 (amide), 1322 and 1135 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.89-0.98 (6 H, m, CH_3CCH_3 and CH_3CH_2), 1.17 (3 H, s, CH_3CCH_3), 1.24-1.29 (3 H, m, OCH_2CH_3), 1.32-1.43 (2 H, m, alkyl-H), 1.56-1.74 (2 H, m, alkyl-H), 1.87-1.96 (3 H, m, alkyl-H), 2.04-2.16 (2 H, m, alkyl-H), 2.78-2.89 (2 H, m, alkyl-H), 3.16 (1 H, dd, *J* 8.9 and 16.6, $COCHHCH$), 3.44 (AB system, 1 H, d, *J* 13.8, $CHHSO_2$), 3.50 (AB system, 1 H, d, *J* 13.8, $CHHSO_2$), 3.87 (1 H, app t, *J* 7.6, CHN) and 4.10-4.27 (2 H, m, OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 11.7 (CH_3), 14.4 (CH_3), 20.1 (CH_3), 21.0 (CH_3), 25.2 (CH_2), 26.6 (CH_2), 33.0 (CH_2), 36.7 (CH_2), 38.5 (CH_2), 42.6 (CH), 44.8 (CH), 47.9 (C), 48.7 (C), 53.1 (CH_2), 60.7 (CH_2), 65.4 (CH), 170.3 (C=O) and 174.7 (C=O); *m/z* (EI) 371 (M^+, 0.5%), 326 (12) and 157 (100); (Found M^+ 371.1765; $C_{18}H_{29}NO_5S$ requires M^+ 371.1766).

8.4.1.3 (-)-(2*R*)-*N*-[(3*R*)-3-(Ethoxycarbonyl)-3-benzylpropanoyl]bornane-10,2-sultam 272

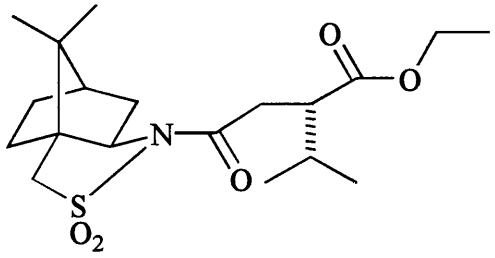


272

Using benzyl magnesium chloride (7.2 cm^3 of a 1 mol dm^{-3} solution in Et_2O) and **264** on a 3.25 mmol scale following General procedure 7 gave a mixture of diastereoisomers **272** (1.34 g, 96%) as a colourless oil. $[\alpha]_D$ -73 (*c* 1.5, EtOAc);

υ_{max}(NaCl)/cm^{-1} 2962 (CH), 1695 (amide), 1333 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.97 (3 H, s, CH_3CCH_3), 1.13 (3 H, s, CH_3CCH_3), 1.17 (3 H, t, *J* 7.2, CH_3CH_2O), 1.86-1.96 (3 H, m, alkyl-H), 2.01-2.07 (2 H, m, alkyl-H), 2.79-2.90 (2 H, m, alkyl-H), 3.05 (ABX system, 1 H, dd, *J* 6.8 and 13.7, COCH*H*CH), 3.13-3.25 (2 H, m, alkyl-H), 3.39-3.51 (2 H, m, alkyl-H), 3.82-3.87 (1 H, m, C*H*N), 4.07-4.17 (2 H, m, OCH_2CH_3) and 7.19-7.31 (5 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 14.2 (CH_3), 20.1 (CH_3), 21.0 (CH_3), 26.6 (CH_2), 30.0 (CH_2), 36.9 (CH_2), 37.9 (CH_2), 38.6 (CH_2), 43.1 (*C*H), 44.8 (*C*H), 47.9 (*C*), 48.7 (*C*), 53.0 (CH_2), 60.8 (CH_2), 65.4 (*C*H), 126.8 (Ar*C*H), 128.6 (2 x Ar*C*H), 129.3 (2 x Ar*C*H), 138.6 (Ar*C*), 170.1 (*C*=O) and 174.1 (C=O); *m/z* (EI) 433 (M^+, 30%), 190 (76) and 135 (100); (Found M^+ 433.1924; $C_{23}H_{31}NO_5S$ requires M^+ 433.1923).

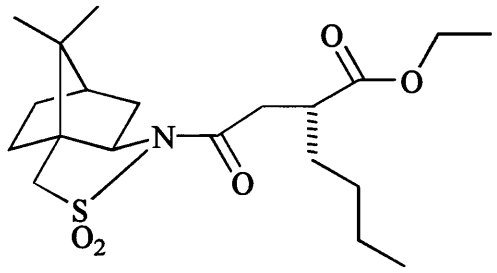
8.4.1.4 (-)-(2*R*)-*N*-[(3*R*)-3-(Ethoxycarbonyl)-3-isopropylpropanoyl]bornane-10,2-sultam 273



273

Using isopropyl magnesium chloride (3.2 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **264** on a 2.9 mmol scale following General procedure 7 produced a mixture of diastereoisomers **273** (0.73 g, 65 %) as a colourless oil. $[\alpha]_D$ -75 (*c* 1.5, EtOAc); υ_{max}(NaCl)/cm^{-1} 2962 (CH), 1730 (ester), 1697 (amide), 1333 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.94 (9 H, m, CH_3CCH_3, CH_3CCH_3), 1.16 (3 H, s, CH_3CCH_3), 1.23-1.43 (7 H, m, alkyl-H), 1.86-2.13 (4 H, m, alkyl-H), 2.75-2.87 (2 H, m, alkyl-H), 3.17 (ABX system, 1 H, dd, *J* 2.8 and 10.8, COCH*H*CH), 3.44 (ABX system, 1 H, dd, *J* 6.8 and 14.0, COCH*H*CH), 3.49-3.54 (1 H, m, $COCH_2CH$), 3.83-3.89 (1 H, m, C*H*N) and 4.10-4.20 (2 H, m, OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 14.4 (CH_3), 19.8 (CH_3), 20.1 (CH_3), 20.3 (CH_3), 21.0 (CH_3), 26.7 (CH_2), 30.3 (*C*H), 32.9 (CH_2), 34.1 (CH_2), 35.0 (CH_2), 38.6 (CH_2), 47.0 (*C*H), 47.4 (*C*H), 48.7 (*C*), 53.1 (*C*), 60.5 (CH_2), 65.3 (*C*H), 170.7 (*C*=O) and 174.2 (*C*=O); *m/z* (FAB+) 386 [$(M+H)^+$, 59%] 171 (100) and 135 (14); [Found $(M+Na)^+$ 408.1833; $C_{19}H_{31}NO_5S$ requires 408.1821].

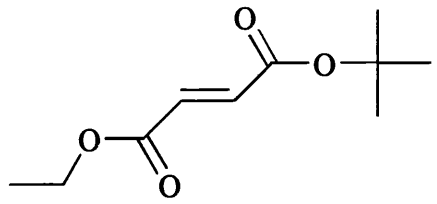
8.4.1.5 (-)-(2*R*)-*N*-[(3*R*)-3-(Ethoxycarbonyl)-3-butylpropanoyl]bornane-10,2-sultam 274



274

Using butyl magnesium chloride (3.2 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **264** on a 2.9 mmol scale following General procedure 7 produced a mixture of diastereoisomers **274** (0.97 g, 84%) as a colourless oil. $[\alpha]_D$ -69 (*c* 1.5, EtOAc); υ_{max}(NaCl)/cm^{-1} 2960 (CH), 1733 (ester), 1695 (amide), 1336 and 1135 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.1, C$H_3$$CH_2$), 0.98 (3 H, s, C$H_3$$CCH_3$), 1.17 (3 H, s, C$H_3$$CCH_3$), 1.24-1.43 (10 H, m, alkyl-H), 1.50-1.68 (2 H, m, alkyl-H), 1.87-1.96 (2 H, m, alkyl-H), 2.04-2.18 (2 H, m, alkyl-H), 2.84-2.93 (2 H, m, alkyl-H), 3.15 (ABX system, 1 H, dd, *J* 10.2 and 17.8, COCH*H*CH), 3.41-3.52 (2 H, m, alkyl-H), 3.85-3.89 (1 H, m, C*H*N) and 4.10-4.22 (2 H, m, OC$H_2$$CH_3$); δ_C(100 MHz; $CDCl_3$) 13.8 (*C*H_3), 14.2 (*C*H_3), 20.7 (*C*H_3), 21.6 (*C*H_3), 23.3 (*C*H_2), 27.2 (*C*H_2), 29.9 (*C*H_2), 32.4 (*C*H_2), 33.6 (*C*H_2), 38.1 (*C*H_2), 39.1 (*C*H_2), 41.8 (*C*H), 48.6 (*C*), 49.3 (*C*), 53.7 (*C*H_2), 53.9 (*C*), 61.2 (*C*H_2), 65.9 (*C*H), 171.0 (*C*=O) and 175.5 (*C*=O); *m/z* (EI) 399 (M^+, 30%), 185 (M^+- camphorsultam, 100); (Found M^+ 399.2080; $C_{20}H_{33}NO_5S$ requires M^+ 399.2079).

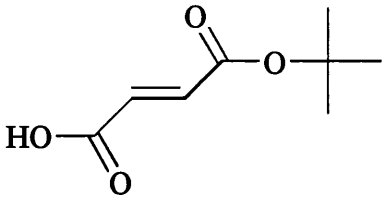
8.4.1.6 *tert*-Butyl ethyl fumarate 268[140]



268

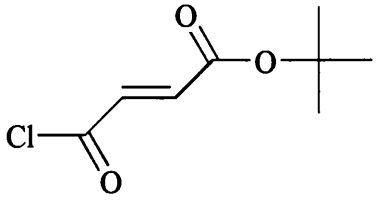
Compound **268** was prepared in 53% yield on a 0.14 mol scale by the method of Steglich and co-workers.[140] δ_H(400 MHz, $CDCl_3$) 1.32 (3 H, t, *J* 7.2, C$H_3$$CH_2O$), 1.51 (9 H, s, OCC$H_3$), 4.26 (2 H, q, *J* 7.1, CH_3CH_2O), 6.75 (1 H, d, *J* 15.8, C*H*=CH) and 6.79 (1 H, d, *J* 15.8, C*H*=CH).

8.4.1.7 *tert*-Butyl fumaric acid[141]



At 0 °C, *tert*-butyl ethyl fumarate **268** (12.6 g, 63 mmol) was dissolved in tetrahydrofuran (50 cm^3) before lithium hydroxide (2.6 g, 63 mmol) was added. The reaction mixture was stirred for 5 h at 0 °C, then sat. aq. NH_4Cl (10 cm^3) was added. The mixture was stirred for a further 10 min, after which ethyl acetate (20 cm^3) was poured onto the reaction mixture. The aqueous layer was extracted and acidified to pH 2 using 1M HCl. The aqueous layer was extracted using ethyl acetate (3 x 20 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give *tert*-butyl fumaric acid as a white solid (7.7 g, 71%). mp 127 °C; υ_{max}(KBr)/cm^{-1} 3012 (CH) and 1700 (C=O); δ_H(400 MHz, $CDCl_3$) 1.52 (9 H, s, OCCH_3), 6.76 (1 H, d, *J* 15.7, C*H*=CH) and 6.79 (1 H, d, *J* 15.8, C*H*=CH); *m/z* (CI^+ mode, isobutane) 173 (MH^+, 100%) and 145 (10); (Found MH^+ 173.0795; $C_8H_{12}O_4$ requires 173.0814).

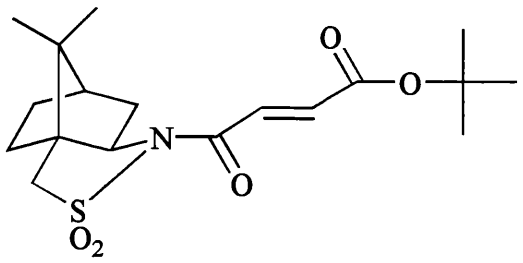
8.4.1.8 *tert*-Butyl fumaroyl chloride 269



269

tert-Butyl fumaric acid and thionyl chloride (4 equiv.) were placed in a round-bottomed flask, equipped with water condenser, HCl trap, and assembled under nitrogen. The reaction was heated to reflux until no more gas was given off. The excess thionyl chloride was removed under reduced pressure and the product was used with no further purification.

8.4.1.9 (-)-(2*R*)-*N*-[(*E*)-3-(*tert*-Butoxycarbonyl)prop-2-enoyl]bornane-10,2-sultam 265



265

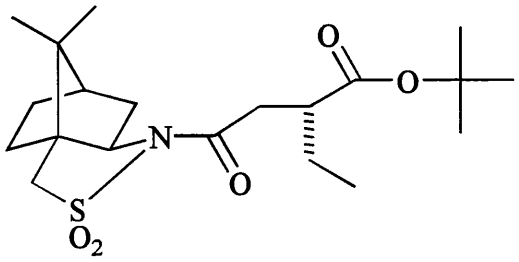
(1*S*,2*R*)-(-)-2,10-Camphorsultam **111** (2.2 g, 10 mmol, 1 equiv.) in toluene (30 cm^3) was added dropwise to a suspension of NaH (0.37 g, 15 mmol, 1.5 equiv.) and stirred for 2 h at room temperature. Then fumaroyl chloride *tert*butyl ester **269** (2.2 g, 12 mmol, 1 equiv.) in toluene (5 cm^3) was added dropwise and the mixture was stirred for 10 min, quenched by addition of saturated ammonium chloride (10 cm^3) and poured onto saturated ammonium chloride (10 cm^3). The aqueous layer was washed with toluene (3 x 25 cm^3). The combined organic extracts were washed with brine (30 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and chromatographed [SiO_2, EtOAc-hexane (3:7)] to give the fumarate **265** (1.5 g, 40%) as an orange oil. $[\alpha]_D$ –57.9 (*c* 2.0, EtOAc); υ_{max}(NaCl)/cm^{-1} 2937 (CH), 1735 (ester), 1684 (amide), 1319 and 1153 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.99 (3 H, s, CCH_3), 1.18 (3 H, s, CCH_3), 1.25-1.49 (4 H, m, alkyl-H), 1.51 (9 H, s. [C(CH_3)$_3$], 1.91-1.95 (2 H, m, alkyl-H), 2.09-2.15 (1 H, m, alkyl-H), 3.51 (2 H, AB system, *J* 13.8, CH_2SO_2), 3.94-3.96 (1 H, m, C*H*N), 6.85 (1 H, d, *J* 15.2, C*H*=CH) and 7.47 (1 H, d, *J* 15.2, C*H*=CH); δ_C(100 MHz; $CDCl_3$) 20.3 (*C*H_3), 21.2 (*C*H_3), 26.9 (*C*H_2), 28.3 (3 x *C*H_3), 33.3 (*C*H_2), 38.7 (*C*H_2), 45.0 (*C*H), 48.3 (*C*), 49.1 (*C*), 53.4 (*C*H_2), 65.5 (*C*H), 82.4 (*C*), 131.7 (*C*H), 136.6 (*C*H), 163.1 (*C*=O) and 164.2 (*C*=O); *m/z* (EI) 369 (M^+, 4%), 135 (63) and 99 (100); (Found M^+ 369.1609; $C_{18}H_{27}NO_5S$ requires M^+ 369.1610).

General procedure 8 for the 1,4-addition of Grignard reagents to (-)-(2*R*)-*N*-[(*E*)-3-(*tert*-Butoxycarbonyl)prop-2-enoyl]bornane-10,2-sultam 265.

The Grignard reagent (2.2 equiv.) in diethyl ether was added dropwise to a stirred solution of (-)-(2*R*)-*N*-[(*E*)-3-(*tert*-butoxycarbonyl)prop-2-enoyl]bornane-10,2-sultam **265** (1 equiv.) in dry THF (20 cm^3) under N_2 at –78 °C. After 3 h at –78 °C the reaction mixture was quenched with sat. aq. NH_4Cl soln. (15 cm^3) and then poured onto sat. aq.

NH_4Cl soln (15 cm^3). The product was extracted with ethyl acetate (2 x 20 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

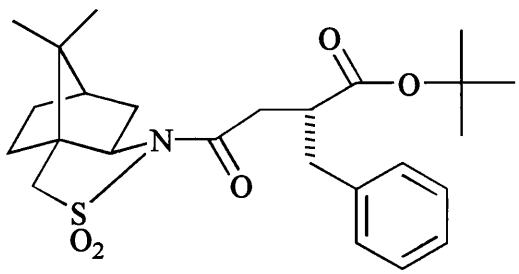
8.4.1.10 (-)-(2*R*)-*N*-[(3*R*)-3-(*tert*-Butoxycarbonyl)-3-ethylpropanoyl]bornane-10,2-sultam 275



275

Using ethyl magnesium chloride (1.0 cm^3 of a 3 mol dm^{-3} solution in Et_2O) and **265** on a 1.36 mmol scale following General procedure 8 produced a mixture of diastereoisomers **275** (0.45 g, 83%) as a colourless oil. $[\alpha]_D$ -53 (*c* 1.0, EtOAc); υ_{max}(NaCl)/cm^{-1} 2968 (CH), 1724 (C=O), 1701 (C=O), 1333 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.94 (3 H, t, *J* 7.2, CH_3CH_2), 0.98 (3 H, s, CH_3CCH_3), 1.17 (3 H, s, CH_3CCH_3), 1.47 (9 H, s, $C(CH_3)_3$), 1.54-1.70 (2 H, m, alkyl-H), 1.88-1.94 (4 H, m, alkyl-H), 2.05-2.12 (2 H, m, alkyl-H), 2.68-2.74 (1 H, m, alkyl-H), 2.81 (ABX system, 1 H, dd, *J* 4.8 and 17.2, COCH*H*CH), 3.09 (ABX system, 1 H, dd, *J* 9.3 and 17.0, COCH*H*CH), 3.42-3.51 (3 H, m, CH_2SO_2 and COCHHC*H*) and 3.85-3.89 (1 H, m, C*H*N); δ_C(100 MHz; $CDCl_3$) 11.8 (CH_3), 20.3 (CH_3), 21.2 (CH_3), 25.5 (CH_2), 26.8 (CH_2), 28.4 (3 x CH_3), 33.2 (CH_2), 37.5 (CH_2), 38.8 (CH_2), 43.7 (*C*H), 45.0 (*C*H), 48.2 (*C*), 48.9 (*C*), 53.3 (CH_2), 65.6 (*C*H), 80.7 (*C*), 170.6 (*C*=O) and 174.0 (C=O); *m/z* (CI^+ mode, isobutane) 400 (MH^+, 9%) 344 (78) and 216 (56); (Found MH^+ 400.2156; $C_{20}H_{33}NO_5S$ requires 400.2158).

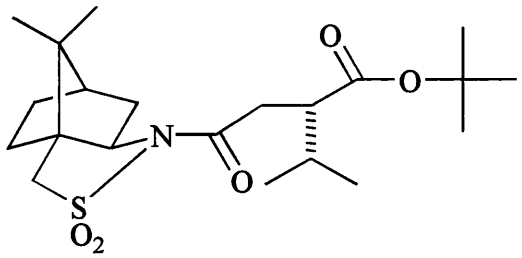
8.4.1.11 (-)-(2*R*)-*N*-[(3*R*)-3-(*tert*-Butoxycarbonyl)-3-benzylpropanoyl]bornane-10,2-sultam 276



276

Using benzyl magnesium chloride (3.0 cm^3 of a 1 mol dm^{-3} solution in Et_2O) and **265** on a 1.36 mmol scale following General procedure 8 produced a mixture of diastereoisomers **276** (0.38 g, 60%) as a colourless oil. $[\alpha]_D$ -40 (*c* 1.0, EtOAc); υ_{max}(NaCl)/cm^{-1} 2964 (CH), 1726 (C=O), 1701 (C=O), 1333 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.95 (3 H, s, CH_3CCH_3), 1.14 (3 H, s, CH_3CCH_3), 1.36 (9 H, s, $C(CH_3)_3$), 1.41-1.52 (3 H, m, alkyl-H), 1.86-1.92 (4 H, m, alkyl-H), 2.77-3.15 (5 H, m, alkyl-H), 3.37-3.50 (2 H, m, CH_2SO_2), 3.85-3.89 (1 H, m, CHN) and 7.11-7.32 (5 H, m, ArCH); δ_C(100 MHz; $CDCl_3$) 20.3 (CH_3), 21.3 (CH_3), 26.8 (CH_2), 28.3 (3 x CH_3), 33.2 (CH_2), 37.4 (CH_2), 38.3 (CH_2), 38.8 (CH_2), 44.0 (CH), 45.0 (CH), 48.1 (C), 48.9 (C), 53.2 (CH_2), 65.5 (CH), 81.0 (C), 126.8 (ArCH), 128.7 (2 x ArCH), 129.1 (2 x ArCH), 139.0 (ArC), 170.3 (C=O) and 173.4 (C=O); *m/z* (EI) 461 (M^+, 2%), 405 (40), 257 (74), 216 (45) and 135 (100); (Found M^+ 461.2236; $C_{25}H_{35}NO_5S$ requires M^+ 461.2236).

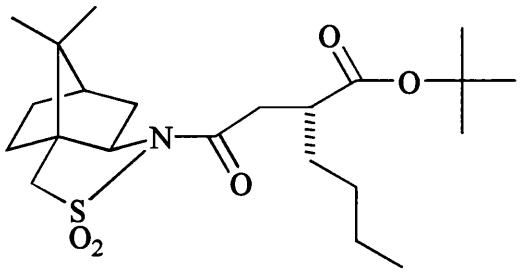
8.4.1.12 (-)-(2*R*)-*N*-[(3*R*)-3-(*tert*-Butoxycarbonyl)-3-*iso*propylpropanoyl]bornane-10,2-sultam 277



277

Using isopropyl magnesium chloride (2.0 cm^3 of a 2 mol dm^{-3} solution in THF) and **265** on a 1.8 mmol scale following General procedure 8 produced a mixture of diastereoisomers **277** (0.65 g, 86%) as a colourless oil. $[\alpha]_D$ -59 (*c* 1.5, EtOAc); υ_{max}(NaCl)/cm^{-1} 2966 (CH), 1725 (C=O), 1701 (C=O), 1331 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.95-0.97 (9 H, m, CH_3CHCH_3 and CH_3CCH_3), 1.16 (3 H, s, CH_3CCH_3), 1.44 (9 H, s, $C(CH_3)_3$), 1.86-2.12 (8 H, m, alkyl-H), 2.62-2.82 (2 H, m, $COCH_2CH$), 3.06-3.16 (1 H, m, $COCH_2CH$), 3.40-3.52 (2 H, m, CH_2SO_2) and 3.83-3.88 (1 H, m, CHN); δ_C(100 MHz; $CDCl_3$) 20.2 (CH_3), 20.5 (2 x CH_3), 21.2 (CH_3), 26.9 (CH_2), 28.4 (3 x CH_3), 30.5 (C), 30.6 (CH), 33.2 (CH_2), 34.7 (CH_2), 38.8 (CH_2), 45.0 (CH), 48.2 (CH), 48.9 (C), 53.3 (CH_2), 65.6 (CH), 80.7 (C), 171.2 (C=O) and 173.4 (C=O); *m/z* (CI^+ mode, isobutane) 414 (MH^+, 30%) 358 (100) and 216 (82); (Found MH^+ 414.2312; $C_{21}H_{35}NO_5S$ requires 414.2314).

8.4.1.13 (-)-(2*R*)-*N*-[(3*R*)-3-(*tert*-Butoxycarbonyl)-3-butylpropanoyl]bornane-10,2-sultam 278



278

Using butyl magnesium chloride (2.2 cm^3 of a 2 mol dm^{-3} solution in Et_2O) and **265** on a 2.0 mmol scale following General procedure 8 produced a mixture of diastereoisomers **278** (0.75 g, 88%) as a colourless oil. $[\alpha]_D$ -50 (*c* 1.5, EtOAc); υ_{max}(NaCl)/cm^{-1} 2963 (CH), 1724 (C=O), 1701 (C=O), 1332 and 1134 (-SO_2-N); δ_H(400 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.2, CH_3CH_2), 0.98 (3 H, s, CH_3CCH_3), 1.17 (3 H, s, CH_3CCH_3), 1.23-1.41 (8 H, m, alkyl-H), 1.45 (9 H, s, $C(CH_3)_3$), 1.48-1.68 (2 H, m, alkyl-H), 1.87-1.94 (2 H, m, alkyl-H), 2.04-2.12 (1 H, m, alkyl-H), 2.73-2.83 (2 H, m, alkyl-H), 3.09 (ABX system, 1 H, dd, *J* 9.2 and 16.8, COCH*H*CH) 3.47 (2 H, AB system, *J* 13.8, CH_2SO_2) and 3.85-3.88 (1 H, m, C*H*N); δ_C(100 MHz; $CDCl_3$) 14.1 (CH_3), 20.1 (CH_3), 21.0 (CH_3), 22.7 (CH_2), 26.6 (CH_2), 28.3 (3 x CH_3), 29.3 (CH_2), 31.9 (CH_2), 33.0 (CH_2), 37.7 (CH_2), 38.5 (CH_2), 42.1 (CH), 44.9 (CH), 48.0 (*C*), 48.7 (*C*), 53.1 (CH_2), 65.4 (CH), 80.5 (*C*), 170.4 (*C*=O) and 174.0 (C=O); *m/z* (CI^+ mode, isobutane) 428 (MH^+, 33%) 372 (100) and 216 (78); (Found MH^+ 428.2473; $C_{22}H_{37}NO_5S$ requires 428.2471).

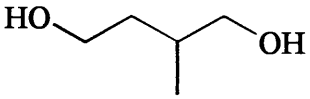
8.5 Experimental for Chapter 7

8.5.1 Synthesis of 2-substituted butane-1,4-diols

General 9 procedure for the reduction of 2-substituted succinic acids into 2-substituted butane-1,4-diols.

Borane (1.0 mol dm^{-3} solution in THF, 5 equiv.) was added dropwise to a stirred solution of 2-substituted succinic acid (1.0 g) in dry THF (20 cm^3) under N_2 at 0 °C. After 4 h at 0 °C the excess borane was quenched with addition of methanol (20 cm^3) and the reaction mixture was concentrated under reduced pressure. The residue was redissolved in methanol (20 cm^3) and concentrated under reduced pressure (x3).

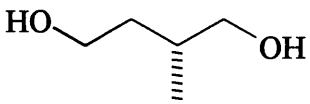
8.5.1.1 (±)-2-Methylbutane-1,4-diol 301[142]



301

Using (±)-2-methylsuccinic acid 7.6 mmol following General procedure 9 gave a residue which was chromatographed [SiO_2, acetone-hexane (1:1)] to give (±)-2-methylbutane-1,4-diol **301** (0.68 g, 85 %) as a colourless oil. δ_H(400 MHz; $CDCl_3$) 0.94 (3 H, d, *J* 6.8, C*H*$_3$CH), 1.56-1.69 (2 H, m, C*H*$_2$CH$_2$OH), 1.79-1.85 (1 H, m, CH$_3$C*H*), 1.44 (2 H, br s, O*H*), 3.45 (ABX system, 1 H, dd, *J* 7.6 and 10.8, CHCH*H*OH), 3.58 (ABX system, 1 H, dd, *J* 4.4 and 10.8, CHCH*H*OH) 3.64-3.70 (1 H, m, CH$_2$CH*H*OH) and 3.76-3.81 (1 H, m, CH$_2$CH*H*OH).

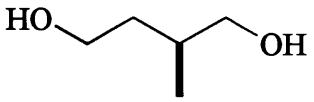
8.5.1.2 (2*R*)-2-Methylbutane-1,4-diol 302[143]



302

Using (2*R*)-2-methylsuccinic acid 7.6 mmol following General procedure 9 gave a residue which was chromatographed [SiO_2, acetone-hexane (1:1)] to give (2*R*)-2-methylbutane-1,4-diol **302** (0.60 g, 75 %) as a colourless oil. Spectral data were identical to racemate **301**. $[\alpha]_D$ +11 (*c* 3.3, MeOH) [lit.[143] +13.6, (*c* 3.3, MeOH)].

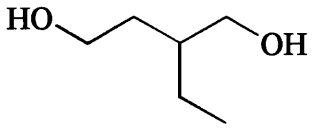
8.5.1.3 (2*S*)-2-Methylbutane-1,4-diol 303[143]



303

Using 2*S*-2-methylsuccinic acid (1.0 g, 7.6 mmol) following General procedure 9 gave a residue which was chromatographed [SiO_2, acetone-hexane (1:1)] to give (2*S*)-2-methylbutane-1,4-diol **303** (0.76 g, 95%) as a colourless oil. Spectral data were identical to racemate **301**. $[\alpha]_D$ -12 (*c* 3.3, MeOH) [lit.[143] -13.4, (*c* 3.3, MeOH)].

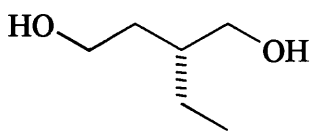
8.5.1.4 (±)-2-Ethylbutane-1,4-diol 304[144]



304

Ethyl *tert*-butyl succinate **129** (0.80 g, 4.0 mmol) in dry THF (10 cm^3) was added dropwise to a stirred solution of lithium aluminium hydride (0.75 g, 20 mmol) in dry THF (50 cm^3) under N_2 at 0 °C. After 3 h at 0 °C the reaction mixture was quenched with sat. aq. NH_4Cl soln. (4 cm^3). The mixture was filtered and concentrated under reduced pressure. The residue was chromatographed [SiO_2, acetone-hexane (2:3)] to give (±)-2-ethylbutane-1,4-diol **304** (0.38 g, 81%) as a colourless oil. υ_{max}(NaCl)/cm^{-1} 3367 (OH) and 2927 (alkyl); δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 7.5, C*H*$_3$CH$_2$), 1.25-1.45 (2 H, m, CH$_3$C*H*$_2$), 1.54-1.64 (2 H, m, C*H*$_2$CH$_2$OH), 1.68-1.77 (1 H, m, C*H*), 2.48 (2 H, br s, O*H*), 3.52 (ABX system, 1 H, dd, *J* 6.6 and 10.8, CHCH*H*OH), 3.65-3.61 (2 H, m, CH$_2$C*H*$_2$OH) and 3.78-3.83 (1 H, m, CHCH*H*OH); δ_C(100 MHz; $CDCl_3$) 11.5 (*C*H$_3$), 24.4 (*C*H$_2$), 35.4 (*C*H$_2$), 40.9 (*C*H), 61.2 (*C*H$_2$) and 66.0 (*C*H$_2$); *m/z* (CI^+ mode, isobutane) 119 (MH^+, 100%) 101 (64) and 83 (19); (Found MH^+ 119.1073; $C_6H_{14}O_2$ requires 119.1072).

8.5.1.5 (2*R*)-2-Ethylbutane-1,4-diol 305[145]

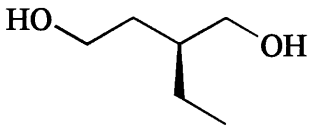


305

(2*R*)-*N*,*N*'-Bis[(2*R*)-bornane-10,2-sultam]-2-ethylsuccinamide **186** (1.10 g, 2.0 mmol) in dry THF (10 cm^3) was added dropwise to a stirred solution of lithium aluminium

hydride (0.38 g, 10 mmol) in dry THF (50 cm^3) under N_2 at 0 °C. After 3 h at 0 °C the reaction mixture was quenched with sat. aq. NH_4Cl soln. (4 cm^3). The mixture was filtered and concentrated under reduced pressure. The mixture was chromatographed [SiO_2, acetone-hexane (2:3)] to give (2*R*)-2-ethylbutane-1,4-diol **305** (0.14 g, 58%) as a colourless oil. Spectral data were identical to racemate **304**. $[\alpha]_D$ +11 (*c* 1.5, $CHCl_3$) [lit.[141] +14, (*c* 1.5, $CHCl_3$)]; *m/z* (FAB+) 141 [$(M+Na)^+$, 100%] and 119 [$(M+H)^+$, 26]; [Found $(M+Na)^+$ 141.0892; $C_6H_{14}O_2$ requires 141.0891].

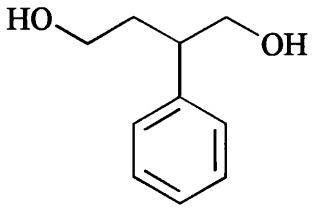
8.5.1.6 (2*S*)-2-Ethylbutane-1,4-diol 306[145]



306

(2*S*)-*N*,*N*'-Bis[(2*S*)-bornane-10,2-sultam]-2-ethylsuccinamide (1.18 g, 2.2 mmol) in dry THF (10 cm^3) was added dropwise to a stirred solution of lithium aluminium hydride (0.42 g, 11 mmol) in dry THF (50 cm^3) under N_2 at 0 °C. After 3 h at 0 °C the reaction mixture was quenched with sat. aq. NH_4Cl soln. (4 cm^3). The mixture was filtered and concentrated under reduced pressure. The mixture was chromatographed [SiO_2, acetone-hexane (2:3)] to give (2*S*)-2-ethylbutane-1,4-diol **306** (0.16 g, 62%) as a colourless oil. Spectral data were identical to racemate **304**. $[\alpha]_D$ -14.2 (*c* 1.5, $CHCl_3$); *m/z* (CI^+ mode, isobutane) 119 (MH^+, 100%) 101 (40) and 83 (12); (Found MH^+ 119.1070; $C_6H_{14}O_2$ requires 119.1072).

8.5.1.7 (±)-2-Phenylbutane-1,4-diol 307[146]

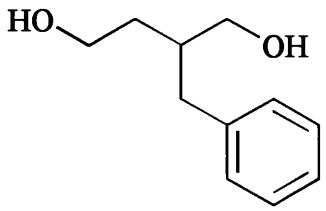


307

Using (±)-2-phenylsuccinic acid 5.2 mmol) following General procedure 9 gave a residue which was chromatographed [SiO_2, acetone-hexane (2:3)] to give (±)-2-phenylbutane-1,4-diol **307** (0.68 g, 79 %) as a colourless oil. δ_H(400 MHz; $CDCl_3$) 1.69 (2 H, br s, O*H*), 1.87-1.95 (1 H, m, CH*H*CH_2OH), 2.00-2.08 (1 H, m, CH*H*CH_2OH), 2.95-3.02 (1 H, m, C*H*CH_2OH), 3.57-3.63 (1 H, m, CH_2CH*H*OH), 3.68-3.74 (1 H, m,

$CH_2CH\mathit{H}OH$) 3.80 (2 H, d, *J* 6.6, $CHC\mathit{H}_2OH$), 7.23-7.27 (3 H, m, ArC*H*) and 7.35 (2H, t, *J* 7.5, ArC*H*).

8.5.1.8 (±)-2-Benzylbutane-1,4-diol 308[149]



308

tert-Butyl benzylsuccinate **134** (1.15 g, 4.4 mmol) in dry THF (10 cm^3) was added dropwise to a stirred solution of lithium aluminium hydride (0.83 g, 22 mmol) in dry THF (50 cm^3) under N_2 at 0 °C. After 3 h at 0 °C the reaction mixture was quenched with sat. aq. NH_4Cl soln. (4 cm^3). The mixture was filtered and concentrated under reduced pressure. The residue was chromatographed [SiO_2, acetone-hexane (2:3)] to give (±)-2-benzylbutane-1,4-diol **308** (0.45 g, 58 %) as a colourless oil. υ_{max}(NaCl)/cm^{-1} 3340 (OH) and 2927 (alkyl); δ_H(400 MHz; $CDCl_3$) 1.58-1.67 (1 H, m, ArCH*H*CH), 1.70-1.77 (1 H, m, ArCH*H*CH), 1.97-2.06 (1 H, m, $ArCH_2C\mathit{H}$), 2.16 (2 H, br s, O*H*), 2.58 (1 H, dd, *J* 7.4 and 13.6, $CH\mathit{H}CH_2OH$), 2.70 (1 H, dd, *J* 7.6 and 13.7, $CH\mathit{H}CH_2OH$), 3.53 (1 H, dd, *J* 6.5 and 10.9 CHCH*H*OH), 3.65-3.70 (2 H, m, $CH_2C\mathit{H}_2OH$), 3.77-3.83 (1 H, m, CHCH*H*OH) and 7.18-7.31 (5 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 35.2 ($\mathit{C}H_2$), 38.2 ($\mathit{C}H_2$), 41.1 (*C*H), 61.1. ($\mathit{C}H_2$), 65.6 ($\mathit{C}H_2$), 126.0 (Ar*C*H), 128.4 (2 x Ar*C*H), 129.1 (2 x Ar*C*H) and 138.1(Ar*C*); *m/z* (CI^+ mode, isobutane) 181 (MH^+, 100%) 163 (70) and 145 (27); (Found MH^+ 181.1228; $C_{11}H_{16}O_2$ requires 181.1229).

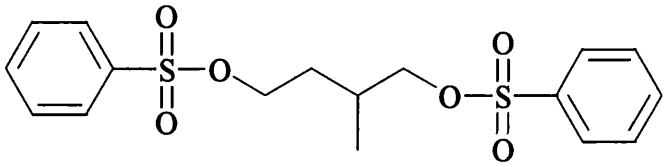
8.5.2 Synthesis of 2-substituted butane-1,4-ditosylates

General procedure 10 for the conversion of 2-substituted butane-1,4-diols into 2-substituted butane-1,4-ditosylates.

To an ice-cooled solution of benzensulfonyl chloride or *p*-toluenesulfonyl chloride (3 equiv.) in dry pyridine (5 cm^3) was added dropwise a solution of diol (~0.5 g) in dry pyridine (5 cm^3). The mixture was stirred at 0 °C for 3 h, then poured into ice-cooled water (30 cm^3) and extracted with ethyl acetate (3 x 30 cm^3). Organic extracts were washed with

1M HCl (40 cm^3), water (40 cm^3) and sodium bicarbonate solution (40 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

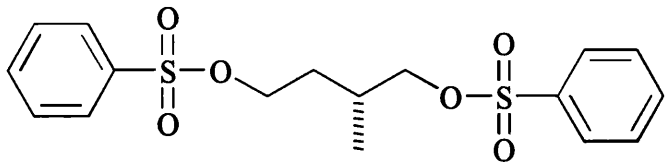
8.5.2.1 (±)-2-Methyl-1,4-bis(benzenesulfonyloxy)butane 309



309

Using benzenesulfonyl chloride and (±)-2-methylbutane-1,4-diol **301** on a 5.4 mmol scale following General procedure 10 gave a residue which was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (±)-2-methyl-1,4-bis(benzenesulfonyloxy)butane **309** (0.8 g, 39%) as a colourless oil. υ_{max}(NaCl)/cm^{-1} 2970 (alkyl), 1357 and 1189 (-SO_2-O); δ_H(400 MHz; $CDCl_3$) 0.87 (3 H, d, *J* 6.8, C*H*$_3$CH), 1.45-1.54 (1 H, m, CH*H*CH$_2$O), 1.73-1.82 (1 H, m, CH*H*CH$_2$O), 1.92-2.00 (1 H, m, CH$_3$C*H*), 3.82-3.90 (2 H, m, CHC*H*$_2$O), 4.01-4.09 (2 H, m, CH$_2$C*H*$_2$O), 7.55-7.59 (4 H, m, ArC*H*), 7.66-7.70 (2 H, m, ArC*H*) and 7.88-7.91 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 16.3 (*C*H$_3$), 29.9 (*C*H), 32.2 (*C*H$_2$), 68.4 (*C*H$_2$), 77.5 (*C*H$_2$), 128.1 (2 x Ar*C*H), 128.2 (2 x Ar*C*H), 129.7 (4 x Ar*C*H), 134.2 (2 x Ar*C*H), 136.2 (Ar*C*) and 136.3 (Ar*C*); *m/z* (CI^+ mode, isobutane) 385 (MH^+, 6%) 149 (28) and 87 (100); (Found MH^+ 385.0779; $C_{17}H_{20}O_6S_2$ requires 385.0780).

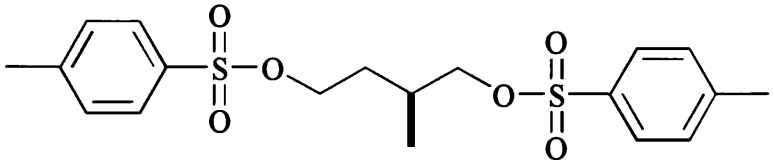
8.5.2.2 (2*R*)-2-Methyl-1,4-bis(benzenesulfonyloxy)butane 310



310

Using benzenesulfonyl chloride and 2*R*-methylbutane-1,4-diol **302** on a 2.3 mmol scale following General procedure 10 gave a residue which was chromatographed [SiO_2, EtOAc-hexane (1:1)] to give (2*R*)-2-methyl-1,4-bis(benzenesulfonyloxy)butane **310** (0.23 g, 26 %) as a colourless oil. Spectral data were identical to racemate **309**. $[\alpha]_D$ +0.7 (*c* 1.0, $CHCl_3$); *m/z* (CI^+ mode, isobutane) 385 (MH^+, 17%) 227 (28) and 87 (100); (Found MH^+ 385.0778; $C_{17}H_{20}O_6S_2$ requires 385.0780).

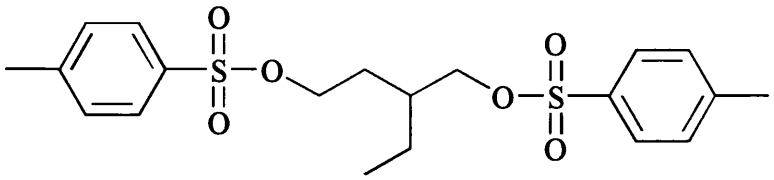
8.5.2.3 (2*S*)-2-Methyl-1,4-bis(*p*-toluenesulfonyloxy)butane 311



311

Using *p*-toluenesulfonyl chloride and (2*S*)-2-methylbutane-1,4-diol **303** on a 2.9 mmol scale following General procedure 10 gave a residue which was chromatographed [SiO_2, EtOAc-hexane (2:3)] to give (2*S*)-2-methyl-1,4-bis(*p*-toluenesulfonyloxy)butane **311** (0.61 g, 51%) as a colourless oil. $[\alpha]_D$ -0.5 (*c* 0.3, $CHCl_3$); υ_{max}(NaCl)/cm^{-1} 2968 (alkyl), 1358 and 1190 (-SO_2-O); δ_H(400 MHz; $CDCl_3$) 0.86 (3 H, d, *J* 6.8, C*H*$_3$CH), 1.43-1.52 (1 H, m, CH*H*CH$_2$O), 1.71-1.79 (1 H, m, CH*H*CH$_2$O), 1.90-1.98 (1 H, m, CH$_3$C*H*), 2.46 (6 H, s, 2 x C*H*$_3$), 3.78-3.86 (2 H, m, CHC*H*$_2$O), 4.00-4.05 (2 H, m, CH$_2$C*H*$_2$O), 7.36 (4 H, d, *J* 8.0, ArC*H*), and 7.69 (4 H, d, *J* 8.3, ArC*H*); δ_C(100 MHz; $CDCl_3$) 16.1 (*C*H$_3$), 21.8 (2 x *C*H$_3$), 29.6 (*C*H), 32.0 (*C*H$_2$), 68.0 (*C*H$_2$), 74.2 (*C*H$_2$), 128.1 (4 x Ar*C*H), 130.1 (4 x Ar*C*H), 134.0 (2 x Ar*C*H) and 145.3 (2 x Ar*C*); *m/z* (EI) 412 (M^+, 6%), 241 (24), 173 (22), 155 (74), 91 (100) and 69 (90); (Found M^+ 412.1013; $C_{19}H_{24}O_6S_2$ requires M^+ 412.1014).

8.5.2.4 (±)-2-Ethyl-1,4-bis(*p*-toluenesulfonyloxy)butane 312

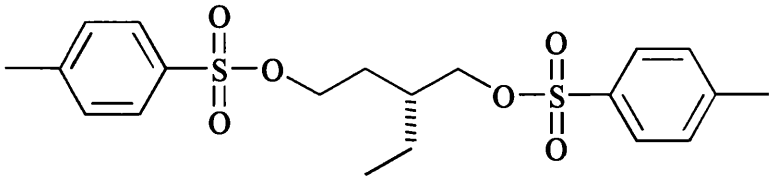


312

Using *p*-toluenesulfonyl chloride and (±)-2-ethylbutane-1,4-diol **304** on a 2.5 mmol scale following General procedure 10 gave a residue which was chromatographed [SiO_2, EtOAc-hexane (2:3)] to give (±)-2-ethyl-1,4-bis(*p*-toluenesulfonyloxy)butane **312** (0.8 g, 73%) as a colourless oil. υ_{max}(NaCl)/cm^{-1} 2966 (alkyl), 1358 and 1174 (-SO_2-O); δ_H(400 MHz; $CDCl_3$) 0.77 (3 H, t, *J* 7.2, C*H*$_3$CH$_2$), 1.25-1.33 (2 H, m, C*H*$_2$CH$_2$O), 1.62-1.69 (3 H, m, C*H*CH$_2$CH$_3$), 2.47 (6 H, s, 2 x ArCC*H*$_3$), 3.87-3.95 (2 H, m, CHC*H*$_2$O), 4.01-4.04 (2 H, m, CH$_2$C*H*$_2$O), 7.36 (4 H, d, *J* 8.0, ArC*H*) and 7.75-7.78 (4 H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 10.8 (*C*H$_3$), 21.7 (2 x *C*H$_3$), 23.0 (*C*H$_2$), 29.9 (*C*H$_2$), 35.7 (*C*H), 68.0 (*C*H$_2$), 71.2 (*C*H$_2$), 127.9 (4 x Ar*C*H), 130.0 (4 x Ar*C*H), 133.0 (2 x Ar*C*) and 142.0 (2 x Ar*C*); *m/z* (EI)

426 (M^+, 6%), 255 (19), 155 (59) and 83 (100); (Found M^+ 426.1172; $C_{20}H_{26}O_6S_2$ requires M^+ 426.1171).

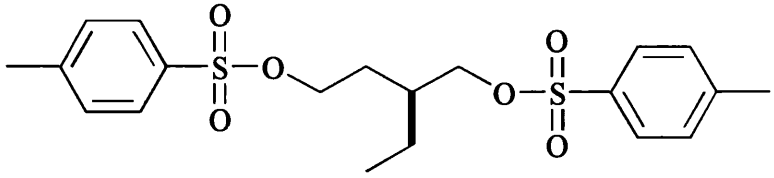
8.5.2.5 (2*R*)-2-Ethyl-1,4-bis(*p*-toluenesulfonyloxy)butane 313[110]



313

Using *p*-toluenesulfonyl chloride and (2*R*)-ethylbutane-1,4-diol **305** on a 1.4 mmol scale following General procedure 10 gave a residue which was chromatographed [SiO_2, EtOAc-hexane (2:3)] to give (2*R*)-2-ethyl-1,4-bis(*p*-toluenesulfonyloxy)butane **313** (0.35 g, 65%) as a colourless oil. Spectral data were identical to racemate **312**. $[\alpha]_D$ -5 (*c* 1.0, EtOAc); *m/z* (EI) 426 (M^+, 6%), 255 (20), 155 (57) and 83 (100); (Found M^+ 426.1172; $C_{20}H_{26}O_6S_2$ requires M^+ 426.1171).

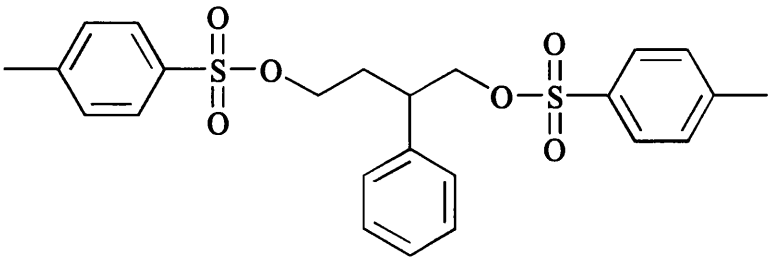
8.5.2.6 (2*S*)-2-Ethyl-1,4-bis(*p*-toluenesulfonyloxy)butane 314[110]



314

Using *p*-toluenesulfonyl chloride and (2*S*)-2-ethylbutane-1,4-diol **306** on a 1.0 mmol scale following General procedure 10 gave a residue which was chromatographed [SiO_2, EtOAc-hexane (2:3)] to give (2*S*)-2-ethyl-1,4-bis(*p*-toluenesulfonyloxy)butane **314** (0.2 g, 61%) as a colourless oil. Spectral data were identical to racemate **312**. $[\alpha]_D$ +3.1 (*c* 1.0, EtOAc); *m/z* (EI) 426 (M^+, 8%), 255 (20), 155 (55) and 83 (100); (Found M^+ 426.1172; $C_{20}H_{26}O_6S_2$ requires M^+ 426.1171).

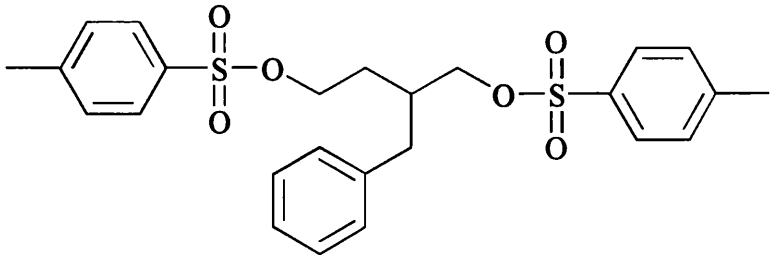
8.5.2.7 (±)-2-Phenyl-1,4-bis(*p*-toluenesulfonyloxy)butane 315[148]



315

Using *p*-toluenesulfonyl chloride and (±)-2-phenylbutane-1,4-diol **307** on a 2.2 mmol scale following General procedure 10 gave a residue which was chromatographed [SiO_2, EtOAc-hexane (2:3)] to give (±)-2-phenyl-1,4-bis(*p*-toluenesulfonyloxy)butane **315** (0.28 g, 32%) as a colourless oil. υ_{max}(NaCl)/cm^{-1} 2958 (alkyl), 1360 and 1176 (-SO_2-O); δ_H(400 MHz; $CDCl_3$) 1.82-1.90 (1 H, m, CH*H*CHCH$_2$O), 2.12-2.21 (1 H, m, CH*H*CHCH$_2$O), 2.43 (3 H, s, ArCC*H*$_3$), 2.46 (3 H, s, ArCC*H*$_3$), 2.99-3.06 (1 H, m, C*H*CH$_2$O), 3.84-3.89 (1 H, m, CHCH*H*O), 4.05-4.10 (1 H, m, CHCH*H*O), 4.13-4.21 (2 H, m, CH$_2$C*H*$_2$O), 7.07-7.09 (2 H, m, ArC*H*), 7.32-7.35 (3 H, m, ArC*H*), 7.40-7.44 (4 H, m, ArC*H*), 7.77 (2 H, d, *J* 8.3, ArC*H*) and 7.82 (2 H, d, *J* 8.3, ArC*H*); δ_C(100 MHz; $CDCl_3$) 21.8 (2 x *C*H$_3$), 31.2 (*C*H$_2$), 41.3 (*C*H), 67.8 (*C*H$_2$), 73.1 (*C*H$_2$), 127.7 (Ar*C*H), 128.0 (6 x Ar*C*H), 129.0 (2 x Ar*C*H), 130.0 (4 x Ar*C*H), 132.8 (Ar*C*), 133.0 (Ar*C*), 138.4 (Ar*C*) and 145.0 (2 x Ar*C*); *m/z* (EI) 475 (M^+, 14%), 303 (40) and 131 (100); (Found M^+ 475.1247; $C_{24}H_{26}O_6S_2$ requires M^+ 475.1249).

8.5.2.8 (±)-2-Benzyl-1,4-bis(*p*-toluenesulfonyloxy)butane 316



316

Using *p*-toluenesulfonyl chloride and (±)-2-benzylbutane-1,4-diol **308** on a 1.6 mmol scale following General procedure 10 gave a residue which was chromatographed [SiO_2, EtOAc-hexane (2:3)] to give (±)-2-benzyl-1,4-bis(*p*-toluenesulfonyloxy)butane **316** (0.29 g, 38%) as white crystals. mp 98-99 °C; υ_{max}(NaCl)/cm^{-1} 2937 (alkyl), 1353 and 1176 (-SO_2-O); δ_H(400 MHz; $CDCl_3$) 1.69-1.75 (2 H, m, C*H*$_2$CHCH$_2$O), 2.01-2.10 (1 H,

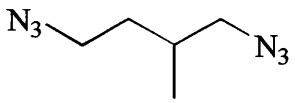
m, CH_2CHCH_2O), 2.46 (3 H, s, $ArCCH_3$), 2.47 (3 H, s, $ArCCH_3$), 2.54-2.56 (2 H, m, $ArCCH_2$), 3.78 (1 H, dd, *J* 4.4, 10.0, $CHCHHO$), 3.87 (1 H, dd, *J* 4.0, 9.6, $CHCHHO$), 4.01-4.03 (2 H, m, CH_2CH_2O), 6.95-6.97 (2 H, m, ArC*H*), 7.17-7.22 (3 H, m, ArC*H*), 7.36 (4 H, m, ArC*H*), 7.74 (2 H, d, *J* 6.4, ArC*H*) and 7.76 (2 H, d, *J* 6.4, ArC*H*); δ_C(100 MHz; $CDCl_3$) 21.8 (2 x CH_3), 30.1 (CH_2), 36.4 (*C*H), 36.8 (CH_2), 68.0 (CH_2), 70.8 (CH_2), 126.6 (Ar*C*H), 127.7 (2 x Ar*C*H), 128.1 (2 x Ar*C*H), 128.7 (2 x Ar*C*H), 129.2 (2 x Ar*C*H), 130.1 (4 x Ar*C*H), 132.8 (Ar*C*), 133.0 (Ar*C*), 138.3 (Ar*C*), 138.5 (Ar*C*) and 145.1 (2 x Ar*C*); *m/z* (EI) 511 (M^+, 84%), 145 (100), 92 (38) and 74 (35); (Found M^+ 511.1224; $C_{25}H_{28}O_6S_2$ requires M^+ 511.1225).

8.5.3 Synthesis of 2-substituted butane-1,4-diazides

General procedure 11 for the conversion of 2-substituted butane-1,4-ditosylates into 2-substituted butane-1,4-diazides.

The sulfonate diester (~0.2 g, 1 equiv.) was dissolved in dry DMF (5 cm^3) and added to this was sodium azide (6 equiv.). The reaction mixture was stirred at 60 °C overnight. After cooling the reaction mixture was diluted with water (5 cm^3) and extracted with hexane (3 x 10 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

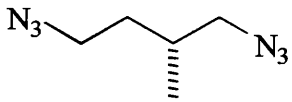
8.5.3.1 (±)-2-Methylbutane-1,4-diazide 317



317

Using (±)-2-methyl-1,4-bis(benzenesulfonyloxy)butane **309** on a 1 mmol scale following General procedure 11 gave (±)-2-methylbutane-1,4-diazide **317** (0.14 g, 95%) as a colourless oil. υ_{max}(NaCl)/cm^{-1} 2933 (alkyl), 2106 and 1265 (N_3); δ_H(400 MHz; $CDCl_3$) 1.00 (3 H, d, *J* 6.7, CH_3CH), 1.42-1.51 (1 H, m, alkyl-H), 1.69-1.78 (1 H, m, alkyl-H), 1.82-1.91 (1 H, m, alkyl-H), 3.20-3.29 (2 H, m, $CHCH_2N_3$) and 3.31-3.42 (2 H, m, $N_3CH_2CH_2$).

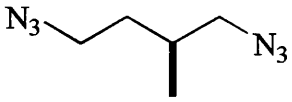
8.5.3.2 (2*R*)-2-Methylbutane-1,4-diazide 318



318

Using (2*R*)-2-methyl-1,4-bis(benzenesulfonyloxy)butane **310** on a 0.6 mmol scale following General procedure 11 gave (2*R*)-2-methylbutane-1,4-diazide **318** (51 mg, 55%) as a colourless oil. Spectral data were identical to racemate **317**.

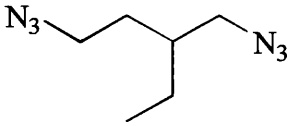
8.5.3.3 (2*S*)-2-Methylbutane-1,4-diazide 319



319

Using (2*S*)-2-methyl-1,4-bis(*p*-toluenesulfonyloxy)butane **311** on a 1.5 mmol scale following General procedure 11 gave (2*S*)-2-methylbutane-1,4-diazide **319** (0.12 g, 52%) as a colourless oil. Spectral data were identical to racemate **317**.

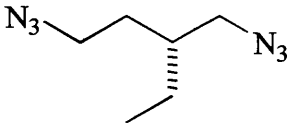
8.5.3.4 (±)-2-Ethylbutane-1,4-diazide 320



320

Using (±)-2-ethyl-1,4-bis(*p*-toluenesulfonyloxy)butane **312** on a 0.5 mmol scale following General procedure 11 gave (±)-2-ethylbutane-1,4-diazide **320** (68 mg, 81%) as a brown oil. υ_{max}(NaCl)/cm^{-1} 2966 (alkyl), 2100 and 1265 (N_3); δ_H(400 MHz; $CDCl_3$) 0.95 (3 H, t, *J* 7.5, CH_3CH_2), 1.33-1.46 (2 H, m, alkyl-H), 1.60-1.70 (3 H, m, alkyl-H) and 3.28-3.38 (4 H, m, $N_3CH_2CH_2$ and $CHCH_2N_3$).

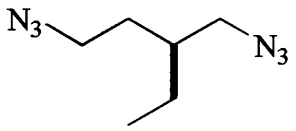
8.5.3.5 (2*R*)-2-Ethylbutane-1,4-diazide 321



321

Using (2*R*)-2-ethyl-1,4-bis(*p*-toluenesulfonyloxyl)butane **313** on a 0.5 mmol scale following General procedure 11 gave (2*R*)-2-ethylbutane-1,4-diazide **321** (55 mg, 65%) as a colourless oil. Spectral data were identical to racemate **320**.

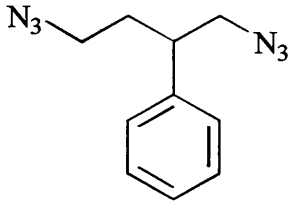
8.5.3.6 (2*S*)-2-Ethylbutane-1,4-diazide 322



322

Using (2*S*)-2-ethyl-1,4-bis(*p*-toluenesulfonyloxyl)butane **314** on a 0.56 mmol scale following General procedure 11 gave (2*S*)-2-ethylbutane-1,4-diazide **322** (50 mg, 53%) as a colourless oil. Spectral data were identical to racemate **320**.

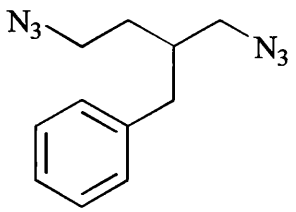
8.5.3.7 (±)-2-Phenylbutane-1,4-diazide 323



323

Using (±)-2-phenyl-1,4-bis(*p*-toluenesulfonyloxy)butane **315** on a 0.86 mmol scale following General procedure 11 gave (±)-2-phenylbutane-1,4-diazide **323** (0.14 g, 74%) as a colourless oil. υ_{max}(NaCl)/cm^{-1} 2931 (alkyl), 2094 and 1287 (N_3); δ_H(400 MHz; $CDCl_3$) 1.81-1.92 (1 H, m, $N_3CH_2CH\mathit{H}$), 2.03-2.12 (1 H, m, $N_3CH_2CH\mathit{H}$), 2.94-3.02 (1 H, m, $C\mathit{H}CH_2N_3$), 3.05-3.14 (1 H, m, $N_3CH\mathit{H}CH_2$), 3.23-3.29 (1 H, m, $N_3CH\mathit{H}CH_2$), 3.47 (1 H, dd, *J* 6.8 and 12.0, $CHCH\mathit{H}N_3$), 3.55 (1 H, dd, *J* 7.2 and 12.0, $CHCH\mathit{H}N_3$) and 7.21-7.39 (5 H, m, Ar$C\mathit{H}$).

8.5.3.8 (±)-2-Benzylbutane-1,4-diazide 324



324

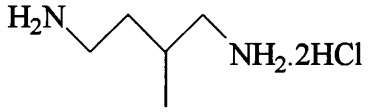
Using (±)-2-benzyl-1,4-bis(*p*-toluenesulfonyloxy)butane **316** on a 0.37 mmol scale following General procedure 11 gave (±)-2-benzylbutane-1,4-diazide **324** (45 mg, 53%) as a colourless oil. υ_{max}(NaCl)/cm^{-1} 2931 (alkyl), 2100 and 1286 (N_3); δ_H(400 MHz; $CDCl_3$) 1.61-1.76 (2 H, m, $N_3CH_2CH_2$), 1.98-2.08 (1 H, m, $CHCH_2N_3$), 2.58 (2 H, dd, *J* 3.2 and 8.0, $ArCCH_2$), 3.25 (2 H, dd, *J* 5.6 and 12.4, N_3CHHCH_2 and $CHCHHN_3$) and 7.17-7.34 (5 H, m, ArCH).

8.5.4 Conversion of diazides into diamines

General procedure 12 for the conversion of 2-substituted butane-1,4-diazides into 2-substituted butane-1,4-diamines.

Lithium aluminium hydride (3 equiv.) was added dropwise to a stirred solution of 2-substituted-butane-1,4-diazide (1 equiv.) in dry THF (10 cm^3) under N_2 at room temperature. The reaction mixture was stirred at 60 °C overnight and then treated slowly with 15% NaOH solution until a white, granular precipitate was formed. After filtration through Celite, the mixture was partitioned between 2 M hydrochloric acid (20 cm^3) and dichloromethane (20 cm^3). The aqueous layer was further extracted with dichloromethane (2 x 20 cm^3). The aqueous layer was evaporated to dryness under reduced pressure and crystallised from aqueous ethanol to give 2-substituted butane-1,4-diamine dihydrochloride.

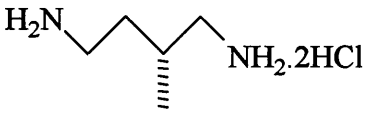
8.5.4.1 (±)-2-Methylbutane-1,4-diamine dihydrochloride 325[149]



325

Using (±)-2-methylbutane-1,4-diazide **317** on a 1 mmol scale following General procedure 12 gave (±)-2-methylbutane-1,4-diamine dihydrochloride **325** (72 mg, 40%) as a brown solid. mp 148-150 °C; υ_{max}(KBr)/cm^{-1} 3016 (-NH_3^+), 2869 (alkyl), 1608 and 1479 (-NH_3^+); δ_H(400 MHz; D_2O) 0.97 (3 H, d, *J* 6.7, CH_3CH), 1.37-1.47 (1 H, m, NCH_2CHH), 1.57-1.66 (1 H, m, NCH_2CHH), 1.73-1.83 (1 H, m, CH_3CH), 2.69 (1 H, dd, *J* 8.5 and 12.9, $CHCHHN$) and 2.83-2.98 (3 H, m, NCH_2CH_2 and $CHCHHN$); δ_C(100 MHz; D_2O) 15.6 (CH_3), 28.9 (CH), 30.9 (CH_2), 37.1 (CH_2) and 44.6 (CH_2).

8.5.4.2 (2*R*)-2-Methylbutane-1,4-diamine dihydrochloride 326[150]



326

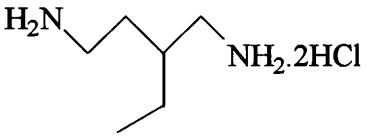
Using (2*R*)-2-methylbutane-1,4-diazide **318** on a 0.4 mmol scale following General procedure 12 gave (2*R*)-2-methylbutane-1,4-diamine dihydrochloride **326** (31 mg, 51%) as a brown hygroscopic solid.

8.5.4.3 (2*S*)-2-Methylbutane-1,4-diamine dihydrochloride 327[78]

327

Using (2*S*)-2-methylbutane-1,4-diazide **319** on a 0.8 mmol scale following General procedure 12 gave (2*S*)-2-methylbutane-1,4-diamine dihydrochloride **327** (40 mg, 29%) as a white solid. Spectral data were identical to racemate **325**. mp 143-145 °C; $[\alpha]_D$ -4 (*c* 1.0, H_2O); *m/z* (CI^+ mode, isobutane) 103 (MH^+, 100%) and 86 (58); (Found MH^+ 103.1235; $C_8H_{16}N_2$ requires 103.1235).

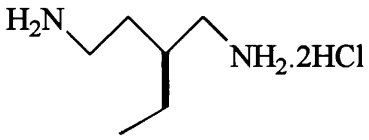
8.5.4.4 (±)-2-Ethylbutane-1,4-diamine dihydrochloride 328[149]



328

Using (±)-2-ethylbutane-1,4-diazide **320** on a 0.4 mmol scale following General procedure 12 gave (±)-2-ethylbutane-1,4-diamine dihydrochloride **328** (50 mg, 66%) as a brown hygroscopic solid. δ_H(400 MHz; D_2O) 0.82 (3 H, t, *J* 7.5, CH_3CH_2), 1.34-1.47 (2 H, m, CH_3CH_2), 1.58-1.78 (2 H, m, NCH_2CH_2) and 2.93-3.02 (4 H, m, NCH_2CH_2 and $CHCH_2N$); δ_C(100 MHz; D_2O) 9.2 (CH_3), 22.5 (CH_2), 35.1 (CH), 37.4 (CH_2) and 42.1 (CH_2).

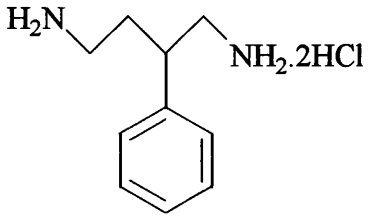
8.5.4.5 (2*S*)-2-Ethylbutane-1,4-diamine dihydrochloride 329



329

Using (2*S*)-2-ethylbutane-1,4-diazide **322** on a 0.3 mmol scale following General procedure 12 gave (2*S*)-2-ethylbutane-1,4-diamine dihydrochloride **329** (28 mg, 49%) as a brown hygroscopic solid. Spectral data were identical to racemate **325**.

8.5.4.6 (±)-2-Phenylbutane-1,4-diamine dihydrochloride 330[151]



330

Using (±)-2-phenylbutane-1,4-diazide **323** on a 0.65 mmol scale following General procedure 12 gave (±)-2-phenylbutane-1,4-diamine dihydrochloride **330** (52 mg, 35%) as a white powder. mp 253-255 °C (lit.[151] 254-257 °C); (Found: C, 50.4 H, 7.6 N, 11.3%; $C_{10}H_{18}N_2Cl_2$ requires C, 50.6 H, 7.65 N, 11.8%); υ_{max}(KBr)/cm^{-1} 3027 (-NH_3^+), 2900 (alkyl) and 1602 (-NH_3^+); δ_H(400 MHz; D_2O) 1.84-2.00 (2 H, m, NCH_2CH_2), 2.51-2.59 (1 H, m, $NCHHCH_2$), 2.74-2.81 (1 H, m, $CHCH_2N$), 2.86-2.94 (1 H, m, $CHCHHN$) 3.08-3.14 (1 H, m, $NCHHCH_2$), 3.21 (1 H, dd, *J* 5.0 and 12.0, $CHCHHN$) and 7.21-7.34 (5 H, m, ArC*H*); δ_C(100 MHz; D_2O) 30.7 (CH_2), 37.4 (CH_2), 41.3 (*C*H), 44.3 (CH_2) 128.0 (2 x Ar*C*H), 128.6 (2 x Ar*C*H), 129.6 (2 x Ar*C*H) and 137.8 (Ar*C*); *m/z* (CI$^+$ mode, isobutane) 165 (MH^+, 100%) and 148 (45); (Found MH^+ 165.1391; $C_8H_{16}N_2$ requires 165.1392).

8.5.5 Extraction of Diamine Oxidase from Pea Seedlings[152]

This was carried out by Ms Isabel Freer.

8.5.5.1 Extraction Of Crude extract from Pea seedlings

A quantity of pea seeds (500 g), variety 'Fillbasket', were soaked in tap water for 24 h. The tap water was changed four times. The pea seeds were then sown thickly in Perlite (4-6 cm deep) and covered in Perlite (2-3 cm). The seeds were then left to germinate and grow in the dark for 10-14 days until the shoots were 5-19 cm tall. During this time the Perlite was kept moist. The shoots were stripped of their roots, washed free of Perlite, drained and weighed (1-1.5 kg). The harvested shoots were always kept cool throughout the following process. The seedlings were minced using a pre-cooled Waring blender. The seedlings were strained through cotton mesh and the juice was squeezed out. The solid residue was mixed with 0.1M potassium phosphate buffer (pH 7, 1 ml/g of material) and the juice squeezed as before. A second extract using the same potassium phosphate buffer (0.5 ml/g of material) was performed. The combined extracts (2-3 ml) were cooled to < 5 °C.

8.5.5.2 Isolation of Crude Organic Extract

A solution of ethanol/chloroform (2:1 v/v, 30 ml per 100 ml of extract) was cooled to 10 °C and added to the extract over 30 min. Care was taken to ensure that the temperature of the extract did not rise above 5 °C during this addition. The mixture was allowed to stand for 1 h at 0 °C to 5 °C after which the inactive precipitate was removed by centrifugation at 3000-4000 g for 20 min. The supernatant liquid was collected and saturated with ammonium sulfate (45 g/100 ml) and the temperature was allowed to rise to 10 °C. A solid separated and floated. The lower liquid was siphoned off and discarded. The slurry was centrifuged at 3000 g for 10-15 min. The curd collected was mixed with 0.02M phosphate buffer (pH 7, 400-500 ml) and allowed to stand overnight.

8.5.5.3 Dialysis of the Organic Extract

The dialysis tubing was pre-soaked in distilled water for 2 h. The solution was stirred for 1.5 h at 15-18 °C and the precipitate was removed by centrifugation at 3000-4000 g for 20 min. The supernatant was again saturated with ammonium sulfate (200-300 g) and left for 1.5 h at 8-10 °C. It was then centrifuged at 3000-4000 g for 20 min. The curd was mixed with 0.2M phosphate buffer (pH 7, 20 ml). The solution was dialysed in a 30 cm tube (diameter 15 mm) for 2-3 h with cold running water. Dialysis was then carried out with 0.005M phosphate buffer (pH 7, 1 l) over 36 h at 0-4 °C. The buffer was changed twice during this period.

8.5.5.4 Final Purification Steps

The dialysed material was centrifuged at 3000 g for 10-20 min to remove inactive precipitate. The supernatant liquid was adjusted to pH 5 by slow addition of 0.05M acetic acid at 5 °C and then allowed to stand for 1 h at 0-4 °C. The precipitate was collected by centrifugation and triturated with water (20 ml). The pH was adjusted to pH 7 using 0.05M potassium hydroxide to dissolve the precipitate and then to pH 5 with 0.05M acetic acid. The solution was left for 1 h and centrifuged to collect the precipitate. The precipitate obtained was taken up in 0.01M phosphate buffer (pH 7, 1 ml/100 g of seedlings harvested). It was stored in the freezer (in 0.5 ml batches) at -20 °C and was stable for many months.

The yield was approximately 30 mg per kg of peas. The concentration of PSAO in the samples used was 0.12 mg ml^{-1}.

8.5.6 Determination of Protein Concentration[153]

Coomassie brilliant blue G was prepared as a 0.06% (w/v) solution in 3% perchloric acid. The solution was stirred overnight and filtered to remove any undissolved material.

A standard graph was determined using Bovine Serum Albumin (BSA, 1 mg/ml phosphate buffer pH 6.3).

The experiment was carried out three times and the average value used to plot a graph. This was used to determine the protein concentration of unknown DAO samples by replacing BSA with DAO in the cuvette.

8.5.7 Spectrophotometric Assay

The kinetics of the DAO catalysed oxidation of potential substrates was determined according to the method of Stoner.[154] This involved a peroxidase coupled assay (horseradish peroxidase, E.C 1.11.1.7, from Sigma) to continuously monitor the hydrogen peroxide released during oxidation at 25 °C, 70 mM phosphate buffer (pH 6.3), in the prescence of 3-methyl-2-benzothiazoline hydrazone (MBTH) and 3-(dimethylamino)benzoic acid (DMAB). Oxidative coupling generated stoichiometric quantities of an indiamine dye with a characteristic absorbance maximum at 595 nm. Rates were determined directly in the spectrophotometer.

Stock solutions were prepared as follows:

DMAB	18mM (29.7 mg/ 10 ml phosphate buffer pH 6.3)
MBTH	0.6mM (12.9 mg/ 100 ml distilled water)
Peroxidase	0.68 mg/ 2 ml phosphate buffer pH 6.3
Pea Seedling-Diamine oxidase	0.000615 mg ml^{-1} (0.12 mg ml^{-1} as 5-fold dilution in distilled DAO water)

A typical cuvette of pathlength 1 cm contained 3 ml of solution, made up as follows:

1.68 ml	phosphate
100 µl	MBTH
170 µl	DMAB
50 µl	peroxidase
25 µl	PSAO
300 µl	substrate at varying concentrations

The reaction was initiated by addition of standard enzyme to the thermally equilibrated reaction mixture, followed by the substrate addition. This minimises the possibly inhibitory effects of extensive preincubation of DAO with chromatographic agents.[153] Initial rates were determined over a range of substrate concentrations from linear absorbance changes

observed during the first minute in the reaction. Rate data were analysed for K_m and V_{max} by least squares fitting of Lineweaver-Burke, Eadie-Hofstee and Hanes plots. All experiments were carried out three times with all data quoted being the mean of nine determinations.

8. References

1. W. Marckwald, *Ber. Desch. Chem. Ges.,* 1904, **37**, 1368.
2. A. Zawadzka, A. Leniewski, J. K. Maurin, K. Wojtasiewicz and Z. Czarnocki, *Org. Lett.,* 2001, **3**, 997.
3. Z. Li, R. Wu, R. Michalczyk, R. B. Dunlap, J. D. Odom and L. A. Silks, *J. Am. Chem. Soc.,* 2000, **122**, 386.
4. D. Seebach, A. Sting and R. Hoffmann, *Angew. Chem., Int. Ed.,* 1996, **35**, 2708.
5. A. G. M. Barrett, D. C. Braddock, P. D. de Koning, A. J. P. White and D. J. Williams, *J. Org. Chem.,* 2000, **65**, 375.
6. M. P. Sibi, R. Zhang and S. Manyem, *J. Am. Chem. Soc.,* 2003, **125**, 9306.
7. T. Komnenos, *Liebigs Ann. Chem.,* 1883, **218**, 145.
8. L. Claisen, *J. Prakt. Chem.,* 1887, **35**, 413.
9. A. Michael, *J. Prakt. Chem.,* 1887, **3**, 349 and *Am. Chem. J.,* 1887, **9**, 112.
10. P. Perlmutter, "Conjugate Addition Reactions in Organic Synthesis", Pergamon Press, 1992, 2.
11. I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, London, 1976, 70.
12. (a) M. Kanai, Y. Nakagawa and K. Tomioka, *Tetrahedron*, 1999, **55**, 3843. (b) M. Kanai and K. Tomioka, *Tetrahedron Lett.,* 1995, **36**, 4275. (c) K. Tomioka and Y. Nakagawa, *Heterocycles,* 2000, **52**, 95.
13. M. T. Reetz, A. Gosberg, R. Goddard and S. –H. Kyung, *J. Chem. Soc., Chem. Commun.,* 1998, 2077.
14. M. T. Reetz, A. Gosberg and D. Moulin, *Tetrahedron Lett.,* 2002, **43**, 1189.
15. A. W. Hird and A. H. Hoveyda, *Angew. Chem. Int. Ed.,* 2003, **42**, 1276.
16. D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger and J. Zhang, *J. Am. Chem. Soc.,* 2002, **124**, 13097.
17. S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry,* 1991, **2**, 183.
18. S. G. Davies and O. Ichihara, *Tetrahedron Lett.,* 1998, **39**, 6045.
19. S.G. Davies, N. M. Garrido, P. A. McGee and J. P. Shilvock, *J. Chem. Soc., Perkin Trans. 1,* 1999, 3105.
20. S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry,* 1996, **7**, 1919.

21. M. Hamada, T. Takeuchi, S. Kondo, Y. Ikeda, H. Naganawa, K. Maeda, Y. Okami and H. Umezawa, *J. Antibiot.*, 1970, **23**, 170.
22. W. Oppolzer and H. J. Lőher, *Helv. Chim. Acta,* 1981, **64**, 2808.
23. W. Oppolzer and T. Stevenson, *Tetrahedron Lett.*, 1986, **27**, 1139.
24. A. Alexakis, R. Sedrani, P. Mangeney and J. F. Normant, *Tetrahedron Lett.*, 1988, **29**, 4411.
25. C. Fang, H. Suemune and K. Sakai, *Tetrahedron Lett.*, 1990, **31**, 4751.
26. C. Ullenius and B. Christeson, *Pure Appl. Chem.*, 1988, **60**, 57.
27. T. Ogawa, C. –Lin Fang, H. Suemune and K. Sakai, *J. Chem. Soc., Chem, Commun.*, 1991, 1438.
28. T. Ogawa, H. Suemune and K. Sakai, *Chem. Pharm. Bull.*, 1993, **41**, 1652.
29. F. Orsini and S. Rinaldi, *Tetrahedron: Asymmetry,* 1997, **8**, 1039.
30. F. Orsini and F. Pelizzoni, *Tetrahedron: Asymmetry,* 1996, **7**, 1033.
31. G. Helmchen and G. Wegner, *Tetrahedron Lett.*, 1985, **26**, 6051.
32. E. Urban, G. Richs and G. Knühl, *Tetrahedron*, 1995, **51**, 11149.
33. E. Urban, G. Knühl and G. Helmchen, *Tetrahedron*, 1996, **52**, 971.
34. J. Cossy, O. Mirguet, D. G. Pardo and J. Desmurs, *Tetrahedron Lett.*, 2001, **42**, 7805 and J. Cossy, O. Mirguet, D. G. Pardo and J. Desmurs, *New Journal of Chemistry,* 2003, 475.
35. H. Spreitzer, A. Pichler, W. Holzer, I. Toth and B. Zuchart, *Helv. Chim. Acta,* 1997, **80**, 139.
36. E. Piers, B. W.A. Yeung, F. F. Fleming, *Can. J. Chem.*, 1993, **71**, 280
37. W. Oppolzer, C. Chapuis and G. Bernardinelli, *Tetrahedron Lett.*, 1984, **25**, 5885.
38. W. Oppolzer, P. Dudfield, T. Stevenson and T. Godel, *Helv. Chim. Acta,* 1985, **68**, 212.
39. P. Somfai, D. Tanner and T. Olsson, *Tetrahedron,* 1985, **41**, 5973.
40. K. Totani, T. Nagatsuka, K. –I. Takao, S. Ohba and K. –I. Tadano, *Org. Lett.*, 1999, **1**, 1447.
41. G. Cardillo, L. Gentilucci, A. Tolomelli and C. Tomasini, *Tetrahedron,* 1999, **55**, 6231.
42. N. T. Patil, J. N. Tilekar and D. D. Dhavale, *J. Org. Chem.*, 2001, **66**, 1066.
43. J. Touet, S. Baudouin and E. Brown, *J. Chem. Res. (S),* 1996, 224.
44. E. Brown, C. Deroye, F. Huet, C Le Grumelec and J. Touet, *J. Chem. Res. (S),* 1997, 348.
45. J. R. Gage and D. A. Evans, *Org. Synth.*, 1989, **68**, 77.

46. D. R. Williams, W. S. Kissel and J. J. Li, *Tetrahedron Lett.*, 1998, **39**, 8593.

47. E. Nicholàs, K. C. Russell and V. J. Hruby, *J. Org. Chem.*, 1993, **58**, 766.

48. G. Li, M. A. Jarosinski and V. J. Hruby, *Tetrahedron Lett.*, 1993, **34**, 2561.

49. M. P. Sibi, J. Ji, J. B. Sausker and C. P. Jasperse, *J. Am. Chem. Soc.*, 1999, **121**, 7517.

50. J. Ezquerra, L. Prieto, C. Avendaño, J. L. Martos and E. de la Cuesta, *Tetrahedron Lett.*, 1999, **40**, 1575.

51. P. S. Van Heerden B. C. B. Bezuidenhoudt and D. Ferreira, *Tetrahedron Lett.*, 1997, **38**, 1821.

52. W. Oppolzer, C. Chapuis and G. Bernardinelli, *Helv. Chim. Acta*, 1984, **67**, 1397.

53. Reviews: a) W. Oppolzer, *Pure Appl. Chem.*, 1990, **62**, 1241. b) W. Oppolzer, *Tetrahedron*, 1987, **43**, 1969. c) B. H. Kim and D. P. Curran, *Tetrahedron*, 1993, **49**, 293.

54. W. Oppolzer, R. J. Mills, W. Pachinger and T. Stevenson, *Helv. Chim. Acta*, 1986, **69**, 1542.

55. C. Palomo, J. M. Aizpura, M. Iturburu and R. Urchegui, *J. Org. Chem.*, 1994, **59**, 240.

56. W. Oppolzer, G. Poli, A. J. Kingma, C. Starkemann and G. Bernardinelli, *Helv. Chim. Acta*, 1987, **70**, 2201.

57. W. Oppolzer, A. J. Kingma and G. Poli, *Tetrahedron*, 1989, **45**, 479.

58. M. D. Fletcher, J. R. Harding, R. A. Hughes, N. M. Kelly, H. Schmalz, A. Sutherland and C. L. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1999, 43.

59. C. –H. Lin, K. –S. Yang, J. –F. Pan and K. Chen, *Tetrahedron Lett.*, 2000, **41**, 6815.

60. A. E. Pegg, *Biochem. J.*, 1986, **234**, 249.

61. D. Walters, *Biologist*, 1987, **34**, 75.

62. A. F. Tiburico, T. Altabella, A. Borrell and C. Masgrau, *Physiol. Plant*, 1997, **100**, 664.

63. O. Heby and L. Persson, *Trends Biochem. Sci.*, 1990, **15**, 153.

64. A. Bouchereau, A. Aziz, F. Larher and J. Martin-Tanguy, *Plant Science*, 1999, **140**, 103.

65. L. Persson, I. Holm, A. Ask and O. Heby, *Cancer Res.*, 1988, **48**, 4807.

66. J. M. Hill, *Methods in Enzymology*, 1971, **17B**, 730.

67. J. M Hill and P. J. G. Mann in "*Recent Aspects of Nitrogen Metabolism in Plants*", (E.J. Hewitt and C.V Cutting, Eds.), Academic Press, London, 1989, 149; J. M. Hill, *J. Exp. Bot.*, 1973, **24**, 525.

68. H. Yamada and K. T. K. Yasunobu, *Biochem. Biophys. Res. Commun.*, 1962, **8**, 387.

69. C. L. Lobenstein, J. A. Jongejan, J. Frank and J. A. Duine, *FEBS Lett.*, 1984, **170**, 305.

70. P. G. Bruinenberg, M. Evers, H. R. Waterham, J. Kuipers, A. C. Arnberg and A. B. Geert, *Biochim. Biophys. Acta,* 1989, **1008**, 157.

71. D. Mu, S. M. Janes, A. J. Smith, D. E. Brown, D. M. Dooley and J. P. Klinman, *J. Biol. Chem.*, 1992, **267**, 7979.

72. M. C. J. Wilce, D. M. Dooley, H. C. Freeman, J. M. Guss, H. Matsunami, W. S. McIntire, C. E. Ruggiero, K. Tanizwa, and H. Yamaguchi, *Biochemistry,* 1997, **36**, 16116.

73. A. Rossi, R. Petruzelli, and A. Finazzi-Agro, *FEBS Lett.,* 1992, **301**, 253.

74. V. Vignevich, D. M. Dooley, J. M. Guss, I. Harvey, M. A. M^{c}Guirl, and H. C. Freeman, *J. Mol. Biol.,* 1993, **229**, 243.

75. V. Kumar, D. M. Dooley, H. C. Freeman, J. M. Guss, I. Harvey, M. A. M^{c}Guirl, M. C. J. Wilce and V. M. Zubak, *Structure,* 1995, **4**, 943.

76. L. Macholan, l. Rozprimova, and E. Sedlackova, *Biochem. Biophys. Acta,* 1967, **136**, 258.

77. E. Santaniello, A. Manzocchi, P. A. Biondi and T. Simonic, *Experientia,* 1982, **38**, 782.

78. E. Santaniello, A. Manzocchi, P. A. Biondi, C. Secchi and T. Simonic, *J. Chem. Soc., Chem. Commun.*, 1984, 803.

79. B. E. Rossiter and N. M. Swingle, *Chem. Rev.*, 1992, **92**, 771.

80. T. Bauer, C. Chapius, A. Kucharsha, D. Rzepechi and J. Jurcak, *Helv. Chim. Acta,* 1998, **81**, 324.

81. (a) C. Chapius, A. Kucharska, P. Rzepechi and J. Jurczak, *Helv Chim. Acta,* 1998. **81**, 2314. (b) C. Chapius, J. de Saint Laumer and M. Marty, *Helv. Chim. Acta,* 1997, **80**, 146. (c) C. Chapius, P. Rzepecki, T. Bauer and J. Jurczak, *Helv. Chim. Acta,* 1995, **78**, 145.

82. J. Raczko, M. Achmatowicz, A. Jezewski, C. Chapius, Z. Urbanczyk-Lipkowska and J. Jurczak, *Helv. Chim. Acta,* 1998, **81**, 1264.

83. D. A. Evans, L. D. Wu, J. J. M. Weimer, J. S. Johnson, D. H. B. Ripin, J. S. Tedrow, *J. Org. Chem.*, 1999, **64**, 6411.

84. G. Cardillo and C. Tomasini, *Chem. Soc. Rev.*, 1996, **25**, 117.

85. F. A. Davis, J. C. Towson, M. C. Weismiller, S. Lal and P. J.Carroll., *J. Am. Chem. Soc.*, 1988, **110**, 8477.

86. M. Vandewalle, J. Van der Eycken., *Tetrahedron*, 1986, **42**, 4035.

87. M. Capet, F. David, L. Bertin and J. C. Hardy, *Synth. Commun.*, 1995, **25**, 3323.

88. W. Oppolzer, J. Blagg, I. Rodriguez and E. Walther, *J. Am. Chem. Soc.,* 1990, **112**, 2767.

89. J. Lin, W. H. Chan, A .W. M. Lee and W. Y Wong, *Tetrahedron,* 1999, **55**, 13983.

90. S. C. Bergmeier and K. A. Ismail, *Synthesis,* 2000, **10**, 1369.

91. F. Ngan and M. Toofan, *J. Chromatographic Science,* 1991, **29**, 8.

92. K. Venkateraman and D. R. Wagle, *Tetrahedron Lett.,* 1979, **20**, 3037.

93. L. Shao, S.Miyata, H. Muramatsu, H. Kawano, Y. Ishii, M. Saburi, and Y. Uchida, *J. Chem. Soc. Perkin Trans. 1,* 1990, **1**, 1441.

94. P.R. Guzzo and M.J. Miller, *J. Chem. Soc.,* 1928, **75**, 78.

95. T. Clutterbuck, P. Raistrick and R. Reuter, *Biochem. J.,* 1937, **31**, 987.

96. R. E. Moore, J. A. Pettus, Jr., and J. Mistysyn, *J. Org. Chem.,* 1974, **39**, 2201.

97. A. Veit, R. Lenz, M. E. Seiler, M. Neuberger, M. Zehnder and B. Giese, *Helv. Chim. Acta,* 1993, **76**, 441.

98. S. G. Cohen and A. Milovanovic, *J. Am. Chem. Soc.,* 1968, **90**, 3495.

99. P. Timmermans and J. van der Haegen, *Bull. Soc. Chim. Belg.,* 1933, **42**, 450.

100. C. Chapius, J de Saint Laumer and M. Marty, *Helv. Chim. Acta,* 1997, **80**, 146.

101. M. P. Sibi and P. K. Deshpande, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1461.

102. M. P. Sibi, P. Liu, J. Ji, S. Hajra and J. Chen, *J. Org. Chem.,* 2002, **67**, 1738.

103. T. Miyazawa, T. Otomatsu, Y. Fukui, T. Yamada and S. Kuwata, *J. Chem. Soc., Chem. Commun.*, 1988, 419.

104. A. Veit, R. Lenz, M. E. Seiler, M. Neuburger, M. Zehnder and B. Giese, *Helv. Chim. Acta,* 1993, **76**, 441.

105. T. W. Stone and L. G. Darlington, *Nature Rev.,* 2002, **1**, 609.

106. A. Giordani, P. Pevarello, M. Cini, R. Bormetti, F. Greco, S. Toma, C. Speciale and M. Varasi, *Biorg. Med. Chem. Lett.,* 1998, **8**, 2907.

107. B. L. Feringa, B. de Lange and J. C. de Jong, *J. Org. Chem.,* 1989, **54**, 2471.

108. J. F. G. A. Jansen and B. L. Feringa, *Tetrahedron Lett.,* 1989, **30**, 5481.

109. N. Lee, Y. W. Kim, K. Chang, K. H. Kim, S. Jew and D Kim, *Tetrahedron Lett.*, 1996, **37**, 2429.

110. J. Lin, W. H. Chan, A .W. M. Lee, W. Y Wong and P. Q. Huang, *Tetrahedron Lett.,* 2000, **41**, 2949.

111. S. Kamlage, M. Seflow, N. Zimmermann and M. G. Peter, *Synlett.,* 2002, 77.

112. H. Krause and C. Sailer, *J. Organometallic Chem.,* 1992, **423**, 271.

113. J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.,* 1969, **34**, 2543.

114. D. A. Evans, M. C. Willis and J. N. Johnston, *Org. Lett.*, 1999, **1**, 865.

115. M. P. Sibi and H. Hasegawa, *Org. Lett.*, 2002, **4**, 3347.

116. J. G. Stack, D. P. Curran, S. V. Geib, J. Rebek, Jr., and P. Ballester, *J. Am. Chem. Soc.*, 1992, **114**, 7007.

117. D. O. A. Garrido, G. Buldain and B. Frydman, *J. Org. Chem.*, 1984, **49**, 2619.

118. D. O. A. Garrido, G. Buldain, M. I. Ojea and B. Frydman, *J. Org. Chem.*, 1988, **53**, 403.

119. C. Lebarbier, F. Carreaux and B. Carboni, *Tetrahedron Lett.*, 1999, **40**, 6233.

120. E. Fabiano, B. T. Golding, and M. M. Sadeghi, *Synthesis Comm.*, 1987, 191.

121. O. Mitsunobu, *Synthesis*, 1981, 1.

122. Y. G. Gololobov, I. N. Zhmurova, and L. F. Kasukhin, *Tetrahedron*, 1981, **37**, 437.

123. A. R. Tunoori, D. Dutta and G. I. Georg, *Tetrahedron Lett.*, 1998, **39**, 8751.

124. J. Skarżewski, and E. Daniluk, *Monatshefte fur Chemie*, 1983, **114**, 1071.

125. RA Alberty and RJ Silbey in *Physical Chemistry*, 2nd Edition, John Wiley, 1996, pp 730-733.

126. PW Atkins in *The Elements of Physical Chemistry*, 2nd Edition, OUP, 1996, pp 266-270.

127. P. D. Bartlett, L. H. Knox, *Organic Syntheses*, Wiley: New York 1973; Collect. **Vol. V**, 194.

128. P. R. Guzzo and M. J. Miller, *J. Org. Chem.*, 1994, **59**, 4862.

129. D. H. Kim and S. Chung, *Tetrahedron: Asymmetry*, 1999, **10**, 3769.

130. R. Ballini, G. Bosica, D. Fiorini and P. Righi, *Synthesis*, 2002, **5**, 681.

131. T. Fredga and E. Sahlberg, *Ark. Kemi*, 1944, **16**, 2.

132. J. Rokach and D. Elad, *J. Org. Chem.*, 1966, **31**, 4210.

133. MNNG Diazomethane Generation Apparatus. *Technical Information Bulletin No. AL-132*, Aldrich Chemical, Milwaukee, Wisconsin.

134. T. Matsuda, *Bull. Chem. Soc. Jpn.*, 1973, 524.

135. J. K. Stille and R. Divakaruni, *J. Org. Chem.*, 1979, **44**, 3474.

136. H. Oikawa, T Kagawa, T. Kobayashi and A. Ichihara, *Tetahedron Lett.*, 1996, **34**, 6169.

137. R. C. Poller and D. Silver, *J. Organometallic Chem.*, 1978, **157**, 247-253.

138. G. Natta, P. Pino and R. Ercoli, *J. Am. Chem. Soc.*, 1952, **74**, 4496.

139. M. Murata, S. Matsuoka, N. Matsumori, G. K. Paul and K. Tachibana, *J. Am. Chem. Soc.*, 1999, **121**, 870.

140. B. Neises and W. Steglich, *Org. Synth.*, 1985, **63**, 183.

141. C. S. Giam, T. E. Goodwin and T. K. Yano, *J. Chem. Soc. Perkin Trans. 2*, 1978, 831.

142. P. Grisenti, P. Ferraboschi, S. Casati, and E. Santaniello, *Tetrahedron: Asymmetry*, 1993, **4**, 997.

143. J. F. G. A. Jansen, and B. L. Feringa, *Synth. Commun.*, 1992, **22**, 1367.

144. B. Wojcik, and H. Adkins, *J. Am. Chem. Soc.*, 1933, **55**, 4939.

145. J. Lin, W. H. Chan, A. W. M. Lee and W. Y. Wong, *Tetrahedron*, 1999, **55**, 13983.

146. A. Rumbero, I. Borreguero, J. V. Sinisterra, and A. R. Alcántara, *Tetrahedron*, 1999, **55**, 14947.

147. U. M. Dzkemilev, A. G. Ibragimov, A. P. Zolotarev, R. R. Muslukhov, G. A. Tolstokov, *Bull. Acad. Sci. USSR*, 1990, **39**, 2570.

148. M. E. H. Howden, A. Maercher, J. Burden and J. D. Roberts, *J. Am. Chem. Soc.*, 1966, **88**, 1732

149. D. O. A. Garrido, G. Buldain, M. I. Ojea and B. Frydman, *J. Org. Chem.*, 1988, **53**, 403.

150. M. Kojima, K. Morita and J. Fujita, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 2947.

151. J. Harley-Mason and A. H. Jackson, *J. Chem. Soc.*, 1954, 1165.

152. J.M. Hill, *Methods in Enzymol.*, 1971, **17B**, 730-749.

153. J.J. Sedmak & S.E. Grossberg, *Anal. Biochem.*, 1977, **79**, 544-550.

154. P. Stoner, *Agents and Actions*, 1985, **15**, 5-13.