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Enantioselective Desymmetrisation of Imides Using Oxazaborolidine Catalysts Derived from *cis*-1-amino-indan-2-ol

A Dissertation Submitted for the Degree of Doctor of Philosophy

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Dedication

This research work is dedicated to my wife Rukayya and my kids for their patience and perseverance and to my late father Usman Kutama who died just before this work was concluded. May Allah have mercy on his soul.

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Declaration

This dissertation records the work carried out in the Department of Chemistry, University of Sheffield, between November 2010 and September 2014 and is original except where acknowledged by reference.

No part of this work is being, nor has been, submitted for a degree, diploma or any other qualification at any other university.

Publication

"Enantioselective Catalytic Desymmetrization of Maleimides by Temporary Removal of an Internal Mirror Plane and Stereoablative Over-reduction: Synthesis of (*R*)-Pyrrolam A", Barry J. Marsh, Harry Adams, Mike D. Barker, Ibrahim U Kutama, Simon Jones *Org. Lett.;* 2014, **16**, 3780–3783.

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Finally, I thank my home Government (the federal republic of Nigeria) and my employers; Kano State University of Science and Technology for sponsoring my PhD.

Abbreviations

ACE	angiotensin-converting enzyme
AD-mix	asymmetric dihydroxylation mixture
app	apparent
BDMPB	*bis*(2,6-dimethoxyphenoxy)borane
BINAL-H	2,2'-dihydroxy-1,1'-binaphthyl lithium aluminium hydride
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binapthyl
Bn	benzyl
Boc	*tert*-butoxy carbonyl
bs	broad singlet
CAN	cerium(IV) ammonium nitrate
cat.	catalyst
CBS	Corey Bakshi Shibata
Cbz	carboxybenzyl
COSY	correlation spectroscopy
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
ddt	doublet of triplets
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIOP	2,3-O-isopropylidene-2,3-dihydroxy-1,4-*bis*(diphenylphosphino)butane
DMAP	4-dimethylaminopyridine
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dp	doublet of pentets
dq	doublet of quartets
dt	doublet of triplets
dtd	doublet of triplet of doublets
ee	enantiomeric excess
er	enantiomeric ratio
Et	ethyl
EtOAc	ethyl acetate
FT-IR	fourier transform infra red spectroscopy
h	hour
HMDS	hexamethyldisilazane
HPLC	high pressure liquid chromatography
Hz	hertz
i-Bu	iso-butyl
i-pr	iso-propyl
IPA	iso-propyl alcohol (propan-2-ol)
Ipc	isopinocampheyl
LDA	lithium di-isopropylamide
LG	leaving group
LUMO	lowest unoccupied molecular orbital

m	multiplet
m/*z*	mass charge ratio
Me	methyl
MEM	2-methoxy ethoxymethyl
MHz	mega hertz
Ms	methane sulfonyl
n-Bu	butyl
NMR	nuclear magnetic resonance
PCC	pyridinium chloro chromate
Ph	phenyl
PLE	porcine liver esterase
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
p-TsOH	*p*-toluene sulfonic acid
q	quartet
qd	quartet of doublets
Red-Al	sodium *bis*(2-methoxyethoxy)aluminumhydride
rt	room temperature
s	singlet
s	selectivity factor
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBS	*tert*-butyl silyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF MS ES	time-of-flight mass spectrometry electron spray
Tol	toluene
t_R	retention time
Ts	*p*-toluene sulfonyl
UV	ultraviolet

Abstract

By repeating and optimizing procedure from earlier work in this group, three *N*-substituted *meso*-anthracene-maleimides have been prepared in excellent yields 88 – 94%. These compounds were successfully desymmetrised to the corresponding 3-methoxy γ-lactams, using *B*-OMe oxazaborolidine catalyst derived from *cis*-1-amino-indan-2-ol. Under the optimized conditions, improved yields and excellent enantioselectivities of 95 – >99% of the methoxy-lactams were obtained. Desymmetrisation of the *N*-PMP substrate gave one enantiomer of the product but proceeded by rapid conversion of the hydroxy-lactam intermediate to the over-reduced pyrrolidine compound. Investigation in to the correlation between this high selectivity and the formation of the over reduced product revealed that an *in-situ* stereoablative process by the (1*R*, 2*S*) version of the *B*-OMe catalyst serves to upgrade the enantioselectivity.

This desymmetrisation methodology has been employed for the total synthesis of natural product, pyrrolam A which was obtained in six steps from the desymmetrised material in 48% overall yield and 94% ee.

By adapting literature methodology, *N*-PMP glutarimide and a number of *N*-benzyl glutarimides have been successfully synthesised via the corresponding glutaric anhydrides in moderate yields (52 – 87%). Desymmetrisation of *N*-PMP-3-phenyl glutarimide to the corresponding δ-lactam using *B*-OMe and *B*-Me oxazaborolidine catalysts derived from *cis*-1-amino-indan-2-ol gave excellent selectivity but low yields of the products with both catalysts due to the formation of over reduced piperidine product. Further investigation revealed an *in-situ* stereoablative process causes an upgrade of ee in both (1*R*, 2*S*) and (1*S*, 2*R*) versions of *B*-Me oxazaborolidine catalyst, with matched and mismatched enantioselectivity with the two enantiomers of the catalyst. The *N*-Bn substrates were successfully desymmetrised, using *B*-Me oxazaborolidine catalyst, to the corresponding δ-lactams in moderate yields (20 – 61%) and high enantioselectivities (54 – 92%). Desymmetrisation of a representative *N*-Bn substrate with the prolinol oxazaborolidine catalyst under the same conditions gave poor yield and enantioselectivity of the product (13% yield, 13% ee).

Functionalisation of a representative *N*-Bn desymmetrised product gave various (3*S*, 4*R*)-disubstituted 2-piperidinones in good yields and excellent diastereoselectivity. Subsequent reduction of the 2-piperidinones gave (3*S*, 4*R*)-disubstituted piperidines which are important structural motifs in many biologically active natural products and pharmaceuticals.

Chapter 1

Introduction

1.1 Chirality

The importance of chirality is well recognised. Many natural products are chiral and their physiological or pharmacological properties depend upon their recognition by chiral receptors, which may interact only with molecules of the proper absolute configuration. In pharmaceuticals, as well as related industries, asymmetry plays an important role, since both enantiomers of a specific drug do not necessarily have the same activity.[1] Duloxetine (Figure 1), for example, is an antidepressant drug targeting the presynaptic cell.[2] It is a dual inhibitor preventing the reuptake of serotonin as well as norepinephrine and is sold in its (*S*)-form as a hydrochloride salt under the name Cymbalta.[3] For duloxetine, the (*S*)-enantiomer has been found to be twice as potent as the (*R*)-enantiomer, whereas for norduloxetine (Figure 1), the (*R*)-enantiomer was found more potent than the (*S*)-enantiomer as a reuptake inhibitor of the human serotonin transporter.[4] Due to this difference in biological activity of the two enantiomers, there was a requirement to have both enantiomers synthesised separately and therefore several different methods have been reported for the enantioselective synthesis of duloxetine.[5, 6, 7, 8, 9] The evaluation of a chiral drug in enantiopure form is now a standard requirement for every new pharmaceutical agent and the development of new synthetic methods to obtain enantiopure compounds has become a key goal for pharmaceutical companies.[1] The search for new and efficient methods for the synthesis of optically pure compounds has thus been an active area of research in organic synthesis.

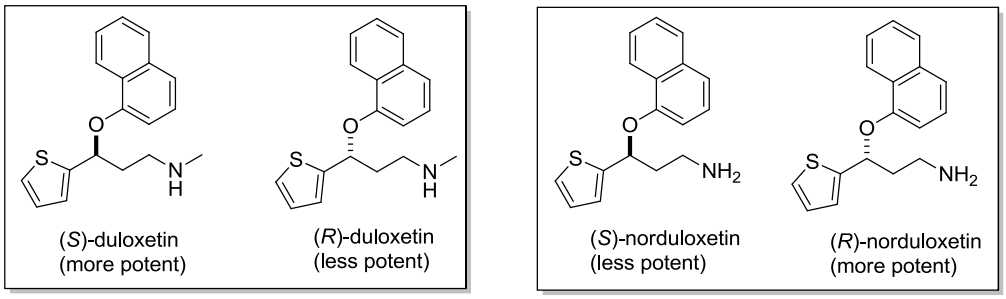


Figure 1. Duloxetin and norduloxetin drugs

1.2 Asymmetric synthesis

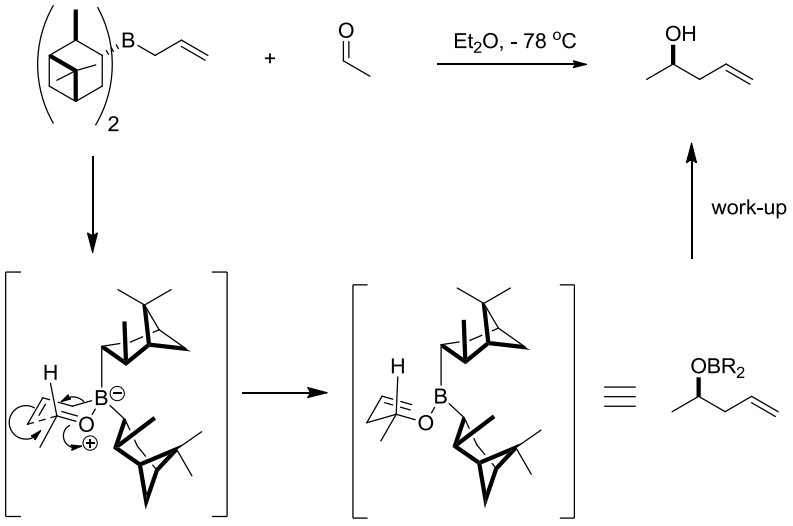
Since enantiomers have the same physical and chemical properties (except in a chiral environment), common laboratory reaction conditions applied in the synthesis of new chiral

compounds usually end up with racemic mixtures as the product. The interaction of an achiral reagent with a prochiral substrate leads to enantiomeric transition states, which in turn leads to a racemic product. However, when a chiral reagent or environment is employed, the two enantiomers may interact differently with the chiral environment, thereby leading to diastereomeric transition states with the potential to have unequal energies. This leads to the formation of a product consisting of an excess of one enantiomer over the other. Such a 'chiral environment' may be an enantiomerically pure molecule or part of a molecule which may be a reagent or a catalyst, or a chiral group covalently attached to the starting material.[10] Chemists have been able to achieve this by a variety of techniques.

1.2.1 Chiral reagent

One way to prepare an enantiomerically enriched chiral molecule is to use a chiral reagent to install the new stereogenic centre. This method needs a stoichiometric amount of the reagent which once consumed may be difficult to recycle. Thus, this method is sometimes expensive.

The enantioselective allylation of aldehydes by the use of allyl diisopinocampheylborane as chiral reagent is one such example and has been intensely studied by Brown *et al*.[11] They postulated that the reaction proceeds via a chair-like six-membered transition state, with the allyl group of the chiral boron reagent oriented away from the large group of the aldehyde. This makes the large substituent in the aldehyde to adopt a *pseudo*-equatorial conformation in the six-membered transition state and the aldehyde facial selectivity is derived from minimisation of steric interactions between the axial Ipc ligand and the allyl group (Scheme 1).[11, 12]



Scheme 1. Brown's postulation of enantioselective allylation of aldehydes

The reaction was found to be general with a range of aldehydes examined, giving the same stereochemical outcome in all cases (Table 1).[13, 12]

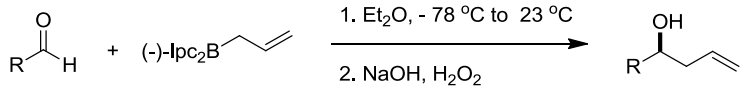


Table 1. Brown's allylation of prochiral aldehydes

Entry	R	Yield (%)	ee (%)	Configuration
1	CH_3	74	93	*R*
2	*n*-C_3H_7	71	86	*R*
3	*n*-C_4H_9	72	87	*R*
4	*i*-C_3H_7	86	90	*S*
5	*t*-C_4H_9	88	83	*S*
6	C_6H_5	81	96	*S*

1.2.2 Chiral auxiliary

Another method used to induce chirality in a molecule is by the use of a chiral auxiliary. This method has three key processes. Firstly, an enantiomerically pure compound (the chiral auxiliary) is attached to the starting material. A chemical reaction is then performed, which due to the presence of the auxiliary favours the formation of one diastereomer. Finally, the auxiliary is removed to give an enantioenriched product (Figure 2). The advantage of this method is that the chiral auxiliary can in most cases be recycled after cleavage, and a single auxiliary can be compatible with different reactions. However, since a stoichiometric amount of the auxiliary is needed, the method can be expensive if the auxiliary cannot be recycled or is difficult to prepare.

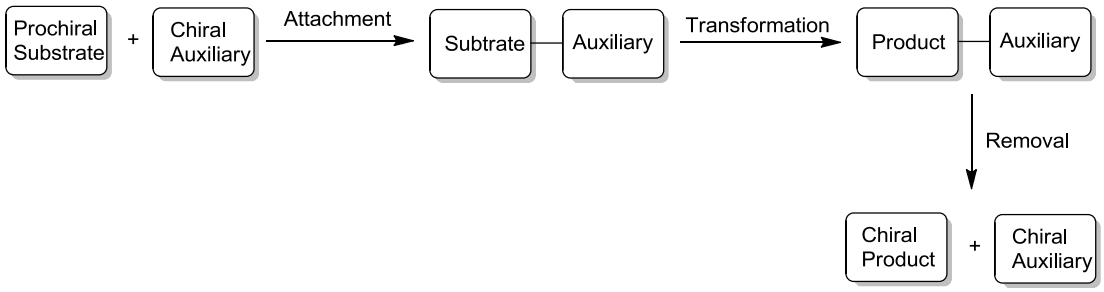


Figure 2. Chiral auxiliary strategy

Perhaps the commonest chiral auxiliaries in asymmetric synthesis are the chiral 2-oxazolidinones **1** and **2** developed by Evans and co-workers (Figure 3).[14] Introduction of the

auxiliary by deprotonation of the oxazolidinone with *n*-BuLi and coupling with a suitable electrophile gives the enantiomerically pure *N*-acyl derivatives such as **3** and **6** (Scheme 2).

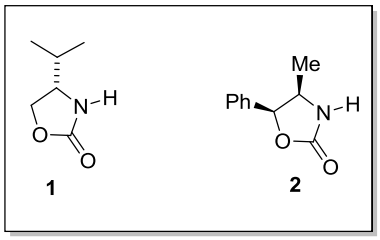
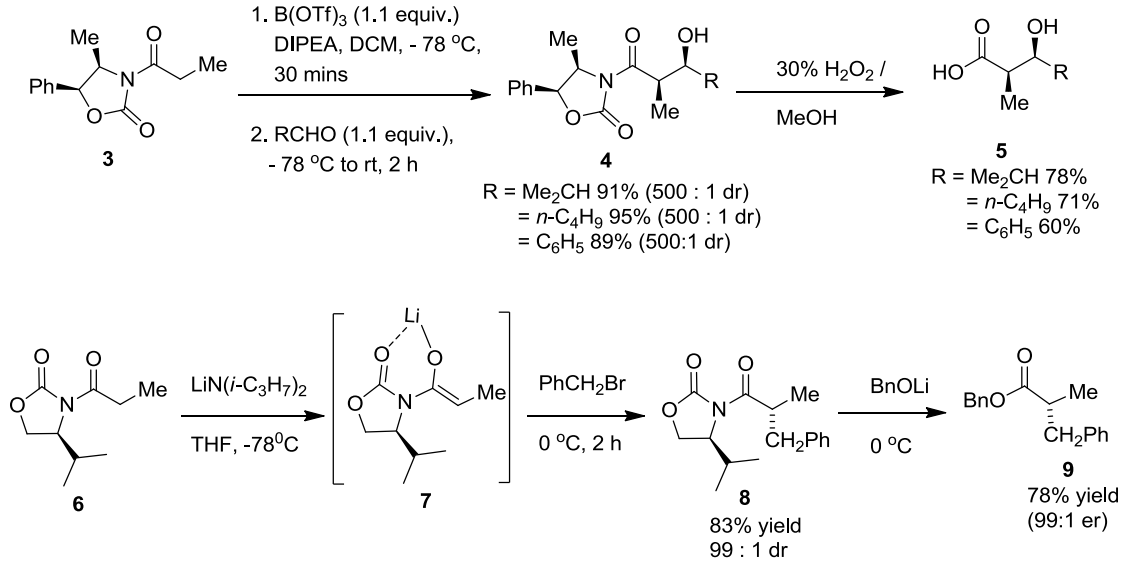


Figure 3. Evans chiral auxiliaries

Evans and co-workers have demonstrated the utility of these auxiliaries to prepare chiral compounds in excellent selectivity. Enantioselective aldol condensation reaction of the *n*-propanoyl derivative **3** with various aldehydes gave the corresponding *syn* methyl alcohols **4** in high yields and excellent diastereoselectivities. The chiral auxiliaries were then removed without racemisation to give the corresponding chiral *syn*-α-methyl-β-hydroxy carboxylic acids **5** in good yields.[15] In a different work, Evans *et al*. employed the chiral auxiliary for the asymmetric alkylation of esters.[14] Reaction of the chiral *N*-propanoyl derivative **6** with 1.1 equivalent of the lithium base, LiN(*i*-Pr)$_2$, at – 78 ^{o}C generated an *in situ* chelated (*Z*)-lithium enolate intermediate **7**, which upon treatment with benzylbromide at 0 ^{o}C gave the alkylated amide **8** in good yield and excellent diastereoselectivity. The chelated intermediate gave the sense of asymmetric induction where the diastereoface selection was dictated by the isopropyl substituent on the C-4 of the oxazolidone ring. Again, the chiral auxiliary was safely removed without racemisation by treating the amide with lithium benzyloxide to obtain the chiral α-benzyl ester **9** in excellent enantioselectivity (Scheme 2).[14]



Scheme 2. Evans' chiral auxiliary strategy for asymmetric reactions

1.2.3 Chiral catalyst

The most elegant and economically attractive way to introduce chirality into a molecule is by using a small amount of a chiral controller to induce the asymmetric transformation. In this type of enantioselective transformation, a relatively small amount of enantiopure molecule is introduced into a reaction where it interacts with the prochiral substrate, thereby activating and directing a stereoselective transformation. Once the reaction is complete, the catalyst dissociates from the substrate allowing initiation of another cycle. This method is less expensive than both the chiral reagent and chiral auxiliary methods since a small amount of catalyst is needed. Hence, it is becoming more popular than any other method in the field of asymmetric synthesis.

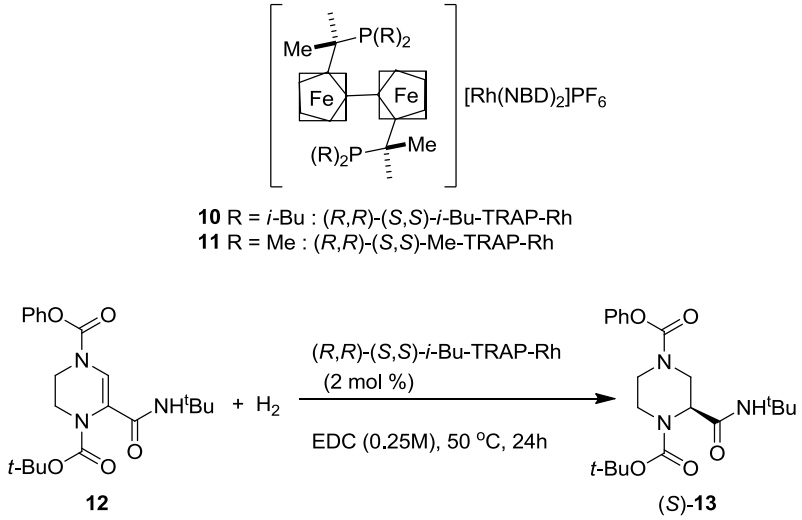
Organic molecules can catalyse reactions by four different mechanisms:[16]

i. Activation of the reaction based on the nucleophilic / electrophilic properties of the catalyst. The chiral catalyst is not consumed in the reaction and does not require parallel regeneration.
ii. Organic molecules that form reactive intermediates. The chiral catalyst is consumed in the reaction and requires regeneration in a parallel catalytic cycle.
iii. Phase-transfer reactions. The chiral catalyst forms a host-guest complex with the substrate and shuttles between the standard organic solvent and a second phase (i.e. the solid or aqueous phase in which the reaction takes place).
iv. Molecular-cavity-accelerated asymmetric transformations, in which the catalyst may select between the competing substrates, depending on size and structure criteria.

The popularity of the use of a chiral catalyst has led to the emergence of a great variety of chiral catalysts that enable the preparation of the required products in the highest possible enantiomeric excess (ee). Some of the most important reactions include asymmetric homogeneous and heterogeneous metal catalytic reactions, asymmetric organocatalytic and enzyme-catalysed procedures.[17]

Asymmetric metal catalysis is an attractive field of organic synthesis. Products with excellent enantioselectivities have been obtained using catalysts with well-defined chiral ligands. Chiral diphosphines and chelating compounds with nitrogen as donor atoms have been given significant attention.[18] With the advent of a very important ligand 2,3-*O*-isopropylidene-2,3-

dihydroxy-1,4-*bis*(diphenylphosphino)butane, DIOP introduced by Kagan and Dang,[19] rhodium complexes became popular in enantioselective catalytic hydrogenation reactions. Studies on the stereochemistry of homogeneous asymmetric reactions have taken their models from the hydrogenation and transfer hydrogenation of prochiral compounds with C=C bonds and prochiral ketones in the presence of Rh and Ru complexes.[17] One of these studies reveals that (*R*,*R*)-(*S*,*S*)-*i*-Bu-TRAP-Rh catalyst **10** provides 97% ee for hydrogenation of a tetrahydropyrazine carboxamide derivative **12** to (*S*)-**13** under mild reaction conditions with a 2 % catalyst loading (Scheme 3, Table 2, entry 1).[18] The same work revealed that phosphorus substituents of TRAP ligand remarkably affected not only the enantioselectivity but also catalytic activity. The rhodium complex coordinated with Ph- and *i*-PrTRAP converted **12** to **13** in only 7 and 5 % yields, respectively, with no ee in both cases (Table 2, entries 3 & 4). It was thought that the bulky phenyl and isopropyl groups on the phosphorus atoms on the chiral ligand might block coordination of the ligand to the rhodium metal centre. Interestingly, a related (*R*,*R*)-(*S*,*S*)-Me-TRAP-Rh catalyst provides the hydrogenation product **13** with an opposite configuration (Table 2, entry 2).[20]



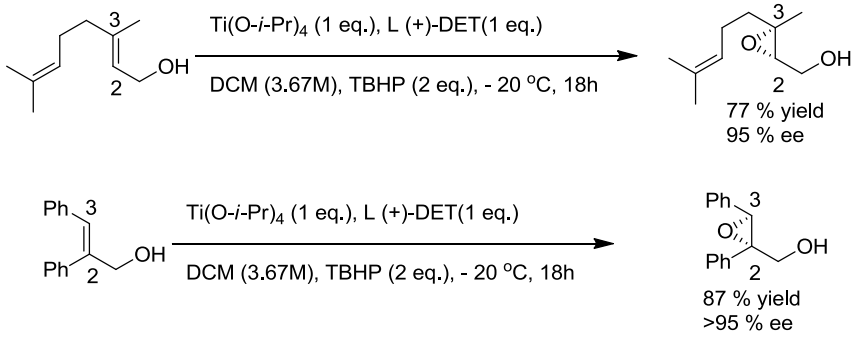
Scheme 3. Asymmetric hydrogenation of tetrahydropyrazine carboxamide derivative

Table 2. Asymmetric hydrogenation of tetrahydropyrazine carboxamide

Entry	Ligand	Conversion (%)	ee of 13 (%)	Configuration of 13
1.	*i*-Bu-TRAP	100	97	*S*
2.	Me-TRAP	34	61	*R*
3.	Ph-TRAP	7	-	-
4.	*i*-PrTRAP	5	-	-

The catalytic asymmetric epoxidation of allylic alcohols discovered by Sharpless and Katsuki in 1980 is another breakthrough in modern asymmetric synthesis.[21] They reported that a

combination of commercially available and inexpensive (+) or (–)-diethyl tartrate, titanium tetraisopropoxide and *tert*-butyl hydroperoxide was found to epoxidise a wide variety of allylic alcohols in high yield and excellent enantiomeric excess (Scheme 4).[21] This methodology has two important features. Firstly, it gives uniformly high asymmetric inductions throughout a range of substitution patterns in the allylic substrates. Secondly, for a given tartrate enantiomer, the epoxide oxygen is delivered from the same enantiotopic face of the olefin regardless of the substitution pattern. Thus, the stereochemistry of the product is completely predictable depending on which enantiomer of the tartrate is used. When the olefinic unit is in the plane of the drawing with the hydroxymethyl substituent at the lower right (Figure 4), the use of (natural) (+)-diethyl tartrate leads to addition of the epoxide oxygen from the bottom. However, when the unnatural isomer (–)-diethyl tartrate is used, the epoxide oxygen is added from the top.[21]



Scheme 4. Sharpless epoxidation of allylic alcohols

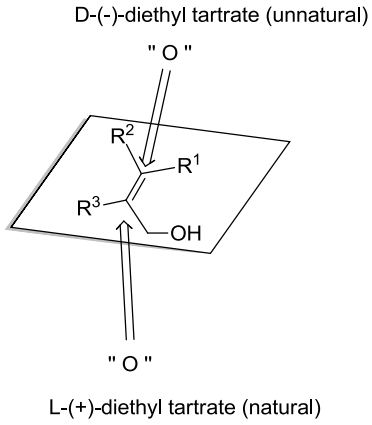
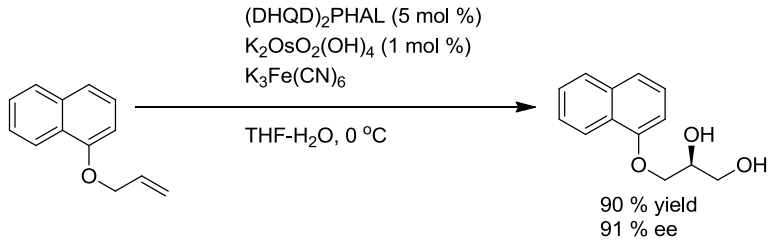


Figure 4. Mnemonic for the Sharpless asymmetric dihydroxylation

In other work, Sharpless and co-workers demonstrated the use of chiral diamine ligands **14** and **15** derived from *Cinchona* alkaloids (Figure 5) as chiral catalysts in the osmium-catalysed asymmetric dihydroxylation of alkenes giving excellent yield and enantiomeric excess (Scheme 5).[22, 23] When alkenes with other functional groups were used, only the

alkene unit was hydroxylated while the other functional groups remained unaffected. They also discovered that the more electron-rich the alkene is, the faster it will react. However, to achieve the highest level of enantioselectivity there must be some difference in size between the substituents attached to the alkene otherwise selectivities are affected.[24]



Scheme 5. Sharpless asymmetric dihydroxylation

This great work was fully developed by Sharpless in collaboration with many chemists into what is now popularly known as the Sharpless catalytic asymmetric dihydroxylation of olefins and is one of the most selective and reliable of known organic transformations to date. They developed a general procedure for a stereochemical addition of K_3FeCN_6 and OsO_4 to olefins in ^tBuOH-H_2O to yield chiral diols and is applicable to a wide range of olefinic substrates.[22–25] Because of the expense and toxicity of osmium, the reagents are available as stable, commercially available solids as pre-formulated mixtures containing $K_2OsO_2(OH)_4$ as the source of OsO_4 and K_3FeCN_6 which is the re-oxidant in the catalytic cycle. The solids are purchased in two variations as 'AD-mix α' or 'AD-mix β' containing the necessary bidentate chiral ligand (Figure 5), stoichiometric oxidant (K_3FeCN_6), and the osmium tetroxide in the form of dipotassium osmate dihydrate [($K_2OsO_2(OH)_4$)] each giving the absolute stereochemistry of the desired diol to a remarkable accuracy.[23]

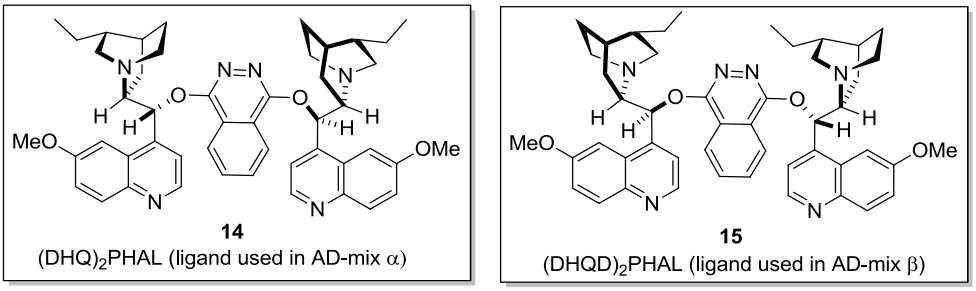


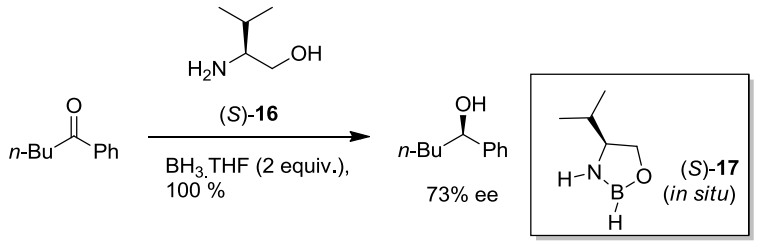
Figure 5. Ligands used in AD-mix α and AD-mix β

1.3 Oxazaborolidines

1.3.1 History

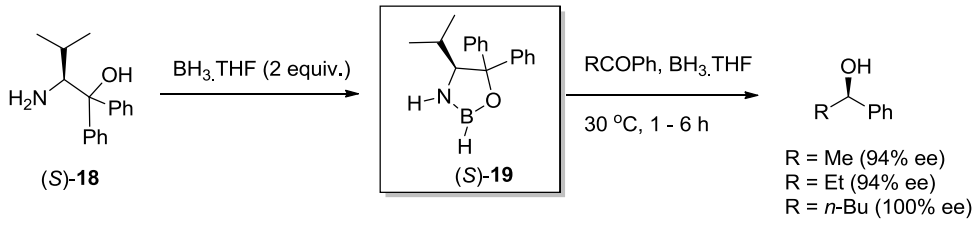
The first effective asymmetric borane reduction of aromatic ketones utilising stoichiometric amounts of optically active 1,3,2-oxazaborolidine **17** prepared *in situ* from the β-amino alcohol **16** and BH_3.THF was reported in 1981 by Itsuno *et al*. (Scheme 6).[26]

In that work and the subsequent ones, a number of prochiral ketones were reduced to the corresponding secondary alcohols with different levels of enantioselectivity using chiral amino alcohols and BH_3.THF in 1:2 ratio. The best results were obtained with (*S*)-valine derivatives. Stereoselectivities of up to 73% ee were reached in the presence of (*S*)-valinol **16** and aromatic ketones such as *n*-BuCOPh (Scheme 6). However reduction of aliphatic ketones proceeded with low ee's. Reduction of *n*-HexCOMe for example gave only 10% ee using the same conditions.[27]



Scheme 6. Itsuno's enantioselective reduction of prochiral ketone

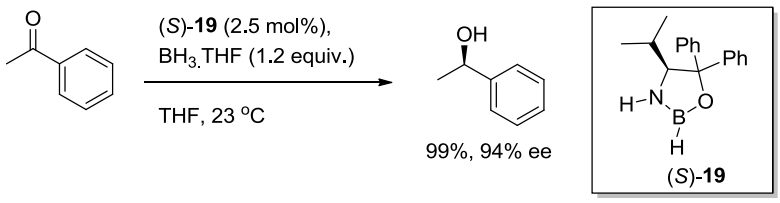
In 1983 Itsuno *et al*. reported a bulkier version of (*S*)-valinol (*S*)-**18**. The asymmetric borane reduction of prochiral aromatic ketones with oxazaborolidine (*S*)-**19**, prepared from (*S*)-**18** and borane *in situ* gave the corresponding aromatic secondary alcohols in 94 – 100% ee and 100% chemical yield.[28] In all cases the (*R*)-enantiomer of the secondary alcohol was formed preferentially (Scheme 7). Although Itsuno and co-workers studied intensively the steric influence of various catalyst substituents and reaction conditions on enantioselectivities, no mechanistic detail was presented.



Scheme 7. Itsuno's enantioselective reduction of prochiral ketones

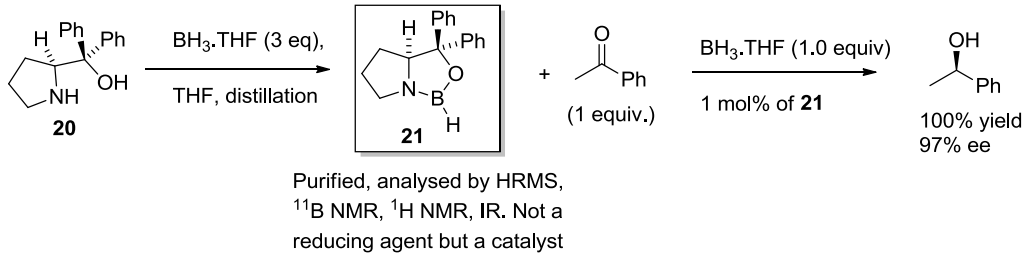
In 1987 Itsuno and co-workers isolated the resulting oxazaborolidine (*S*)-**19** but described it just as a "white solid whose exact structure was not clear" and made the first attempt towards

its characterisation.[29] On the basis of these observations Corey *et al*. fully characterised the "white solid" as optically active oxazaborolidine (*S*)-**19**.[30] Corey and co-workers showed that oxazaborolidine **19** on its own did not reduce acetophenone after several hours at room temperature. However, addition of BH_3.THF (0.6 eq) allowed the rapid reduction of acetophenone at room temperature to produce (*R*)-1-phenylethanol with an enantiomeric excess of 94%, which was quite comparable to the work by Itsuno.[31] In the absence of the oxazaborolidine, BH_3.THF reduced acetophenone relatively slowly at room temperature and the rate acceleration observed in the presence of oxazaborolidine **19** suggested that sub-stoichiometric quantities of the oxazaborolidine **19** could be used to achieve an asymmetric reduction of acetophenone. Bakshi and Shibata later showed that catalytic loading of 2.5 mol% was enough to achieve the same result presented by Itsuno *et al.* using a stoichiometric amount (Scheme).[30]



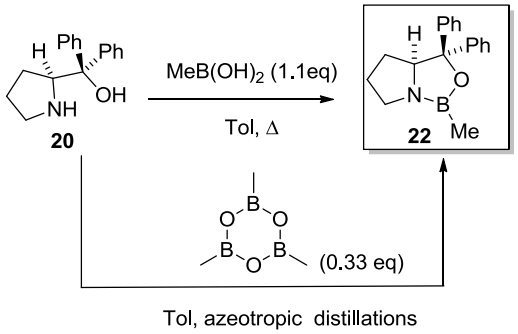
Scheme 8. Oxazaborolidine catalysed asymmetric reduction of acetophenone

The investigations into the mechanism of the stereoinduction were then centred on the nature of the catalyst. It was envisaged that an oxazaborolidine with less conformational flexibility would be able to induce a greater degree of stereoinduction. Hence Corey *et al*. fully characterised and tested the catalytic behaviour of a more rigid and sterically hindered oxazaborolidine **21** derived from (*S*)-(-)-2,2-diphenylhydroxymethylpyrrolidine (α,α-diphenyl prolinol) **20** which was first introduced in borane reductions by Kraatz in 1986 following the procedure of Itsuno.[32] Treatment of the α,α-diphenyl prolinol **20** with BH_3.THF (3 eq) in refluxing THF led to formation of the oxazaborolidine **21** which has become popularly known as CBS catalyst, after Corey, Bakshi and Shibata. The result of the Corey's studies showed that only 1 mol% of oxazaborolidine **21** with BH_3.THF (1 equiv.) was effective in transforming acetophenone to (*R*)-1-phenylethanol in quantitative yield and an impressive 97% enantiomeric excess (Scheme 9).[33, 30]



Scheme 9. Preparation of CBS catalyst and its asymmetric reduction of acetophenone

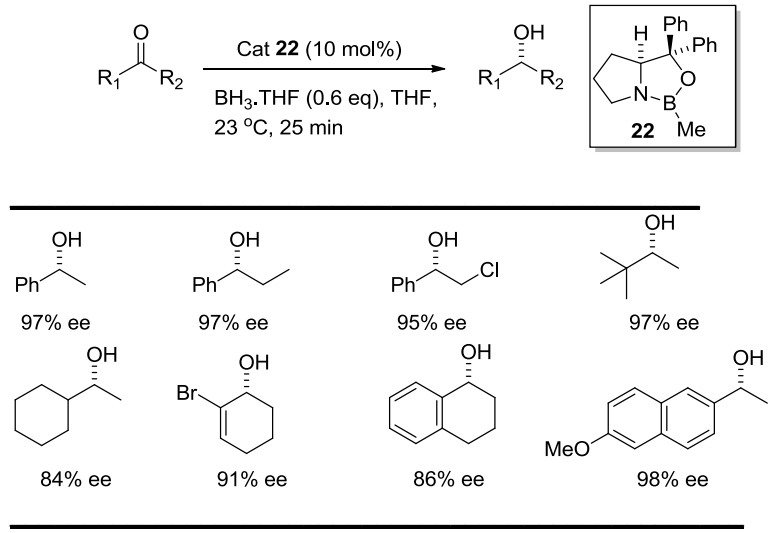
The preparation of *B*-H non-substituted CBS catalyst **21** required the use of excess borane and removal of solvent and borane *in vacuo*. It is also extremely air and moisture sensitive which is a serious setback. The *B*-alkylated versions on the other hand are more stable and can be stored at room temperature.[34] Thus, reaction of the corresponding α,α-diphenyl prolinol **20** with methylboronic acid under dehydrating conditions (4Å molecular sieves or *Dean-Stark* trap) affords (*S*)-**22** as colourless solid (Scheme 10).[34] However, the catalyst gives erratic results if water is not completely removed. Blacklock *et al.* reported that approximately 1 mg of H_2O / 1 g of ketone substrate decreases the ee from 95% to 50%.[35] For this reason Blacklock *et al.* modified the preparation of the oxazaborolidines by using trialkylboroxine instead of alkylboronic acid followed by three successive azeotropic distillations with toluene to remove residual water.[36] This method affords the catalyst in higher purity which is important because any trace of unreacted amino alcohol also decreases the enantioselectivity (Scheme 10).[36]



Scheme 10. Preparation of *B*-Me CBS catalyst

Apart from the stability issues, oxazaborolidine catalyst **22** was found to be a superior enantioselective reduction catalyst. The reduction of ketones with *B*-Me **22** as the catalyst frequently resulted in appreciably higher enantioselectivity than with *B*-H **21**. Moreover the scope of its reduction is very broad. Countless successful applications of this method for the enantioselective synthesis of chiral secondary alcohols from ketones have been described.[33] The chiral alcohols are obtained in excellent enantioselectivities, near quantitative yields, short reaction time and the reaction leads to a product whose absolute configuration can be

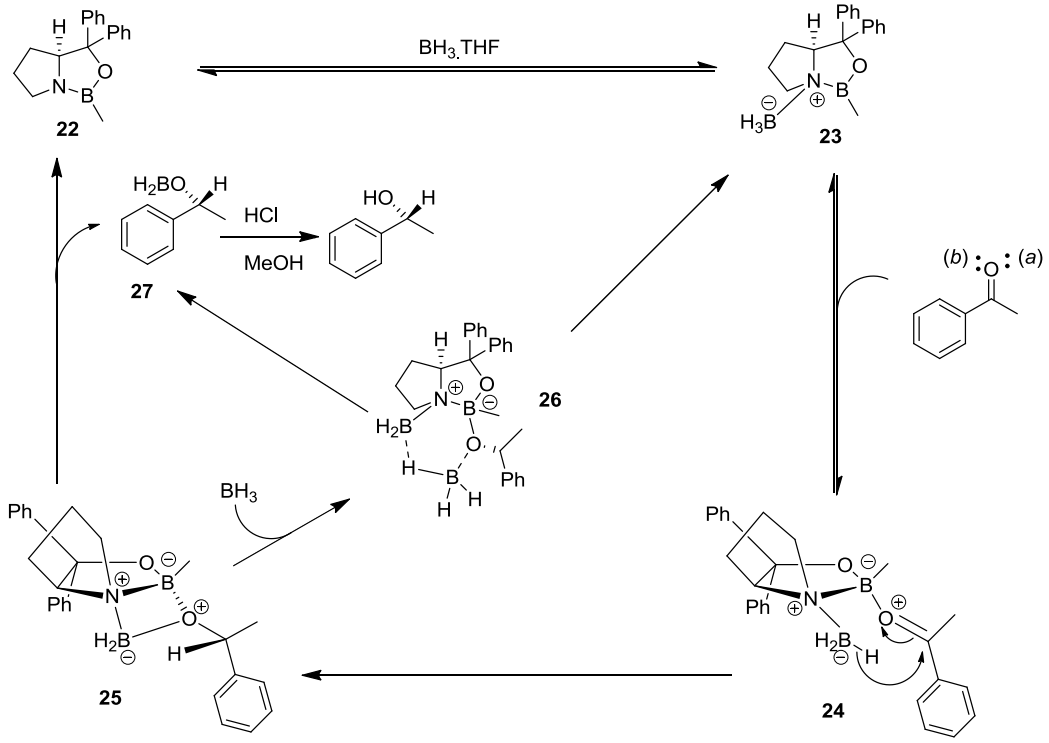
predicted from the relative effective steric bulk of the two carbonyl appendages (Scheme 11).[31, 34]



Scheme 11. CBS reduction of ketones catalysed by *B*-Me catalyst 22

1.3.2 Mechanism

The most logical pathway for the oxazaborolidine-catalysed reduction of ketones by borane as proposed by Corey *et al*. is summarised in Scheme 12. The mechanistic model explains 1) the absolute stereochemistry of the reduction, 2) the outstanding enantioselectivity obtained for the reduction, 3) the exceptional rate enhancement of the reduction, and 4) the turnover of the catalyst.[31, 33]



Scheme 12. Proposed mechanism for the catalytic enantioselective reduction of ketones by CBS

The first step involves the rapid coordination of BH_3 to the Lewis basic nitrogen atom on the α face of oxazaborolidine **22** leading to a *cis*-fused catalyst-BH_3 complex **23**. The crystalline *B*-Me.BH_3 complex **23** consisting of the more stable *cis*-fused geometry (than the corresponding *trans* arrangement) has been isolated and structurally defined by single-crystal X-ray diffraction analysis.[37] The coordination of the electrophilic BH_3 to the nitrogen atom of oxazaborolidine **22** serves to activate BH_3 as a hydride donor and also to increase strongly the Lewis acidity of the endocyclic boron atom. The latter property leads to facile complexation with ketonic oxygen of the (acetophenone) substrate at the more sterically accessible electron lone pair (a in the case of acetophenone) leading to the more stable complex **24**. This manner of binding minimises unfavourable steric interactions between the oxazaborolidine and the ketone, and aligns the electronically deficient carbonyl carbon atom and the coordinated BH_3 for face-selective hydride transfer via a six-membered transition state **24**.[38, 39] The size of the phenyl substituents on the oxazaborolidine ring restricts rotation about the B-OCR_2 bond of **22** such that intramolecular hydride transfer from boron to carbon produces complex **25** with high *π*-facial selectivity. The ketone reduction eventually produces dialkoxyborane $(RO)_2BH$ with regeneration of catalyst **22** possibly by addition of BH_3 to complex **25** to form a six-membered BH_3-bridge species **26**, which decomposes to produce the catalyst-BH_3 complex **23** and borinate **27**.[40] The catalyst may also be directly regenerated from complex **25** by cycloelimination forming the borinate **27** simultaneously in the process.[41] Thus, the (*S*)-proline-derived catalyst **22** selectively promotes the formation of (*R*)-1-phenylethanol from acetophenone and BH_3·THF.

A final issue posed by the proposed mechanistic model (Scheme 12) is whether the complexation of the ketone by the CBS catalyst or the subsequent hydride transfer to form complex **25** is the rate-limiting step of the reduction.[31] To answer this question, the rates of reduction of acetophenone and the *p*-NO_2 and *p*-MeO derivatives catalyzed by *B*-Me-**22** were measured.[42] The relative rates of reduction were found to be 3.4 (*p*-NO_2), 1.8 (*p*-MeO), and 1.0 (*p*-H). This implies that the coordination of the ketone to the *B*-Me catalyst is not strictly rate-limiting for these substrates. Additional information was obtained from the ^1H – ^2H kinetic isotope effect (k_H/k_D) for hydride transfer, which was measured with an excess of a 1:1 mixture of B^1H_3 and B^2H_3 (6 equiv. of each) in THF with two equivalents of oxazaborolidine *B*-Me-**22** and one equivalent of acetophenone. The ratio of ^1H to ^2H in the reduction product 1-phenylethanol at low conversion was determined by mass spectrometry to be 1.7, which is then the approximate value of k_H/k_D.[42] This low value is indicative of an early transition state for highly exothermic transfer of hydride from the boron atom to the

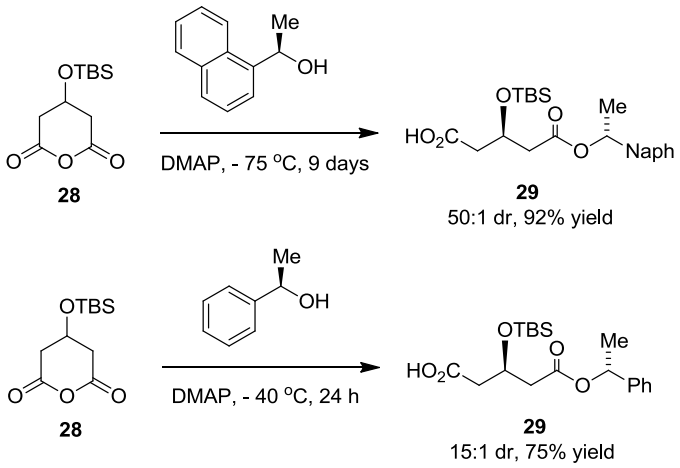
carbonyl group.[42] Thus, both association to the carbonyl compound and hydride transfer are probably fast and comparably rate-limiting.[31]

Since their development, oxazaborolidine catalysts have been utilized for the highly effective asymmetric synthesis of intermediates leading to a broad range of chiral natural products and bioactive compounds[43, 44] such as lactones and macrolides[45], terpenoids e.g. (-)-herbertenediol[46], alkaloids e.g. sanjoine A[47], and many important drugs and pharmaceuticals such as antitumor drugs (-)-acylfulvene and (-)-irofulven.[48, 49]

1.4 Enantioselective desymmetrisation

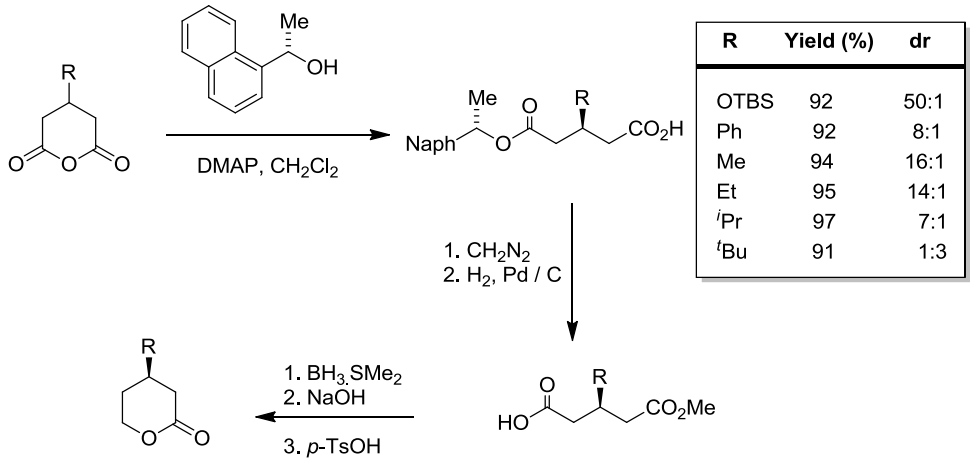
1.4.1 Background

Desymmetrisation of an achiral or *meso* molecule to yield enantiomerically enriched products is a powerful synthetic tool. In general, an enantioselective symmetry breaking synthetic operation is achieved when two enantiotopic functional groups are differentiated by the use of a chiral reagent, enzyme or catalyst.[50] The most common type of enantioselective desymmetrisation involves the formation of carbon-heteroatom bond, of which the formation of carbon-oxygen bonds are the most common. For this reason, compounds with oxygen-containing functional groups such as anhydrides, epoxides, alcohols, ketones or aldehydes are commonly used as substrates. There have been several reports of the addition of chiral alcohol nucleophiles to cyclic achiral or *meso*-anhydrides to achieve diastereomerically enriched mono-ester products.[50] Theisan and Heathcock reported the addition of 1-(1'-naphthyl)ethanol to 3-OTBS substituted glutaric anhydride **28** to deliver enantioenriched ester **29** (scheme 13).[51] The work revealed that far higher levels of diastereoselectivity were obtained using 1-(1'-naphthyl)ethanol as the nucleophile in preference to 1-(1'-phenyl)ethanol (50:1 *versus* 15:1 diastereoselectivity).



Scheme 13. Heathcock's desymmetrisation of *meso* anhydride

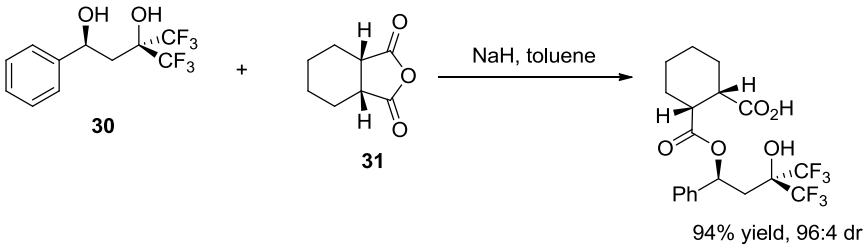
This desymmetrisation work was later extended by the same workers to 3-phenylsubstituted anhydride and a variety of 3-alkylsubstituted *meso*-anhydrides.[52] Results from this investigation revealed that more sterically hindered isopropyl- and *tert*-butyl- substituted substrates resulted in lower selectivities (Scheme 14). The chiral mono-esters were esterified by treatment with diazomethane followed by hydrogenation to obtain the corresponding methyl esters which were efficiently converted to the corresponding chiral δ-lactones in three steps sequence (Scheme 14).[52]



R	Yield (%)	dr
OTBS	92	50:1
Ph	92	8:1
Me	94	16:1
Et	95	14:1
^{i}Pr	97	7:1
^{t}Bu	91	1:3

Scheme 14. Heathcock's desymmetrisation of 3-substituted *meso* anhydrides

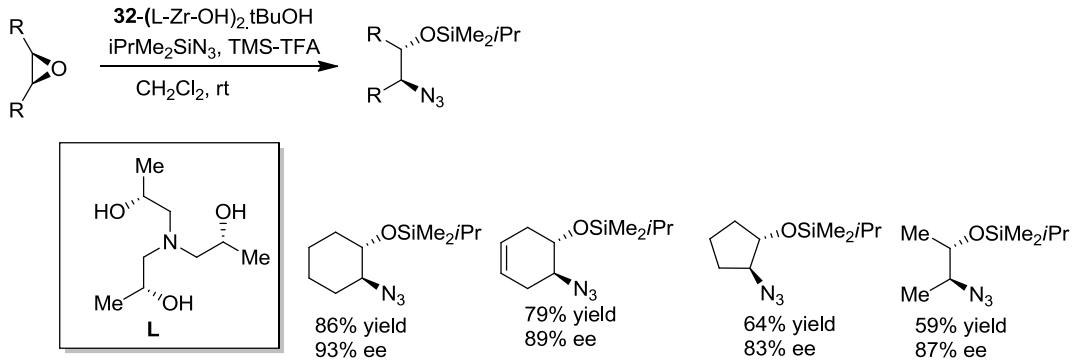
Taguchi and co-workers have also developed a system for the diastereoselective opening of *meso*-succinic anhydrides **31** using 1-phenyl-3,3-bis(trifluoromethyl)propane-1,3-diol **30** as the chiral nucleophile (scheme 15). They reported that to achieve a good level of selectivity, it was necessary to use the sodium salt of the diol **30** and to conduct the reactions in a non-polar solvent.[50]



Scheme 15. Taguchi's desymmetrisation of *meso* anhydrides

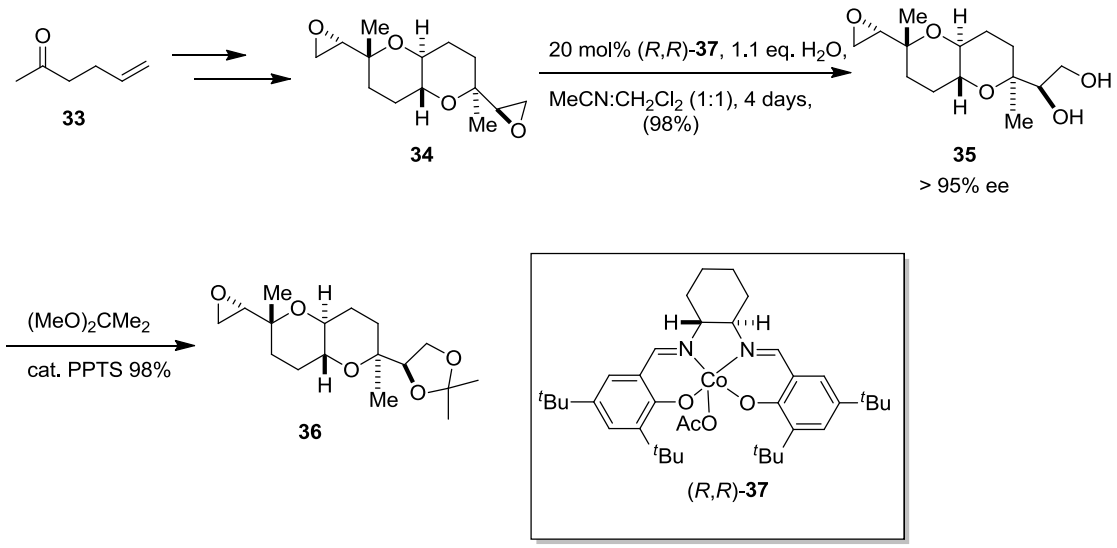
Readily available stereochemically defined epoxides obtained from simple alkene precursors are popularly used as substrates in desymmetrisation chemistry. Nugent reported a range of C_3-symmetric zirconium (IV) complexes **32**-(L-Zr-OH)$_2$.tBuOH that catalyse the addition of azide nucleophiles to *meso*-epoxides (scheme 16).[53] The reaction is compatible with a range

of cyclic and acyclic epoxides with a particularly notable example being the use of but-2-ene oxide which provided the ring-opened product in an impressive 87% ee.



Scheme 16. Nugent's desymmetrisation of *meso* epoxides

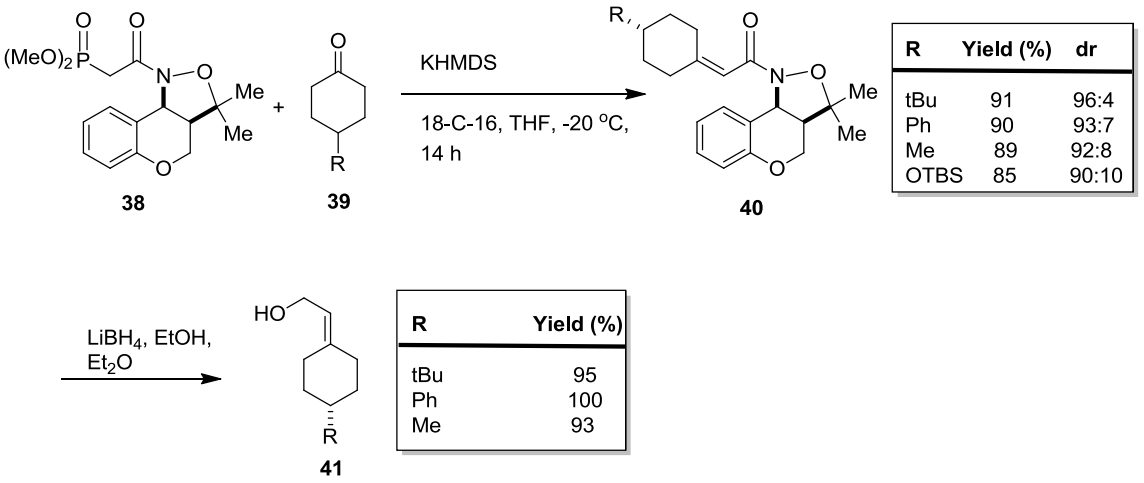
Nelson and co-workers employed a Jacobsen enantioselective epoxide hydrolysis to effect the desymmetrisation of centrosymmetric diepoxide **34** prepared from a simple alkenyl ketone **33** in seven steps. Treatment of the *meso* diepoxide **34** with 20 mol% of (*R*,*R*)-**37** in MeCN:CH_2Cl_2 (1:1) for 4 days gave selectively the diol **35** in a remarkable 98% yield and > 95% ee (Scheme 17). The diol **35** was converted in to a known synthetic intermediate **36** in a total synthesis of the polyclic ether natural product hemibrevetoxin B.[54, 55]



Scheme 17. Nelson's desymmetrisation of *meso* centrosymmetric diepoxide

Prochiral ketone substrates are also used extensively to achieve desymmetrisation processes. Interesting work reported by Masamune and Abiko used a chiral phosphonate **38** in which the chiral auxiliary was attached *via* the amide unit to desymmetrise 4-substitutedcyclohexanones **39** in an asymmetric Horner-Emmons reaction (Scheme 18).[56] Deprotonation of the chiral

phosphonate **38** using KHMDS in presence of 18-crown-6 at -20 ^{o}C and reacting with achiral 4-substituted cyclohexanones **39** produced the alkenes **40** in good yields and diastereomeric ratios. Cleavage of the benzopyranisoxazoline unit by treatment with lithium borohydride provided the corresponding chiral allylic alcohols **41** in excellent yields, without racemization (Scheme 18).



R	Yield (%)	dr
tBu	91	96:4
Ph	90	93:7
Me	89	92:8
OTBS	85	90:10

R	Yield (%)
tBu	95
Ph	100
Me	93

Scheme 18. Abiko's desymmetrisation of *meso* cyclohexanones

1.4.2 Enantioselective reduction of imides

Enantioselective reduction of imides has received much attention because they form a useful class of starting materials in the field of asymmetric synthesis. An enantioselective reduction of one of the carbonyl groups leads to chiral hydroxy-lactams which have been shown to be versatile building blocks for the synthesis of natural products and numerous heterocyclic compounds, including vitamins, antibiotics, ACE inhibitors, and anticancer drugs such as (+)-biotin, and swainsonine.[57, 58, 59] One of the first approaches towards the asymmetric reduction of imides was by Chamberlin and co-workers. Their work involved the attachment of a chiral auxiliary derived from the commercially available D-(α)-phenylglycinol to the nitrogen atom of the imide **42**, which they envisaged could control the diastereoselective reduction of one of the carbonyl groups over the other (Figure 6).[60] Initial attempts at selective reduction of one of the diastereotopic carbonyl groups relied upon the intramolecular reaction of an alkoxide / metal species from the alcohol **43**. The conformation required for such a reaction places either phenyl or H approximately in-plane with the other carbonyl group, and the latter arrangement should be more favourable (Figure 6). Initially the result was disappointing: $LiAlH_4$ gave a diastereomeric excess (de) of only 22%, while the use of Red-Al resulted in a somewhat better 64% de. However, with tetramethylammonium triacetoxyborohydride,

$Me_4NHB(OAc)_3$, the stereoselectivity improved significantly to levels exceeding 90% de (Scheme 19).[60]

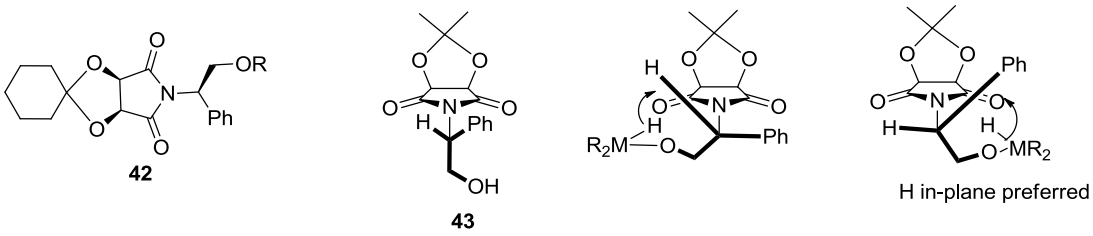
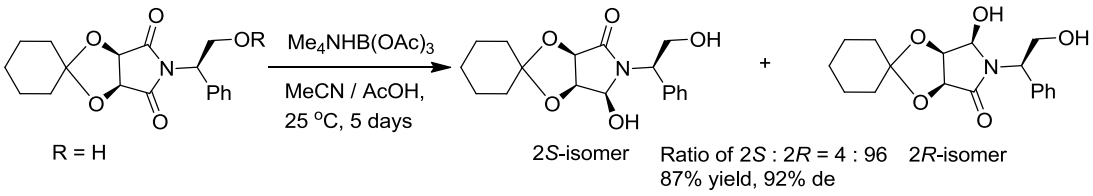
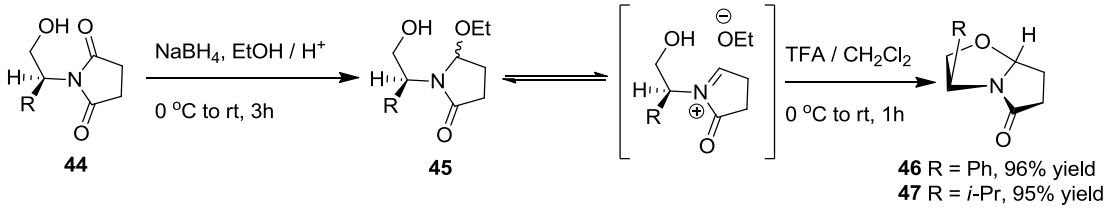


Figure 6. Chamberlin's chiral auxiliary



Scheme 19. Chamberlin's asymmetric reduction of imides

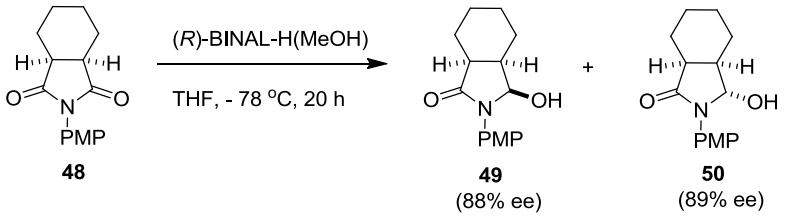
Meyers *et al*. also utilized nitrogen based-chiral auxiliaries for enantioselective reduction of the succinimides **44** by treatment with $NaBH_4$ and 1.0 equivalent of HCl in absolute ethanol. The diastereomeric 2-ethoxy lactams **45** obtained were effectively converted to the corresponding chiral bicyclic lactams **46** & **47** via an acyliminium ion as single diastereomers and in excellent yields, by treatment with 10 equivalents of TFA at 0 °C (Scheme 20).[61]



Scheme 20. Meyer's asymmetric reduction of *meso* imides

Enantioselective reduction methods using optically active BINAL-H complexes have been reported. Matsuki *et al*. examined the reduction of *N*-PMP *meso* imide **48** by treating with 3.5 equivalent amount of (*R*)-BINAL-H(MeOH).[62] A mixture of hydroxy-lactam **49** and **50** was isolated whose ratio depended on the conditions of the work-up. When the reduction was quenched with 10% HCl at -78 °C, the C_3β-hydroxy-lactam isomer **49** was isolated as a sole product in 85% yield (Scheme 21). Quenching the reaction with 10% HCl at room temperature, however, led to epimerization and afforded an equimolar mixture of hydroxy-lactams **49** and **50** (Scheme 21). Also, when the C_3β-hydroxy-lactam **49** was treated with 10% HCl in THF at room temperature for 1 hour, the C_3α-hydroxy-lactam **50** was obtained in

95% yield. To confirm the enantioselectivity of the (*R*)-BINAL-H, both hydroxy-lactams **49** and **50** were separately treated with Et_3SiH / TFA to afford the corresponding lactams quantitatively in 88% ee and 89% ee, respectively.[62]



Work up	Yield of **49** (%)	Yield of **50** (%)
10% HCl at - 78 °C	85	-
10% HCl at room temp.	50	50

Scheme 21. Matsuki's asymmetric reduction of *N*-PMP *meso* imide

The stereochemical outcome was explained using the model put forward by Noyori *et al.*[63] The attack of the BINAL-H on the carbonyl group attached to the (*R*)-centre of the imide from the convex face leads to a more favourable transition state "A" owing to the n / Π* attractive orbital interaction between oxygen non-bonding orbital and the LUMO of the imide moiety affording the C_3β-hydroxy-lactam **49** (Figure 7). The transition state "B" from the attack of the (*R*)-BINAL-H on the carbonyl group attached to (*S*)-centre has no such interaction and is therefore less favoured (Figure 7).[62]

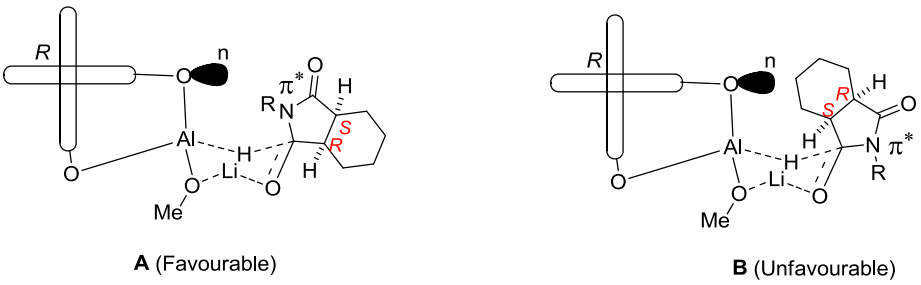
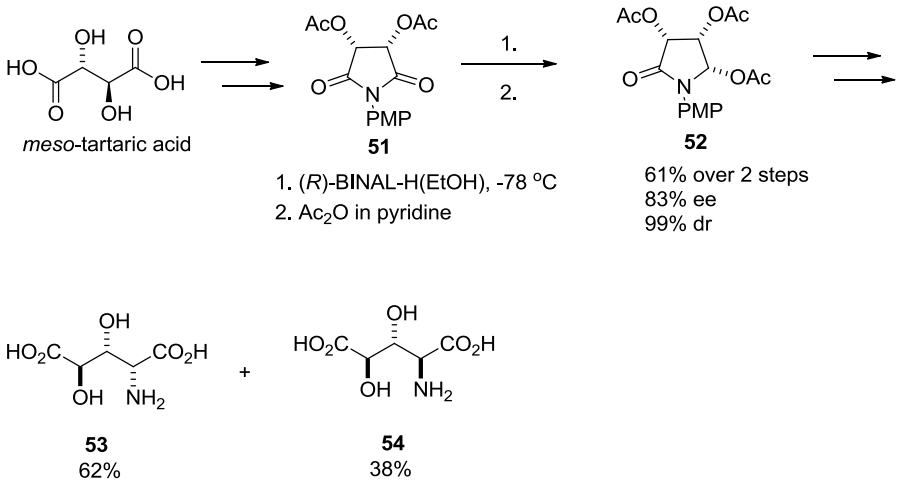


Figure 7. Transition states for the reduction of succinimide 48

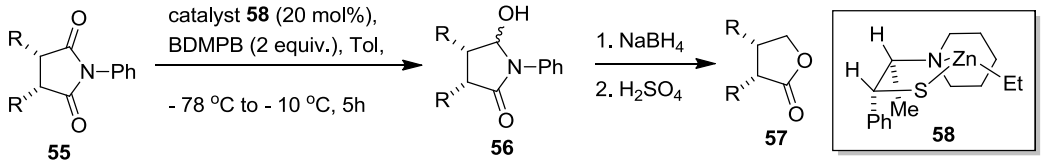
Nishiyama and co-workers employed the use of a BINAL-H(EtOH) complex prepared *in situ* by mixing lithium aluminium hydride with equimolar amounts of (*R*)-(+)-binaphthol and ethanol in THF for the reduction of a *meso*-tartaric acid derived imide **51** in the course of the stereoselective synthesis of chiral diastereomers of 3,4-dihydroxyglutamic acids **53** and **54** (Scheme 22).[64] The triacetate **52** was obtained as a single diastereomer suggesting attack of the (*R*)-BINAL-H reagent from the less hindered face of the carbonyl group attached to the *S* centre of the cyclic *meso* imide. Although they could not explain the reason for the

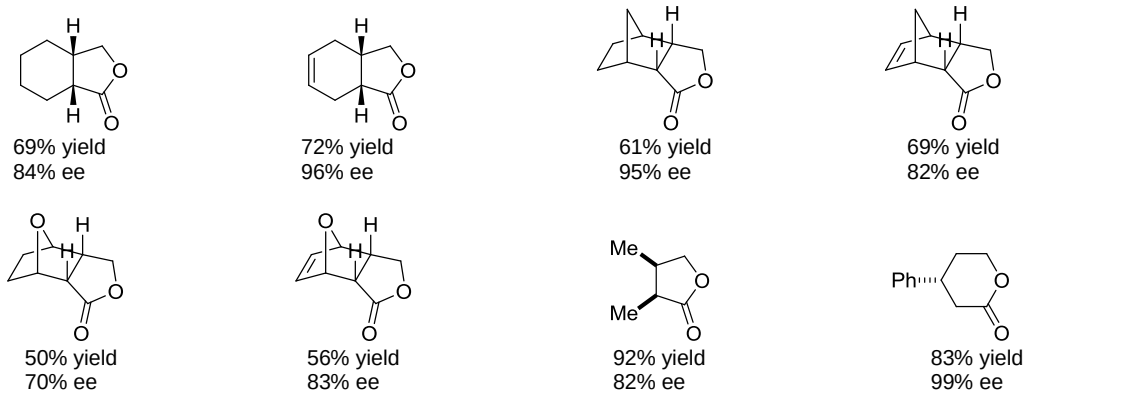
enantioselective discrimination of the enantiotopic imide carbonyl groups, they thought that the interaction of an acetoxy group with the (*R*)-BINAL-H reagent may be responsible for the reversal of enantioselectivity observed in Matsuki's work.[64]



Scheme 22. Nishiyama's asymmetric reduction of *meso* imide 51

Kang *et al*. reported the use of thiazazincolidine complex **58** prepared *in situ* from (1*R*,2*S*)-(-)-1-phenyl-2-(1-piperidino)-1-propanethiol and diethylzinc as a good catalyst for enantioselective reduction of cyclic *meso*-imides in the presence of *bis*(2,6-dimethoxyphenoxy)borane, BDMPB (Scheme 23).[65] The catalyst was previously shown by Kang *et al*. to be an excellent catalyst for enantioselective addition of dialkylzinc to aldehydes[66], and it was thus envisaged that there will be an enantiodiscriminative coordination of the catalyst to one of the carbonyl groups of the imide. Enantioselective reduction of various *meso N*-phenyl imides **55** to corresponding hydroxy-lactams **56** was carried out. The hydroxy-lactams were reduced to the corresponding hydroxy-amides with $NaBH_4$ followed by acid-catalysed lactonization to give the corresponding lactones **57** in good yields and enantioselectivity (Scheme 23).





Scheme 23. Kang's asymmetric reduction of *meso* imides

Two possible transition states A and B for the reduction were proposed by the authors (Figure 8). It was envisaged that the complex B with the phenyl group pointing away from the catalyst should be more favourable. Moreover, it was proposed that the bulky nucleophile BPMPB should selectively attack the indirectly activated carbonyl carbon rather than the directly coordinated carbonyl group, leading to lactone **57** (Figure 8).[65]

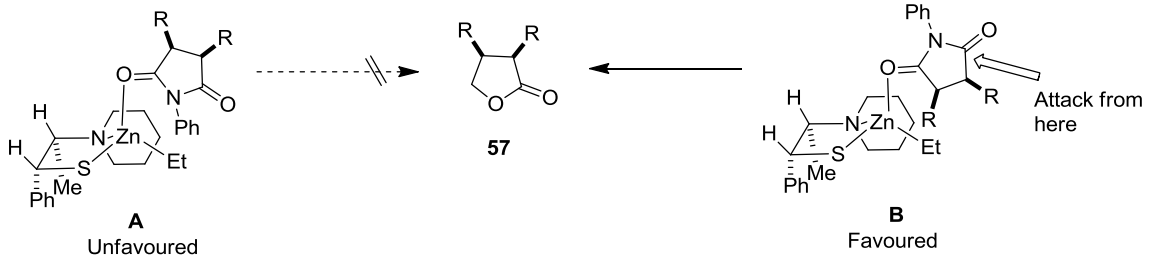


Figure 8. Transition state for thiazazincolidine catalysed reduction

While these works focused on five membered ring *meso* succinimides, the enantioselective reduction of six membered ring achiral glutarimides has not been explored much. There have been only two reports on the enantioselective desymmetrisation of achiral glutarimides, out of which only one, by Ikariya and co-workers, is an enantioselective catalytic reduction. They reported the use of chiral $Cp^*Ru(PN)$ catalysts for the enantioselective hydrogenative desymmetrisation of mono- and bicyclic glutarimides (and succinimides) to furnish chiral hydroxyamides.[67] The chiral ruthenium catalyst **59** in presence of *t*-BuOK caused highly enantioselective hydrogenation of both monocyclic and bicyclic glutarimides to give the corresponding hydroxyamides in near quantitative yields and excellent ee's (Scheme 24). Furthermore the authors observed that the enantioselectivity of products derived from some bicyclic succinimides decreased to the moderate range (52 – 63% ee) with the same chiral

catalyst. However, switching from catalyst **59** to **60** caused significant change in ee in the desymmetrisation of the five-membered ring imides (52 – 92% ee).[67]

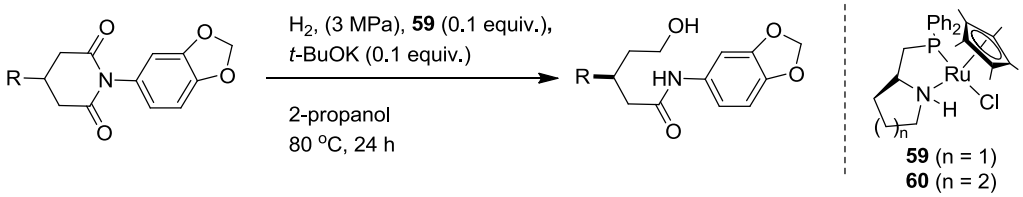
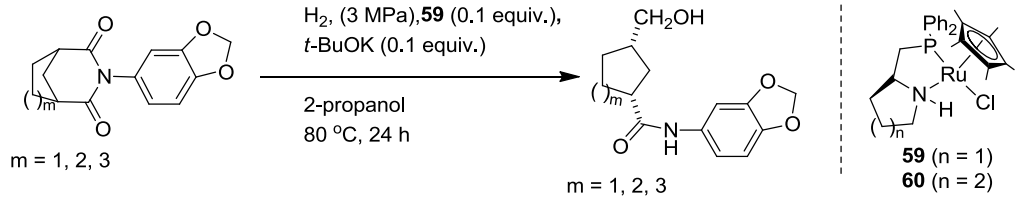


Table 3. Enantioselective hydrogenative desymmetrisation of glutarimides

Entry	Imide	ee of hydroxyamide (%)
1	R = $4FC_6H_4$	98
2	R = $3,4Cl_2FC_6H_4$	91
3	R = C_6H_5	98
4	R = CH_3	88

* Authors indicated >99% conversion



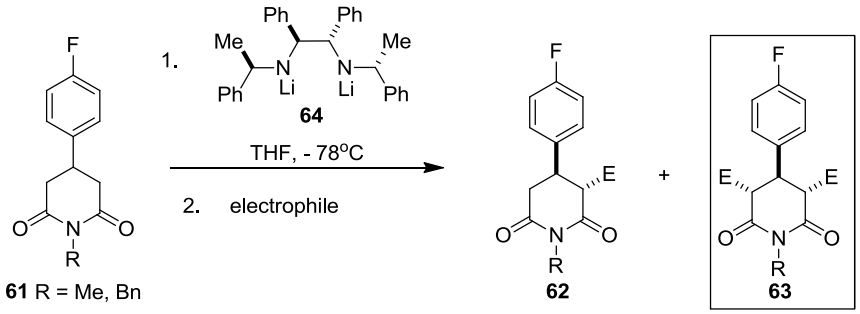
Scheme 24. Ikariya's enantioselective hydrogenative desymmetrisation of glutarimides

Table 4. Enantioselective hydrogenative desymmetrisation of bicyclic glutarimides

Entry	Imide	ee of hydroxyamide (%)
1	m = 1	94
2	m = 2	94
3	m = 3	93

* Authors indicated >99% conversion

In a different strategy, Simpkins and co-workers used the chiral base **64** in its bis-lithiated form to effect an enantioselective desymmetrisation of achiral *N*-Me and *N*-Bn glutarimides **61** (Scheme 25).[68] Under the optimized conditions, the desired products **62** were obtained in good yields, with good to excellent levels of enantioselectivity, and as single diastereomers. However, the formation of the doubly substituted product **63** was observed in all the desymmetrisation products.



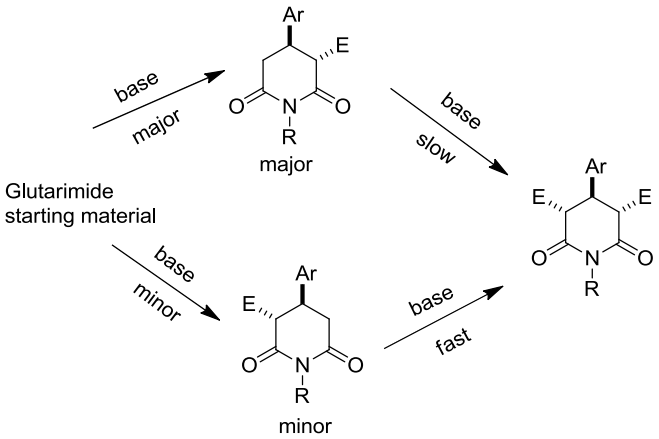
Scheme 25. Simpkin's desymmetrisation of glutarimides using chiral base

Table 5. Chiral base desymmetrisation of glutarimides

Entry	R	Electrophile	Yield of **62** (%)	ee of **62** (%)	**62** / **63**
1.	Me	MeI	73	86	3.5 : 1
2.	Me	BnBr	58	74	2.5 : 1
3.	Me	4-$BrC_6H_4CH_2Br$	63	77	3 : 1
4.	Me	MeO_2CCN	87	75	20 : 1
5.	Bn	MeI	65	97	3 : 1
6.	Bn	AllylBr	52	90	*
7.	Bn	BnBr	61	97	2 : 1
8.	Bn	PhCHO	75	97	-
9.	Bn	MeO_2CCN	71	97	6.5 : 1

* Ratio not determined

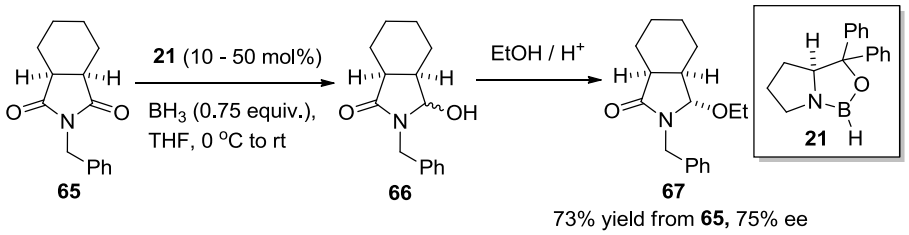
Results from the work showed higher levels of selectivity in *N*-Bn substrates than in the *N*-Me series (Table 5). It was also observed that there was a correlation between high selectivity and the formation of the undesired di-substituted by-product **63**. The authors explained that this observation suggested that the overall ee of the desired product was the result of an initial asymmetric enolisation of the glutarimide starting material, followed by an ee enhancing kinetic resolution (Scheme 26).[68]



Scheme 26. ee enhancing kinetic resolution in desymmetrisation of glutarimides

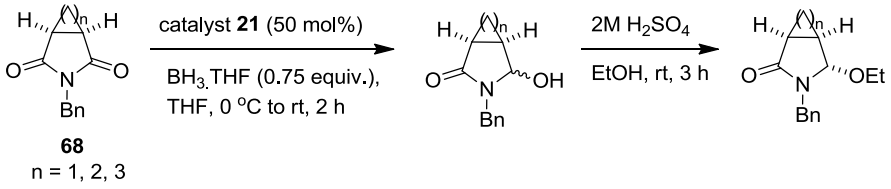
1.4.3 Enantioselective reduction of imides using oxazaborolidines

Studies of the use of a combination of oxazaborolidine catalysts and borane for the enantioselective reduction of *meso*-imides have caught the attention of many research groups. The first enantioselective reduction of *meso*-imides using an oxazaborolidine **21** / BH_3 mixture was reported by Hiemstra and co-workers.[69] When the *meso*-imide **65** was treated with varying amounts of CBS catalyst **21** and BH_3, a mixture of optically active *cis*- and *trans*-5-hydroxy-2-pyrrolidinones **66** was obtained. The crude mixture was immediately treated with $EtOH/H_2SO_4$ giving the ethoxy-lactam **67** that was isolated as a single product in good overall yield and with good enantioselectivity (Scheme 27).[69]



Scheme 27. Hiemstra's asymmetric reduction of *meso* imides

Encouraged by the above results, the reduction was applied to various other *meso N*-benzyl imides **68** in the presence of oxazaborolidine **21** at different catalyst loadings employing BH_3.THF as the hydride source (Scheme 28). Optimal catalyst loading was found to be 0.5 equivalents to achieve maximum enantioselectivity. The corresponding ethoxy-lactams were obtained in good overall yield with complete *trans*-stereoselectivity and high enantioselectivity. The results indicated that there was a direct relationship between enantioselectivity obtained and the size of the bicyclic backbone. The best result was obtained when a cyclobutyl ring (n = 2) was present on the imide giving a maximum ee of 89% (Table 6), while deviation from this size to a larger ring resulted in a drop in ee to 77% for cyclopentyl (n = 3) and 80% for cyclohexyl (Table 6, n = 4).[70]



Scheme 28. Speckamp's CBS catalysed reduction of *meso*-imides

Table 6. Speckamp's reduction of cyclic *meso* imides

Imide	Yield of hydroxy-lactam (%)	Yield of ethoxy-lactam (%)	ee of ethoxy-lactam (%)
n = 1	74	94	88
n = 2	-	68*	89
n = 3	-	85*	77
n = 4 (**65**)	95	87	80

* Yield over 2 steps

The observed stereochemical outcome was explained by adopting Corey's transition state model for CBS-catalysed reduction of acetophenone (Scheme 12).[30] In the case of cyclic *meso*-imides, however, the nitrogen moiety is the large substituent (R_L) and the fused ring moiety is the small substituent (R_S) (Figure 9). The hydride attack should therefore come from the least hindered face of the carbonyl carbon (attached to the *R* centre), producing *cis* hydroxy-lactam **69** as the kinetic product (Figure 9). It was also postulated by Hiemstra and co-workers that enantioselectivity is higher if the difference in size between R_L and R_S is larger, hence imides with small R_S (n = 1 & n = 2) gave higher selectivity (Table 6, n = 1 & 2).[70]

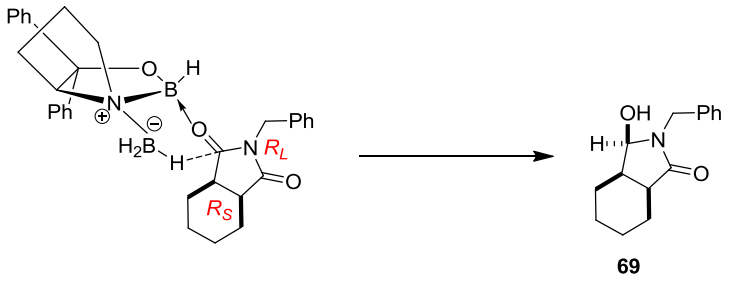
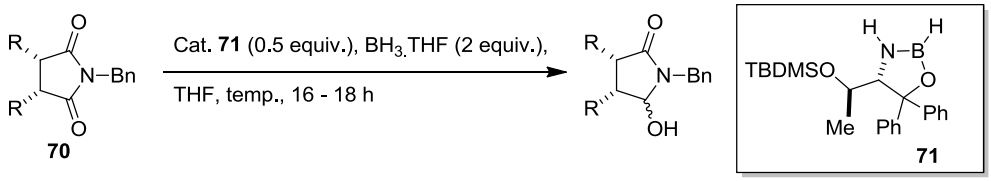


Figure 9. Hiemstra's transition state for CBS catalysed reduction of *meso*-imides

Shimizu *et al*. employed the use of an oxazaborolidine catalyst **71** derived from L-threonine and borane-THF for enantioselective reduction of *meso N*-benzyl succinimides **70** to give the corresponding hydroxy-lactams in high enantiomeric purity (Scheme 29).[71] The optimal oxazaborolidine loading was found to be 0.5 equivalents, otherwise leading to a lower yield of the hydroxy-lactam products.

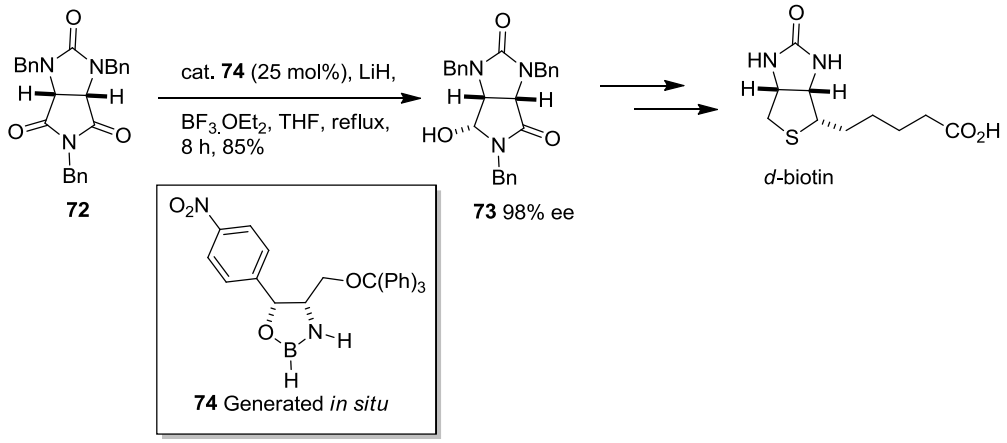


Scheme 29. Shimizu's reduction of *meso*-imides

Table 7. Shimizu's reduction of cyclic *meso* imides

R, R	Temp. (^{o}C)	Yield of hydroxy-lactam (%)	ee (%)
AcO, AcO	0	54	98
-$(CH_2)_4$-	0	50	92
TBDMSO, TBDMSO	rt	76	91
-(Bn)NCON(Bn)-	rt	73	92

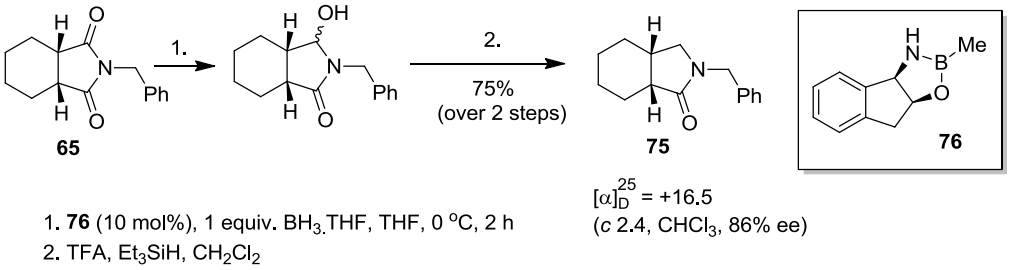
Chen *et al*., in an effort to avoid the relatively expensive and less stable borane (and its complexes), employed enantioselective reduction of *meso*-imide **72** via the use of chiral oxazaborolidine **74** derived from (1*S*,2*S*)-(+)-*threo*-1-(4-nitrophenyl)-2-amino-1,3-propanediol and *in situ* generated borane from LiH / $BF_3.Et_2O$. The corresponding hydroxy-lactam **73** obtained as a single diastereomer in 85% yield and 98% ee led to a synthesis of *d*-biotin (Scheme 30).[72]



Scheme 30. Chen's reduction of *meso*-imide 72

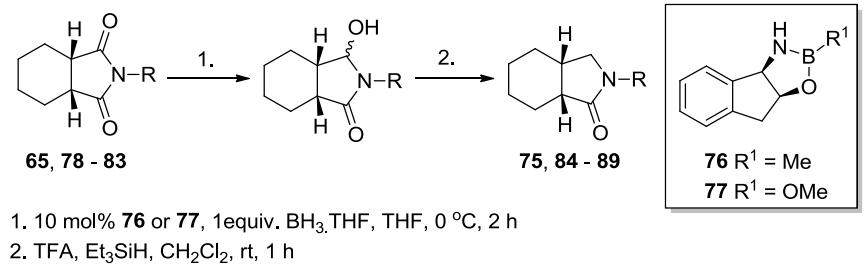
In the continuation of the investigation on the mechanism and catalytic properties of the oxazaborolidine catalysts, the Jones research group has reported application of the catalysts for the reduction of *meso*-imides. Jones and Dixon reported desymmetrisation of *meso*-imide **65** by enantioselective reduction using a chiral oxazaborolidine catalyst **76** derived from (1*R*,2*S*)-*cis*-1-amino-2-indanol followed by reduction of the hydroxy-lactam product to lactam **75**, which proceeded with good enantiomeric excess at significantly lower catalyst loadings compared to reactions using the prolinol-derived (CBS) catalyst **22**.[73] At 5 mol % catalyst loading, 57% yield of lactam **75** was produced at an impressive 84% ee, against the CBS catalyst which gave an enantioselectivity of 45% ee and 44% yield. Reduction in the amount of catalyst to as low as 1 mol % showed no significant drop in enantioselectivity at around 85%, although a slight drop in the overall yield was noted. The best catalyst loading

was observed at 10 mol % which gave 75% yield of the lactam and enantiomeric excess of 86% (Scheme 31).[73]



Scheme 31. Jones' desymmetrisation of *meso* imide using oxazaborolidine catalyst

In separate work, Jones and co-workers reported the crucial role of the nitrogen substituent in the desymmetrisation of cyclic *meso*-imides **65**, & **78** – **83** using *B*-Me **76** and *B*-OMe **77** oxazaborolidine catalysts (Scheme 32).[74] The research work revealed that these oxazaborolidine catalysts are very effective for the enantioselective reduction of a series of *meso*-imides, with the *B*-Me **76** catalyst providing better yield of the lactam products **75**, & **84** – **89** (Table 8). More importantly, the research discovered that varying the nitrogen substituent on the imide greatly affects the level of enantioselectivity, with *N*-aryl groups providing very high enantioselectivity of the lactam product (Scheme 32, Table 8).[74]



Scheme 32. Desymmetrisation of *meso* imide using oxazaborolidine catalysts

Table 8. Reduction of cyclic *meso* imides using catalyst 76 and 77

Entry	Imide	R	Lactam	Catalyst **76**		Catalyst **77**	
				Yield (%)	ee (%)	Yield (%)	ee (%)
1	**65**	Bn	**75**	57	84	53	82
2	**78**	Ph	**84**	49	99	23	99
3	**79**	(*p*-OMe)C_6H_4	**85**	41	99	28	99
4	**80**	(*p*-NO_2) C_6H_4	**86**	24	99	9	99
5	**81**	CH_2=$CHCH_2$	**87**	24	33	24	32
6	**82**	*t*-Bu	**88**	19	0	21	0
7	**83**	Me	**89**	52	75	30	70

Explanations were put forward for the observed results. The reduced yields of the lactams observed in *B*-OMe catalyst were thought to be as a result of the reduced Lewis acidity of the boron centre in the catalyst by the additional oxygen substituent, therefore retarding the rate of reduction. The disappointing yield obtained with R = (p-NO_2)C_6H_4 was attributed to the doubly reduced product observed in the reaction while a competitive hydroboration may be responsible for the poor yield obtained in the *N*-allyl substrate. A model was presented to explain the stereochemical outcome of the reductions. It was envisaged that both the borane and the imide bind to the least hindered convex side of the oxazaborolidine (Figure 10). Also, to avoid unfavourable interactions, the nitrogen substituent was placed away from the *B*-Me group of the oxazaborolidine similar to the transition state model proposed by Corey and hydride was supplied from the *Re* face of the activated carbonyl carbon (Figure 10).[74]

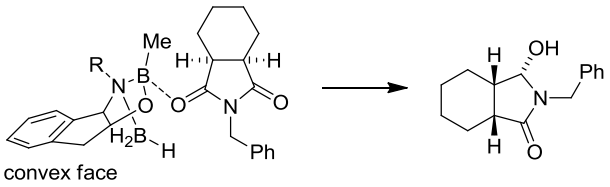
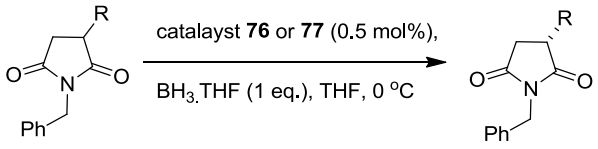


Figure 10. Transition state for *cis*-1-amino-indanol-2-ol oxazaborolidine reductions

In a different approach, the research group has reported the use of oxazaborolidines *B*-Me **76** and *B*-OMe **77** as catalysts for the kinetic resolution of racemic C-3 substituted pyrrolidine-2,5-diones (Scheme 33).[75] Results obtained showed that both catalysts are effective for the kinetic resolution of C-3 substituted pyrrolidine-2,5-dione species at extremely low catalyst loadings (0.5 mol%), giving outstanding regio- and stereocontrol. In the preliminary experiment, reduction of the substrates to hydroxy-lactams with BH_3.THF, employing *B*-OMe oxazaborolidine **77** as the catalyst followed by reduction to corresponding γ-lactams showed full regiocontrol of the reaction in all cases, reducing only the distal carbonyl at the C-5 position. Applying optimised conditions, the kinetic resolution of various C-3 substituted pyrrolidine-2,5-diones was assessed (Table 8).



Scheme 33. Kinetic resolution of C-3 succinimides using oxazaborolidine catalysts

Table 9. Kinetic resolution of *N*-Bn C-3 succinimides using oxazaborolidine catalysts

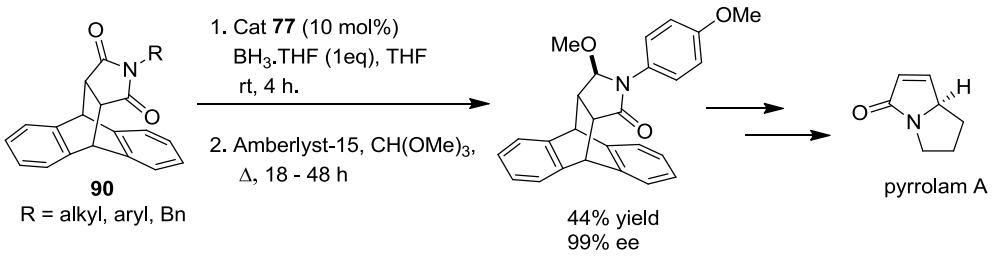
Entry	R	Catalyst[a]	Conversion (%)[b]	ee (%) (of starting material)[c]	*s* factor
1	Me	**76**	46	16	1.8
2	Me	**77**	32	11	1.8
3	Ph	**76**	52	45	3.7
4	Ph	**77**	36	28	3.9
5	3,5-$Me_2C_6H_3$	**76**	48	41	3.8
6	3,5-$Me_2C_6H_3$	**77**	39	32	4.1
7	*o*-Tolyl	**76**	23	24	11.6
8	*o*-Tolyl	**77**	43	57	12.7
9	1-Naphthyl	**76**	21	23	17.3
10	1-Naphthyl	**77**	30	37	19.6
11	*t*-Bu	**76**	38	52	20.4
12	*t*-Bu	**77**	35	47	23.4
13	Mesityl	**76**	31[d]	16	2.5
14	Mesityl	**77**	34[d]	5	1.3

[a] 0.5 mol% catalyst was used in each case. Reactions performed with catalyst **76** were carried out for 120 min, while those with catalyst **77** for 60 min. [b] Conversion determined via ^{1}H NMR spectroscopy using maleimide as an external standard. [c] ee determined via chiral phase HPLC. [d] Conversion determined via ^{1}H NMR spectroscopy using *N*-benzotriazole as an external standard.

Results showed that the level of the selectivity increased with increasing steric bulk at the C-3 position (Table 9). A methyl group gave a poor selectivity, giving *s* factors of 1.8 (Table 9, entries 1 and 2). When the substituent size was increased to phenyl or 3,5-dimethyl phenyl, the level of selectivity increased to between 3.7 and 4.1 (Table 9, entries 3–6). Excellent *s* factors of 12 and 18 were achieved with *o*-tolyl or 1-naphthyl substituents (Table 8, entries 7–10), while the highest *s* factors of 20–23 were achieved with *t*-Bu substituent (Table 8, entries 11 and 12). However, the large mesityl derivative gave very disappointing *s* factors of between 1.3 and 2.5 (Table 9, entries 13 and 14).[75]

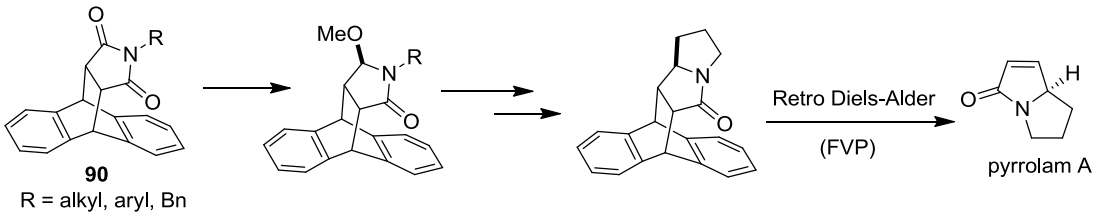
1.5 Aims

Previous work from this group has shown that the oxazaborolidines **76** and **77** are good catalysts for desymmetrisation of five-membered *meso* imides.[73, 74, 75] More recently, the synthesis and desymmetrisation of the anthracene-maleimide cycloadducts **90** have been investigated by a previous research group member. Results from the initial screening of the substrates and the catalysts, showed that the *B*-OMe catalyst **77** gave moderate yield and excellent selectivity of the desymmetrised product from the *N*-PMP substrate (Scheme 34). Encouraged by this result, an incomplete synthesis of pyrrolam A was pursued (Scheme 34).[76]



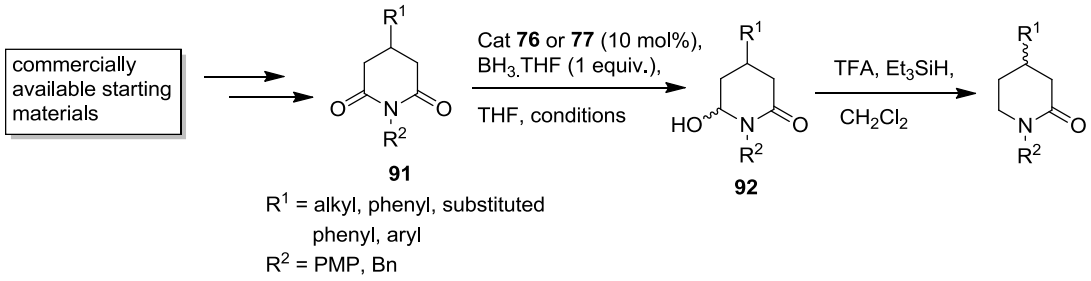
Scheme 34. Desymmetrisation of *meso* anthracene-maleimides

The initial part of this research was aimed at repeating and optimizing the synthesis and desymmetrisation of anthracene-maleimide cycloadducts **90**. Based on the results obtained, the total synthesis of pyrrolidizine alkaloid pyrrolam A would be re-visited. This research group has had successes in the past employing chiral anthracenes as stereocontrolling auxiliaries for organic transformations.[77, 78, 79, 80] It is hoped that the anthracene backbone directs the regioselectivity of subsequent *N*-acyl iminium transformations, directing attacks to the top face. Finally, retro Diels-Alder using flash vacuum pyrrolysis would furnish the target natural product (Scheme 35).



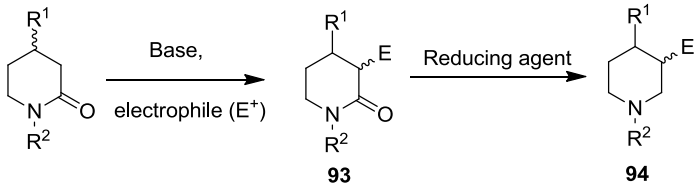
Scheme 35. Desymmetrisation of *meso* anthracene-maleimides and synthesis of pyrrolam A

The second part of the research work would target expanding the scope of the five-membered ring imides desymmetrisation methodology to six-membered ring glutarimides. As this is the first work of its kind in the research group, the initial attempt would be establishing an efficient route to the synthesis of various glutarimide substrates from cheap commercially available materials (Scheme 36). Attention would be paid to the synthesis of *N*-PMP and *N*-Bn substrates since their five-membered ring counterparts have been proved by earlier work to give better yields and selectivity. Once that has been accomplished, the enantioselective desymmetrisation of various achiral 3-substituted glutarimides **91** using oxazaborolidines **76** and **77** would be investigated, assessing the role of the substituent on the C-3 position and investigating the role of the nitrogen protecting groups, *N*-PMP and *N*-Bn, and any difference between the two oxazaborolidine catalysts. The hydroxy-lactams **92**, obtained from the reduction would be converted to the corresponding lactams by an established procedure for ease of analysis (Scheme 36).



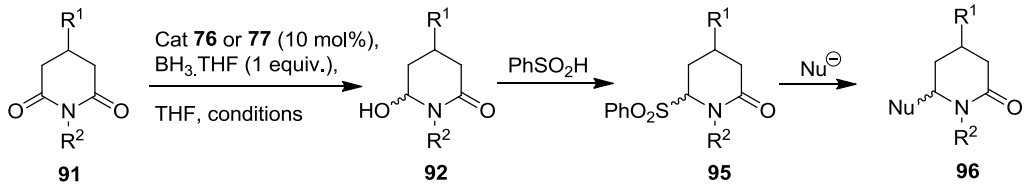
Scheme 36. Synthesis and desymmetrisation of *meso* glutarimides

After the desymmetrisation of the glutarimides has been successfully accomplished, the final part of the research work would be to try some functionalisation experiments on a representative chiral lactam. The first obvious experiment would be to try various C-3 functions on the lactam ring through an enolate chemistry that would furnish chiral 3,4-disubstituted 2-piperidinones **93** (Scheme 37). The stereogenic centre on C-4 is expected to control the stereochemistry of the newly formed C-3 stereogenic centre, as attack of the electrophile is expected to be from the opposite face. The 3,4-disubstituted 2-piperidinones **93** would then be reduced to chiral 3,4-disubstituted piperidines **94** which are important structural motifs in biologically active natural products and pharmaceuticals (Scheme 37).



Scheme 37. Synthesis of chiral 3,4-disubstituted piperidines

The synthesis of 4,6-disubstituted 2-piperidinones **96** would also be attempted by first converting the hydroxy-lactam **92** to a sulfonyl function which is known to be a good leaving group. The resultant 2-sulfonyl lactam **95** would then be made to undergo nucleophilic substitution with various nucleophiles to furnish the corresponding 4,6-disubstituted 2-piperidinones **96** (Scheme 38).



Scheme 38. Synthesis of chiral 4,6-disubstituted 2-piperidinones

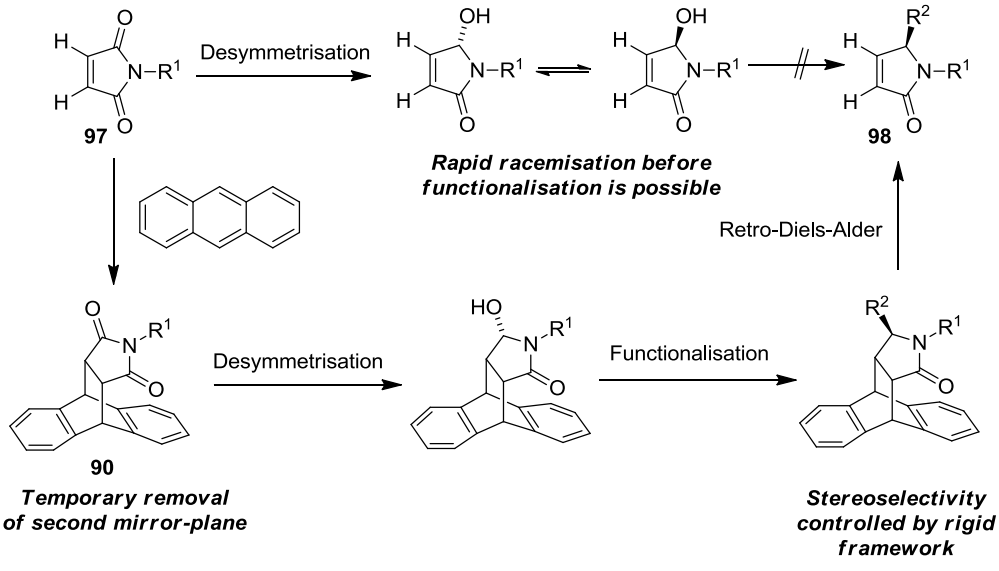
Chapter 2

Desymmetrisation of maleimides

2.1 Synthesis and desymmetrisation of anthracene maleimides

2.1.1 Background

Although there have been many reports on the reductive desymmetrisation of 3,4-disubstituted maleimides or succinimides, the desymmetrisation of un-substituted maleimides or succinimides has not been possible due to the tendency of the newly installed stereogenic centre to rapidly epimerise before functionalisation is achieved. A way to overcome this problem is by the temporary attachment of an anthracene template. Thus *N*-substituted maleimides **97** would undergo a Diels-Alder reaction with anthracene, the resultant anthracene-maleimide cycloadducts **90** subjected to enantioselective desymmetrisation and functionalisation, finally followed by a retro Diels-Alder to liberate the enantioenriched α,β-unsaturated lactam **98** (Scheme 39). Another advantage of this method is that the stereoselectivity of the functionalisation step has been shown by earlier reports from the research group to be enhanced by the anthracene template present in the intermediate before the final retro-Diels-Alder reaction.[77, 78]

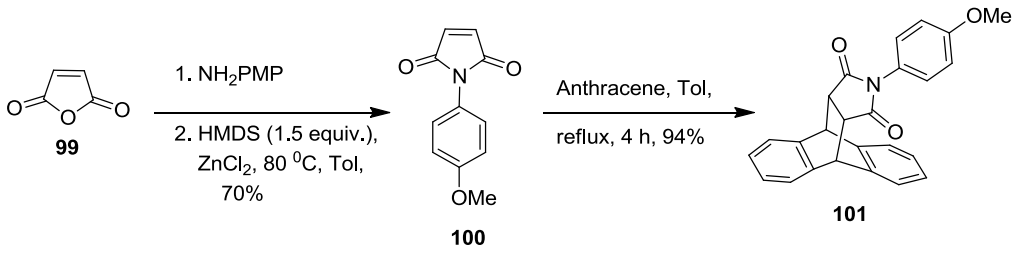


Scheme 39. Use of anthracene template for desymmerisation of *N*-substituted maleimides

2.1.2 Synthesis of anthracene-maleimide cycloadducts

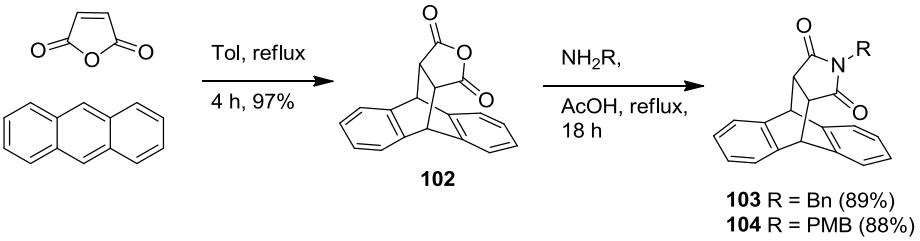
From previous desymmetrisation work, the first obvious candidate would be a substrate bearing an *N*-aryl group, since *N*-alkyl substrates give poor yields and lower enantioselectivity of the desymmetrised products.[76] The *p*-(methoxy)phenyl (PMP) group in particular was reported to give excellent enantioselectivity of the desymmetrised product. Moreover, the *N*-PMP group could be easily cleaved using CAN. However, a common feature of the *N*-PMP system was the tendency for over-reduction in the desymmetrisation step which diminished the yield.[76, 74] Previous studies showed that desymmetrisation of *N*-benzyl or *N*-*p*-(methoxybenzyl) protected *meso*-imides gave higher yields of the products but an enantiomeric excess of around 80%.[76, 74]

The *N*-PMP anthracene-maleimide cycloadduct **101** was synthesised, following a procedure adapted by a previous research group member, in two steps from commercially available maleic anhydride **99** (Scheme 40).[76] Treatment of maleic anhydride **99** with *p*-anisidine in the presence of HMDS and $ZnCl_2$ and heating under reflux in toluene for 4 hours afforded the *N*-protected maleimide **100** in 70% yield. The anthracene-maleimide cycloadduct **101** was accessed in 94% yield by heating under reflux a mixture of the maleimide **100** and anthracene in toluene for 4 hours (Scheme 40). The yield agrees closely with the previously reported yield of 97%.[76]



Scheme 40. Preparation of *N*-PMP cycloadduct

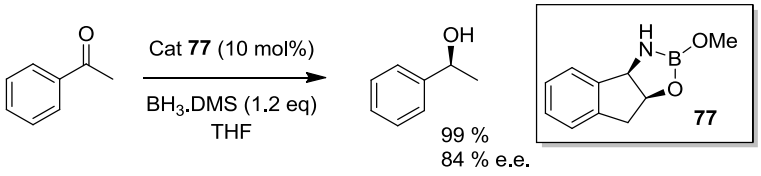
For the synthesis of *N*-Bn **103** and *N*-PMB **104** derivatives, the above method of preparing the corresponding maleimide followed by a Diels-Alder reaction to give the cycloadduct was reported to be low yielding. Instead, the reaction steps were reversed, starting with a Diels-Alder reaction between maleic anhydride **99** and anthracene to furnish the anhydride cycloadduct **102** in 97% yield. Treatment of the anhydride cycloadduct **102** with the corresponding amine gave the desired *N*-benzyl or *N*-PMB imide cycloadducts **103** or **104** in 89% and 88% yields, respectively, which are comparable yields with the previously reported work (Scheme 41).[76]



Scheme 41. Preparation of *N*-benzyl and *N*-PMB cycloadducts

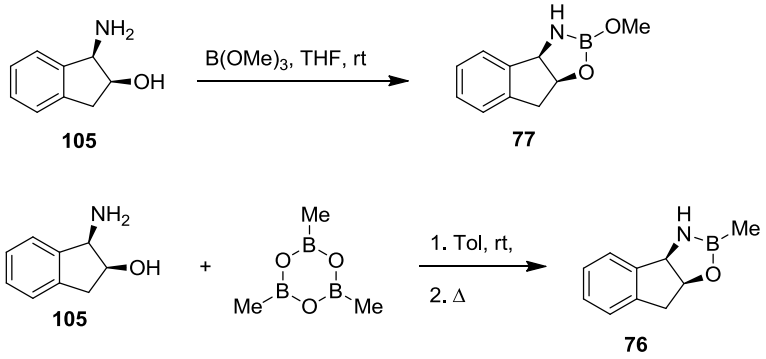
2.1.3 Desymmetrisation of anthracene-maleimide cycloadducts

Oxazaboroline catalysts derived from *cis*-aminoindan-2-ol **105** have been used by the Jones group as chiral catalysts for the asymmetric reduction of various prochiral ketones.[81, 82] The *B*-OMe catalyst **77** showed excellent yield and enantioselectivity in reduction of acetophenone (Scheme 42).[82]



Scheme 42. Enantioselective reduction of acetophenone using *B*-OMe catalyst

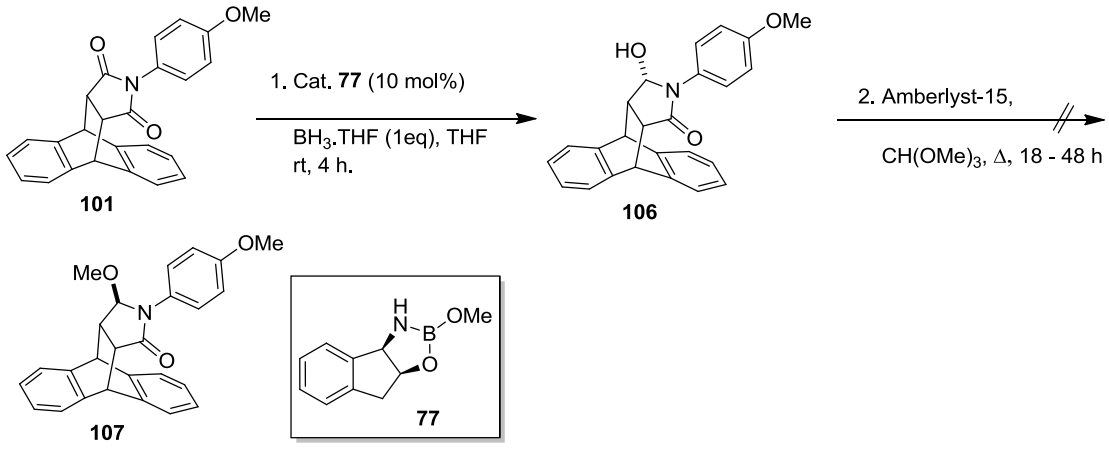
Both *B*-OMe **77** and *B*-Me catalysts **76** were shown to be superior in the desymmetrisation of *meso*-imides **65, 78 – 80** than the traditional CBS catalyst, giving excellent enantioselectivity with lower catalyst loadings.[73] The catalyst *B*-OMe **77** is easier to prepare and store than the analogous *B*-Me oxazaborolidine **76**, being readily prepared under nitrogen as a stock solution prior to use from trimethylborate and *cis*-1-aminoindan-2-ol **105** (Scheme 43). In contrast the *B*-Me oxazaborolidine **76** requires a series of azeotropic distillations under nitrogen to facilitate the condensation of *cis*-1-aminoindan-2-ol with trimethylboroxine. The solvent is then removed *in vacuo* to yield the oxazaborolidine which is diluted to a standard solution and used immediately (Scheme 43).



Scheme 43. Preparations of oxazaborolidines from *cis*-1-aminoindan-2-ol

As the aim of this stage of the project was to repeat and optimize the work by an earlier research group member, screening of the catalysts was unnecessary since it was established that the *B*-OMe catalyst **77** showed superiority over its *B*-Me counterpart in both yields and enantioselectivity in the desymmetrisation of the maleimide-anthracene cycloadducts **90**.[76] It was also established that the optimal catalyst loading was 10 mol% and BH_3.THF was the hydride source as there was no competing background reaction.[73] The initial desymmetrisation work would therefore focus on optimizing the reaction conditions and screening of *N*-aryl analogues.

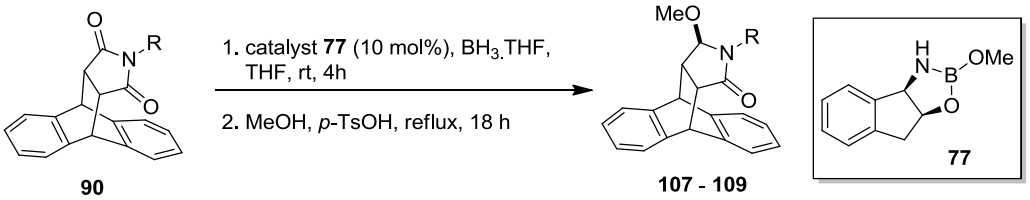
The first desymmetrisation experiment was carried out on the *N*-PMP cycloadduct **101** using oxazaborolidine **77** and employing BH_3.THF as borane source, monitoring the reduction step by TLC. At room temperature and 0 ^oC, formation of the hydroxy-lactam **106** product was observed which reached its highest concentration at 4 hours. Beyond 4 hours the concentration of the hydroxy-lactam started to diminish. Prior work showed the hydroxy-lactam was difficult to purify due to ease of epimerisation and an attempt was made to convert the crude hydroxy-lactam to the more stable methoxy aminal **107** by heating at reflux in trimethylorthoformate in the presence of Amberlyst-15® for 18 hours. Although a 48% yield of the methoxy compound **107** was previously obtained with above method, no conversion of the hydroxy-lactam was observed from the ^1H NMR spectrum of the crude after 18 hours. Extending the reaction time to 48 hours showed no appreciable conversion of the crude hydroxy-lactam (Scheme 44).



Scheme 44. Attempted desymmetrisation of the *N*-PMP cycloadduct 101

Pleasingly, when the reaction was repeated and the crude hydroxy-lactam was treated with 10 mol% of *p*-TsOH in methanol and heated at reflux for 18 hours, the ^1H NMR spectrum showed full conversion of the hydroxy-lactam and the methoxy compound **107** was obtained

as a single diastereomer in 61% yield over the two steps, which was a significant improvement on the earlier reported work (Table 10). The racemic methoxy-lactam was prepared using racemic catalyst prepared from equimolar mixture of (1*R*, 2*S*) and (1*S*, 2*R*) *cis*-1-aminoindan-2-ol. Both the racemic and enantiomeric compounds were successfully separated using chiral phase HPLC analysis, giving >99% ee for the enantiomeric reaction (Table 10, entry 1). The *N*-Bn and *N*-PMB methoxy cycloadducts **108** and **109** were obtained as single diastereomers employing the same conditions as above and also separated using chiral phase HPLC in 75% yield (95% ee) and 39% yield (97% ee), respectively. Comparing this method with the previously reported method of desymmetrisation, in which trimethylorthoformate in the presence of Amberlyst-15® was used in the second step reaction[76], this method showed a significant improvement in both yield and enantioselectivity of the products (Table 10). The only exception is in the yield of the *N*-Bn substrate which dropped from the previously reported 85% to 75%. However, the enantioselectivity increases from the previously reported 75% to 95% (Table 10, entry 2).



Scheme 45. Desymmetrisation of anthracene-maleimide cycloadducts

Table 10. Screening of substrates against *B*-OMe catalyst

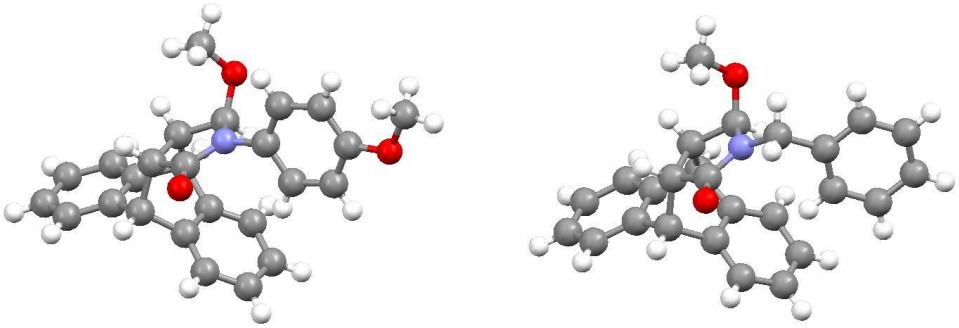
Entry	OMe compound		Yield (%)	ee (%)
1.	R = PMP	**107**	61 (48)	>99 (99)
2.	R = Bn	**108**	75 (85)	95 (75)
3.	R = PMB	**109**	39 (17)	97 (74)

Values in parenthesis represent results from the previously reported work by a research group member.

A solution of the substrate in THF was treated with the catalyst (10 mol%), then BH_3.THF and allowed to stir at room temperature for 4 hrs. After standard work up, the crude product was dissolved in MeOH, treated with *p*-TsOH.H_2O (10 mol%) and heated at a reflux for 18 hrs. The resultant methoxy compound was purified by flash column chromatography.

The stereochemistry of the newly formed stereogenic centre in the methoxy compounds was confirmed as (3*R*) from crystal structures of *N*-PMP methoxy cycloadduct **107** and *N*-Bn methoxy cycloadduct **108** performed by a previous group member clearly indicating that the

methoxy group attacked the *Re*-face of the intermediate iminium ion (Figure 11).[76] This proved the hypothesis which envisaged that the presence of the anthracene would direct attack of the nucleophilic methanol to the top face of the molecule leading to the formation of the (*R*)-methoxy aminals.



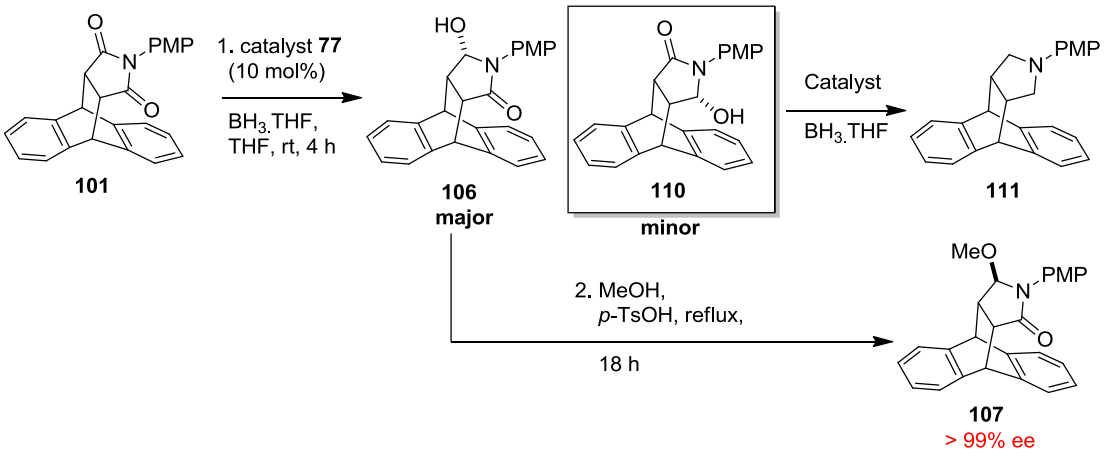
107 **108**

Figure 11. Crystal structures of methoxy cycloadducts 107 and 108

2.1.4 Stereoablative upgrade of enantioselectivity

As can be observed from table 9, the highest selectivity was recorded with the *N*-PMP substrate. However, a rapid conversion of the hydroxy-lactam intermediate to the over reduced pyrrollidine product **111** was observed during the reduction process, thereby confirming the earlier observation on such a substrate. While the crucial role of the nitrogen protecting groups in desymmetrisation of *meso* imides was investigated by the research group, the relationship between the excellent selectivity in *N*-PMP imides and the formation of over reduced product was never investigated. A possible explanation was that a stereoablative process might be operative in reduction process by selective reduction of one enantiomer thereby upgrading the enantiopurity of the product.

Stereoablation is an enantioselective chemical transformation whereby an existing stereocentre in an organic molecule is selectively destroyed.[83] A catalyst selectively reacts with one enantiomer or enantiotopic group in a racemic (or scalemic) mixture, thereby eliminating it from the mixture and leaving behind an enantioenriched material.[83] It was proposed that under the normal reduction conditions the *N*-PMP cycloadduct **101** was enantioselectively reduced to a scalemic mixture of the corresponding hydroxy-lactams **106** and **110** followed by selective reduction of the minor hydroxy-lactam enantiomer **110** to the pyrrolidine cycloadduct **111** (Scheme 46). The upgraded enantiopure material was then converted to the methoxy aminal **107**, essentially as a single enantiomer (Scheme 46).



Scheme 46. Stereoablative upgrade of ee

To investigate this hypothesis, an attempt was made to isolate the hydroxy-lactam intermediate **106**, which prior work showed was not isolable in appreciable yield. However, when the *N*-PMP cycloadduct was reduced under standard conditions using the (1*R*, 2*S*) version of the *B*-OMe catalayst **77**, the pure hydroxy-lactam **106** was isolated in 60% yield as a single diastereomer (Scheme 47). Comparison of the coupling constants between C-3 proton and C-4 proton of the hydroxy-lactam (J = 7.9) with that of the methoxy aminal **107** (J = 1.2) suggests a dihedral angle of around 0^{o} between C-3 and C-4 protons in the hydroxy-lactam. This shows that diastereomer **106** of the hydroxy-lactam was the major product. As expected from the CBS Corey model, the oxazaborolidine catalyst will preferentially coordinate to the carbonyl oxygen with *B*-OMe group away from the nitrogen substituent (R_L) to minimize the steric interaction. This would lead to two possible intermediates A and B (Figure 12) in which only the intermediate B can the H^- be delivered from the less sterically hindered *Re*-face of the molecule producing the (3*S*)-enantiomer of the hydroxy-lactam intermediate (Figure 12).

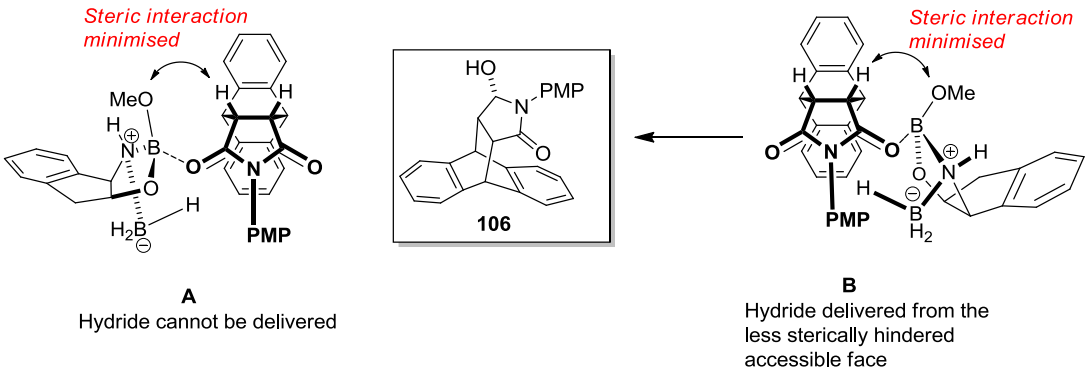
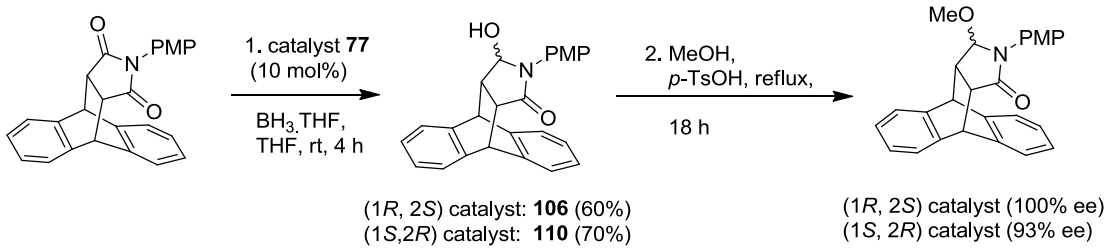


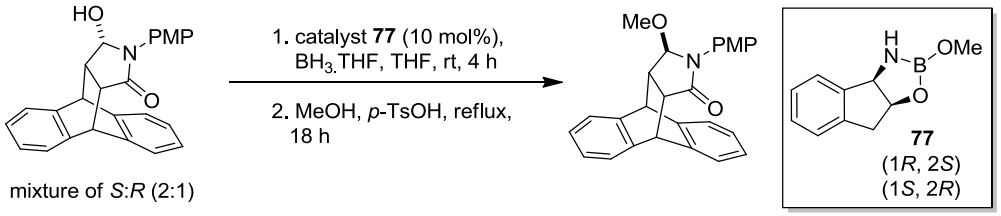
Figure 12. Model for the stereoselectivity of *N*-PMP imide reduction

Repeating the reduction with (1*S*, 2*R*) version of the same catalyst led to isolation of the hydroxy-lactam **110** in 70% yield as a single diastereomer (Scheme 47). To confirm the high selectivity of both versions of the catalyst on the *N*-PMP imide, a portion of each enantiomer of the hydroxy-lactam was converted to the methoxy aminal, giving quantitative yields of the corresponding methoxy compounds in 100% ee and 93% ee respectively (Scheme 47).



Scheme 47. *N*-PMP imide reduction with two versions of *B*-OMe catalyst

A scalemic homogenous mixture of the two enantiomers of the hydroxy-lactam was prepared as a 2:1 ratio of *S* and *R* enantiomers. A portion of the scalemic mixture was quantitatively converted to methoxy compound and the ee of the resultant scalemic methoxy compound was measured. A sample of the scalemic mixture of hydroxy-lactam was then subjected to reduction with (1*R*, 2*S*) version of the *B*-OMe catalyst followed by methylation under standard reaction conditions. The same procedure was repeated with the (1*S*, 2*R*) version of the catalyst. The yield and ee of the methoxy compounds were recorded, and the experiment carried out in duplicate. The results are summarised in table 11.



Scheme 48. Stereoablation experiment

Table 11. Results from stereoablation experiment

Entry	Scalemic hydroxy-lactam ee (%)[a]	Catalyst	Yield (%)	ee (%)
1.	34 (35)[b]	(1*R*, 2*S*)	60 (67)[b]	56 (54)[b]
2.	34 (35)[b]	(1*S*, 2*R*)	76 (74)[b]	33 (32)[b]

[a] Based on derivatisation of a sample of scalemic hydroxy-lactam to the methoxy-lactam and HPLC analysis of this compound. [b] Values in parenthesis represent results from second experiment.
A solution of the scalemic mixture of the hydroxy-lactam was treated with the catalyst (10 mol%), then BH_3.THF and allowed to stir at room temperature for 4 hrs. After standard work up, the crude product was dissolved in MeOH, treated with *p*-TsOH.H_2O (10 mol%) and heated at a reflux for 18 hrs. The resultant methoxy compound was purified by flash column chromatography.

When a representative sample from the scalemic hydroxy-lactam mixture (34% ee) was subjected to reduction with (1*R*, 2*S*) enantiomer of the *B*-OMe catalyst **77** followed by subsequent methylation, the methoxy compound was obtained in 60% yield and 56% ee (Table 11, entry 1). This result showed a 40% conversion of the hydroxy-lactam to the over reduced pyrrolidine occurred in presence of the catalyst. More importantly, there was an upgrade in the ee of the scalemic methoxy compound from 34% to 56%, clearly showing a selective reduction of one enantiomer of the hydroxy-lactam (presumably the minor enantiomer) to the pyrrolidine compound.

On the other hand, when the reaction was repeated with (1*S*, 2*R*) version of the catalyst, a 76% yield and 33% ee of the methoxy compound was obtained (Table 11, entry 2). This result shows that although there was a conversion of the hydroxy-lactam to the pyrrolidine product, the (1*S*, 2*R*) catalyst does not discriminate between the two enantiomers of the hydroxy-lactam. When the experiments were repeated, a near identical series of results were obtained (Table 11, values in parenthesis) proving the validity of the initial result.

2.1.5 Conclusion

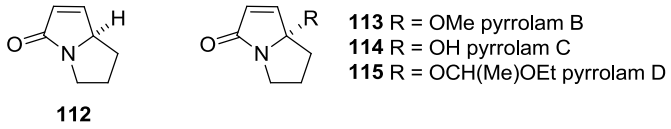
By using a literature procedure adopted by an earlier research group member, three *N*-protected anthracene-maleimides were synthesised in good yields which quite agreed with the previously reported work. These maleimide cycloadducts were subjected to desymmetrisation using *B*-OMe oxazaborolidine catalyst derived from *cis*-aminoindan-2-ol. Results from the desymmetrisation showed that the catalyst gave moderate yield and high enantioselectivity of the desymmetrised products. Optimization of the second step of the desymmetrisation reaction led to significant improvement in both yield and enantioselectivity of the desymmetrised products. Desymmetrisation of the *N*-PMP substrate gave one enantiomer of the product but proceeded by rapid conversion of the hydroxy-lactam intermediate to the over-reduced pyrrolidine compound when the reduction step was monitored by TLC. Investigation on the role of the catalyst in the over reduction of the *N*-PMP substrate revealed an *in-situ* stereoablative process by the (1*R*, 2*S*) version of *B*-OMe catalyst serving to upgrade the enantioselectivity. This process has never before been reported with oxazaborolidine catalysed reductions.

Chapter 3

Synthesis of pyrrolam A

3.1 Investigation towards the synthesis of pyrrolam A

Pyrrolams A-D **112 – 115** are pyrrolizidine alkaloids (Figure 13) and were first isolated in 1990 from the bacterial strain *Streptomyces olivaceus* (strain Tu 3082) by Zeeck and co-workers by elution with methanol from Amberlite XAD-16 resin followed by further purification via column chromatography.[84] Pyrrolam A was shown to have herbicidal activity against wheat and rice seedlings and anti-fertility activity, causing damage to fertilized fish (*Brachydanio rerio*) eggs at a concentration of 5 µg / mL but was inactive against Gram-positive and Gram-negative bacteria, fungi, moulds and tumour cell lines.[84]

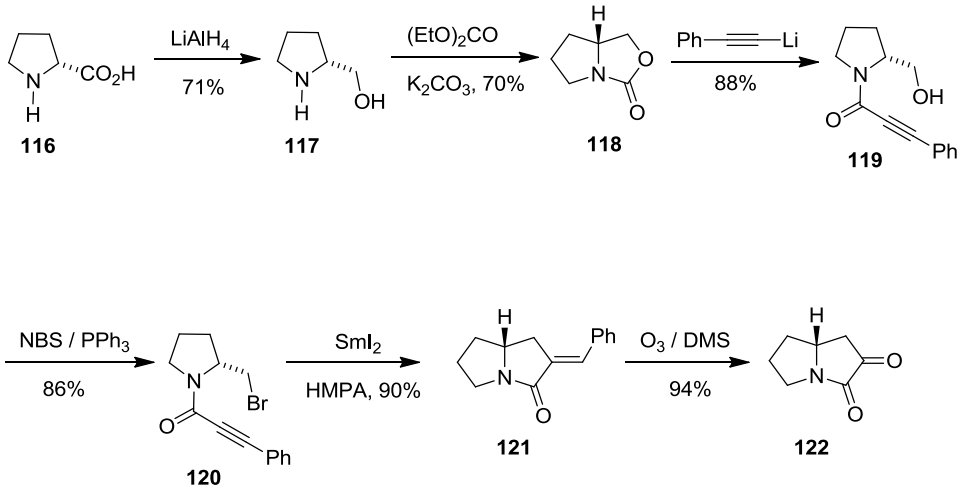


112

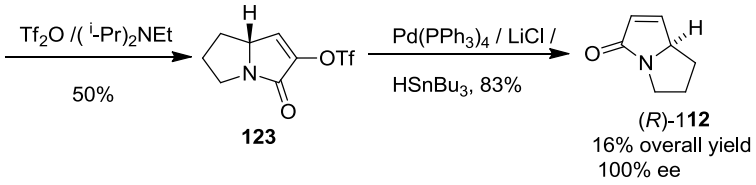
113 R = OMe pyrrolam B
114 R = OH pyrrolam C
115 R = OCH(Me)OEt pyrrolam D

Figure 13. Pyrrolams A – D

Since its initial isolation, as many as ten syntheses of pyrrolam A have been reported, most of which rely on chiral pool strategies depending on the pre-existing stereogenic centre of proline **116** or a derivative. The first total synthesis of pyrrolam A was reported in 1996 by Ohta and co-workers.[85] A chiral pool strategy was employed starting from unnatural (*R*)-proline and obtaining pyrrolam A in 7 steps. The key step in this synthesis was the SmI_2-mediated cyclisation of an alkynyl amide **120** to access the pyrrolidinone core. However, the use of expensive unnatural proline as a starting material is the major setback (Scheme 49).

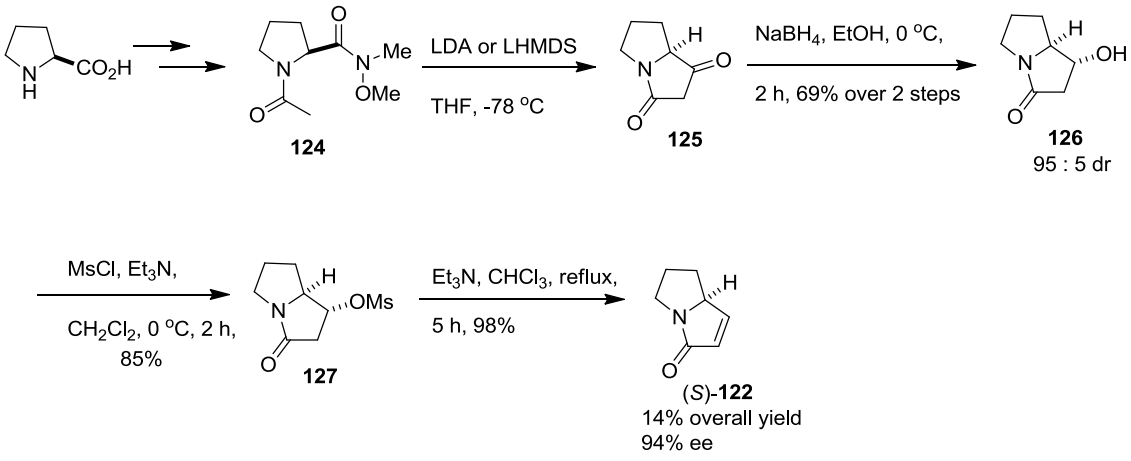


116 **117** **118** **119** **120** **121** **122**



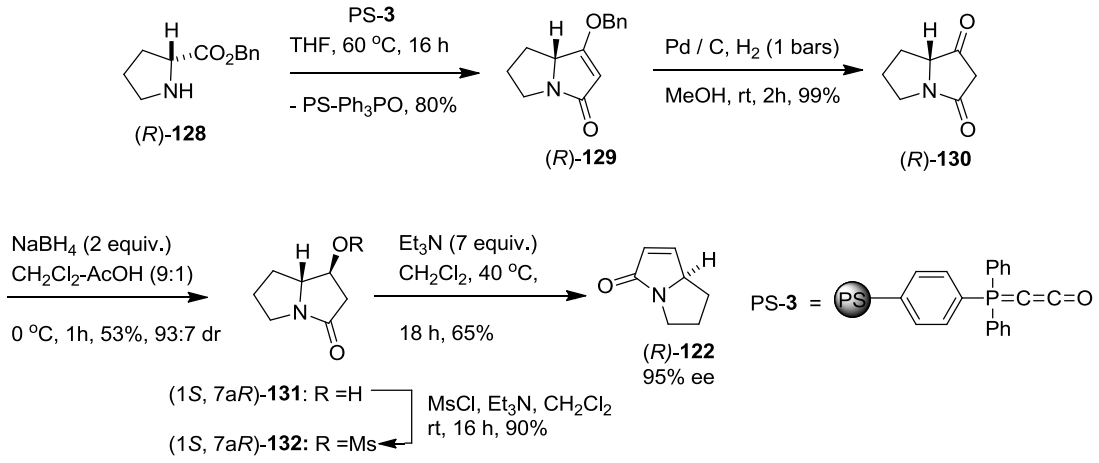
Scheme 49. Ohta's synthesis of pyrrolam A

The second synthesis reported by Murray *et al*. uses an LDA mediated *N*-acyl anion cyclisation process of a proline derivative **124** to give the corresponding dione **125**. This was reduced in 95:5 dr using $NaBH_4$ / EtOH to give the *exo* lactam intermediate **126** in 90% de, which afforded (*S*)-pyrrolam A in two more steps. However, this synthesis has slightly lower yield and ee than the previously reported synthesis (Scheme 50).[86]



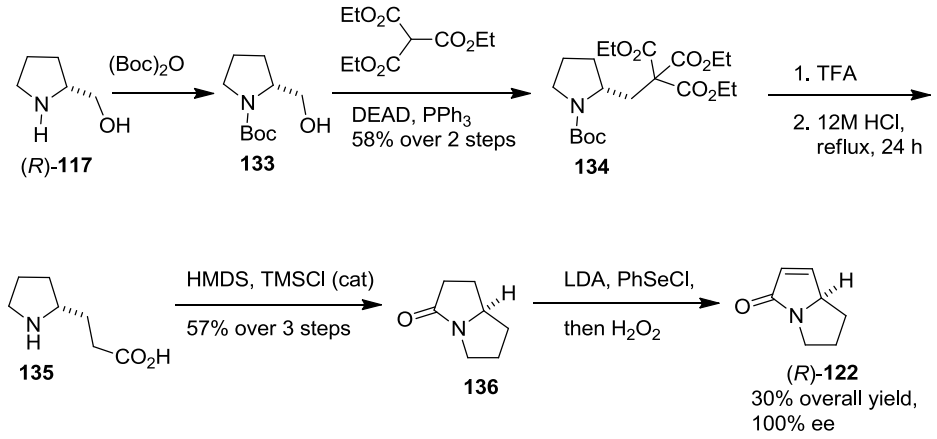
Scheme 50. Murray's synthesis of pyrrolam A

The synthesis by Schobert and Wicklein involved a domino Wittig reaction of the ylide $Ph_2P{=}C{=}C{=}O$ immobilized on polystyrene resin with the benzyl proline derivative **128**, prepared from D-proline, as the key step (Scheme 51). The unprotected amino group of the benzyl proline **128** was added across the C=C bond of the phosphacumulene ylide followed by a subsequent intramolecular Wittig olefination of the acyl ylide to give the pyrrolizidine **129**. Hydrogenative debenzylation of the pyrrolizidine **129** furnished dione **130**, which on subsequent reduction using sodium borohydride, followed by mesylation, gave sulfonate **132**. Heating the sulfonate **132** with triethylamine afforded (*R*)- pyrrolam (Scheme 51).[87]



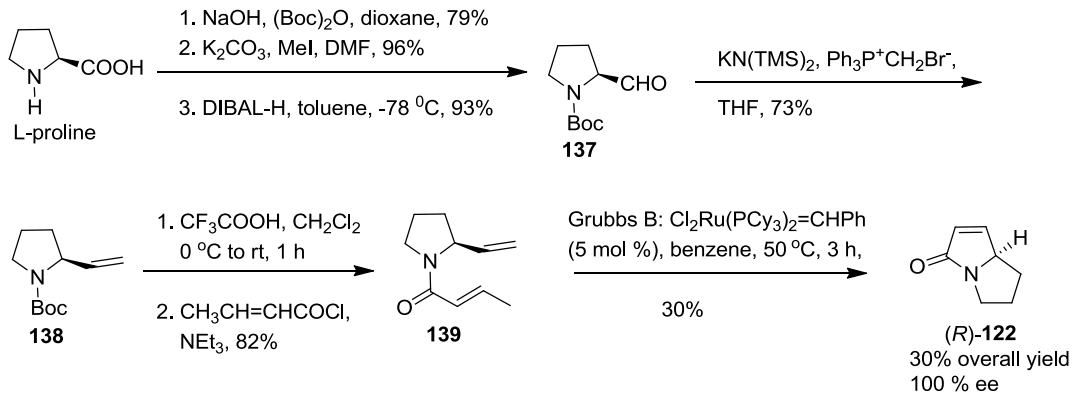
Scheme 51. Schobert's synthesis of pyrrolam A

A synthesis by Palmisano and co-workers again employs the chiral pool strategy from an unnatural proline derivative **117**. The key intermediate was accessed via Mitsunobu coupling of *N*-Boc protected prolinol **133** with a tricarboxylate. Pyrrolam A was accessed in further 5 steps in an overall yield of 30% and a single enantiomer of the compound (Scheme 52).[88]



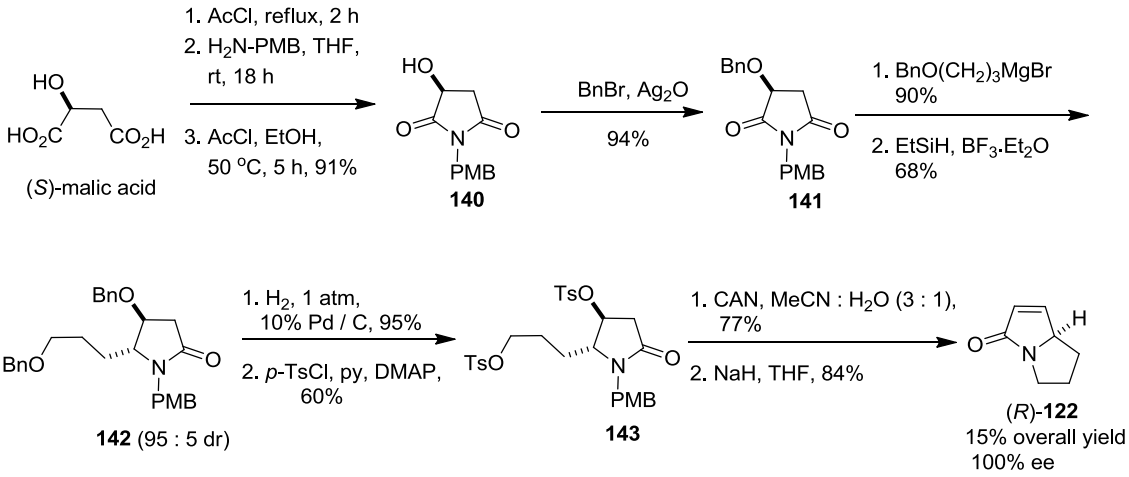
Scheme 52. Palmisano's synthesis of pyrrolam A

A synthesis by Nagakawa and co-workers uses L-proline in a chiral pool approach which is converted in a 6 step sequence to a chiral diene **139**. Ring closing metathesis (RCM) of the chiral diene **139** using Grubbs' catalyst was employed in the last stage of the synthesis to give pyrrolam A in 30% overall yield and 100% ee (Scheme 53).[89, 90]



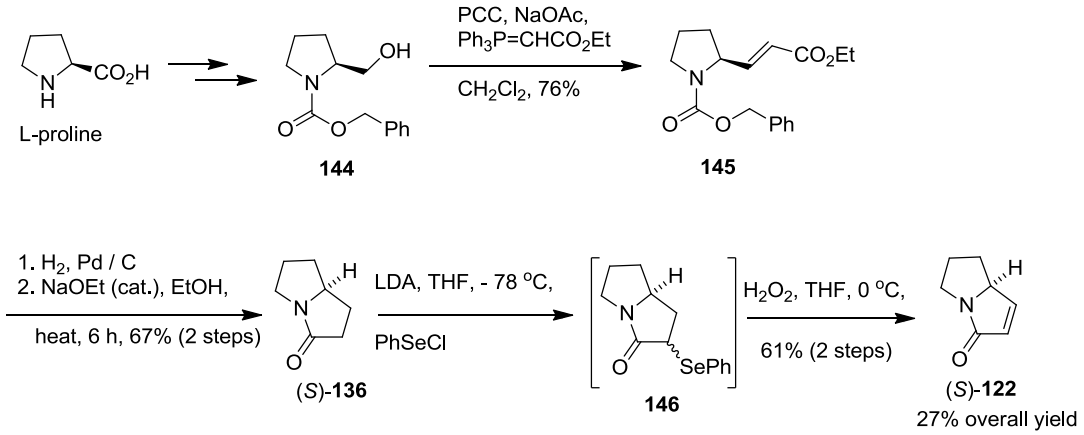
Scheme 53. Nagakawa's synthesis of pyrrolam A

A different chiral pool strategy was adopted by Huang *et al*., this time utilising relatively cheap (*S*)-malic acid as a starting material. However, the synthesis was slightly longer and gave a reduced overall yield (Scheme 54).[91]



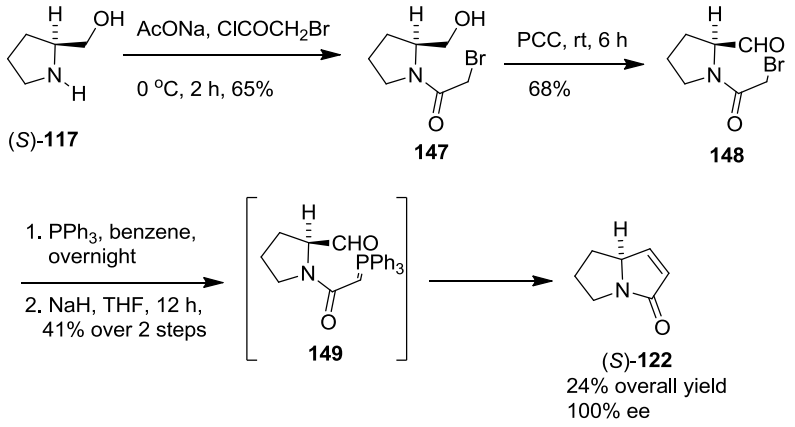
Scheme 54. Huang's synthesis of pyrrolam A

Two total syntheses of pyrrolam A were reported by Tilve and co-workers both of which are chiral pool and employed a Wittig reaction as the key step. The first one used L-proline which was converted to *N*-Cbz-L-prolinol **144** by a known literature procedure. The alcohol was treated with PCC/NaOAc and phosphorane in one pot to give α,β-unsaturated ester **145**. Deprotection of **145** and double bond reduction, followed by cyclization under basic condition (cat. NaOEt) furnished dihydropyrrolam **136**. A one pot selenium addition/elimination process delivered (*S*)-pyrrolam A (Scheme 55).[92]



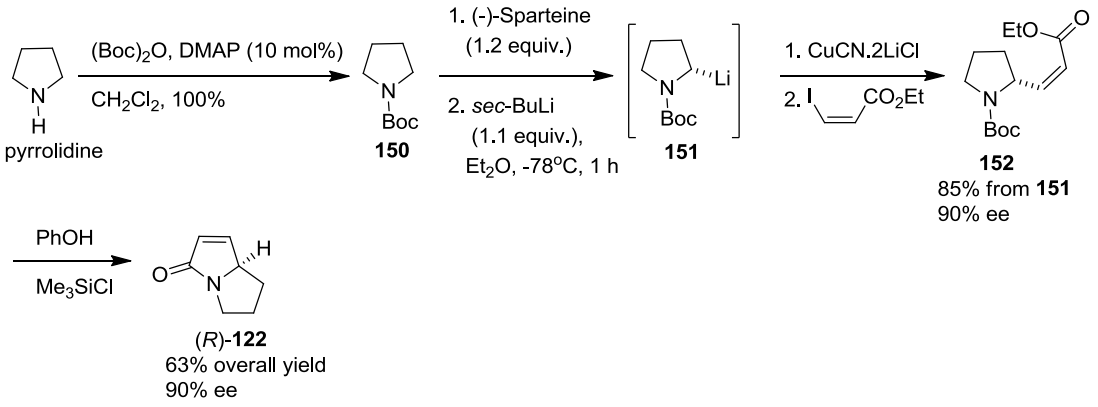
Scheme 55. Tilve's synthesis of pyrrolam A (I)

The second synthesis by Tilve also employs a chiral pool strategy, using (*S*)-prolinol **117**. The key reaction is an intramolecular Wittig reaction of a phosphorane **149** generated *in situ* from (*S*)-*N*-(bromoacetyl)prolinal **148**. The synthesis took 5 steps with an overall yield of 24% (Scheme 56).[93]



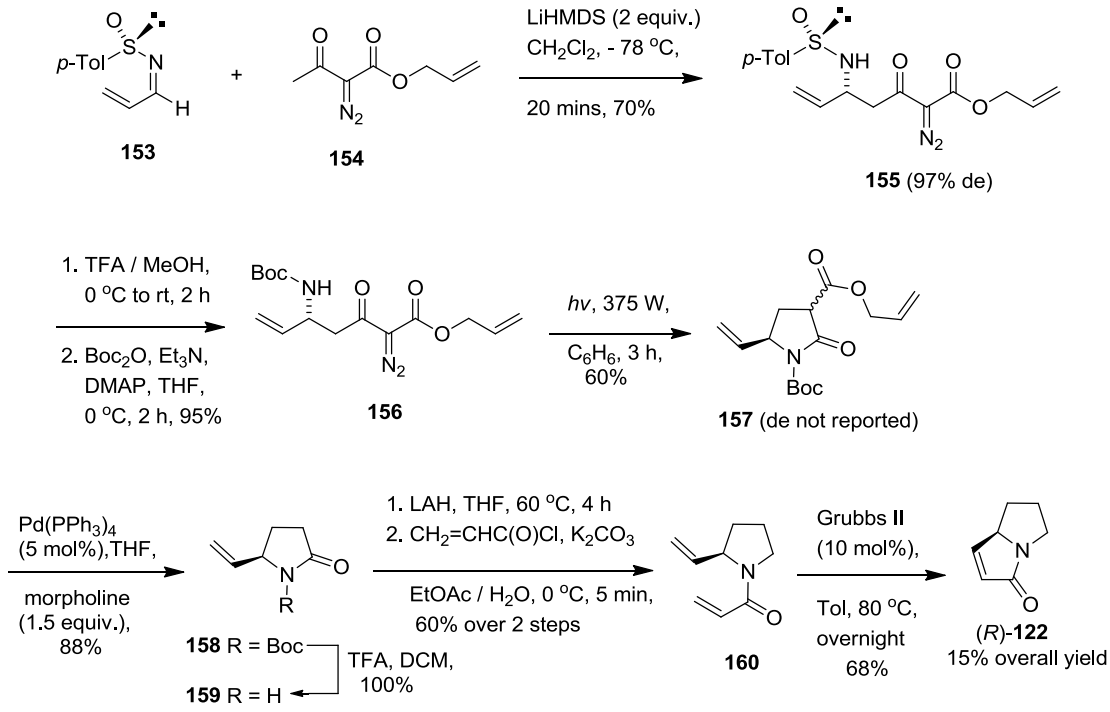
Scheme 56. Tilve's synthesis of pyrrolam A (II)

There are only two non-chiral pool methods of total synthesis of pyrrolam A reported in the literature. The first one, reported by Snyder and co-workers used pyrrolidine as a starting material. The key step in this synthesis was the formation of a chiral organolithium **151** by asymmetric deprotonation of *N*-protected pyrrolidine **150** in Et_2O. This allowed access to pyrrolam A in 3 steps from the starting material in a remarkable overall yield of 63% and 90% ee (Scheme 57).[94]



Scheme 57. Snyder's asymmetric synthesis of pyrrolam A

The latest synthesis of pyrrolam A was by Wang and co-workers reported in 2010.[95] The synthesis involved a diastereoselective nucleophilic addition of the lithium enolate of an α-diazoacetoacetate **154** to a chiral *N*-sulfinylimine **153** to afford δ-*N*-sulfinylamino α-diazo β-ketoester **155** in 70% yield with 97% de. Removal of the *N*-sulfinyl group followed by N-protection gave the N-protected pyrrolidinone **156**, which underwent a photo-induced Wolff rearrangement to the oxo-vinylpyrrolidinone **157**. The (*R*)-pyrrolam A was obtained in a further four steps sequence involving Pd-catalysed deallyloxydecarbonylation and a final ring-closing metathesis (Scheme 58).[95]



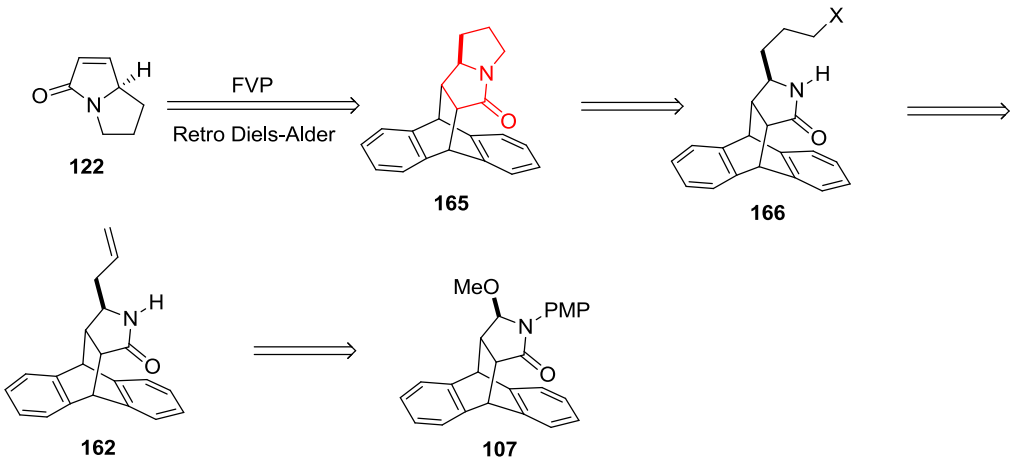
Scheme 58. Wang's synthesis of pyrrolam A

As can be seen all but two reported syntheses of pyrrolam A rely heavily on chiral pool strategy utilizing proline or its derivative, or in one case a suitable amino acid, to transfer the chirality in those molecules to the target compound. Another feature of the syntheses is the reliance on the Wittig olefination or Grubb's ring-closing metathesis for the construction of the lactam-conjugated double bond in the pyrrolizidin-3-one ring. A completely different approach to the synthesis of pyrrolam A, utilizing enantioselective desymmetrisation of *meso* maleimide and avoiding the traditional olefin metathesis would prove the efficiency and wide application of desymmetrisation methodologies in the asymmetric synthesis of natural products.

3.2 Synthesis of pyrrolam A

The starting desymmetrised material for the synthesis of pyrrolam A was the methoxy *N*-PMP maleimide **107** because results from the screening of the nitrogen protected imides **101**, **103** & **104** showed the highest selectivity, a vital criterion for the synthesis, was obtained from the desymmetrisation of the *N*-PMP imide **101** (Table 9). Moreover a reasonable yield of 61% of the desymmetrised methoxy compound **107** was not too far away from its close candidate, the *N*-Bn methoxy compound **108** which was obtained in 75% yield, but 95% ee (Table 9). It was hoped that the selectivity of transformations throughout the synthesis would be controlled by the presence of the anthracene allowing any nucleophilic approach from the top face only, thus obtaining the pyrrolam A in high enantioselectivity.

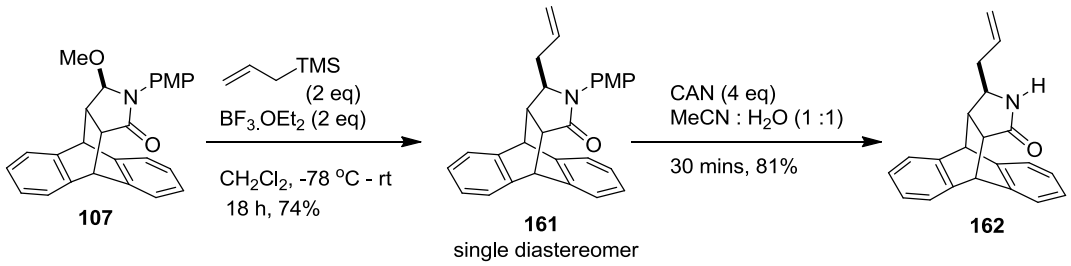
It was envisioned that pyrrolam A **122** should be accessible from the cycloadduct **165** by a retro Diels-Alder reaction (Scheme 59). The synthesis would therefore require accessing the pyrrolizidin-3-one ring in the bicyclic compound **165** with the right stereochemistry on the bridge carbon. This would be obtained by cyclisation of the allyl moiety in compound **162** through functional group manipulation **166** (Scheme 59).



Scheme 59. Retrosynthesis of pyrrolam A

Although the forward synthesis to the above route was initially pursued by a previous group member,[76] some steps were characterised by low yield of products, and pyrrolam A was not isolated. The synthesis would therefore be re-visited, optimizing reaction conditions to get maximum yield of products. More importantly, it was hoped that the total synthesis of the target compound would be accomplished and pyrrolam A would be isolated in an enantiopure form and in reasonable overall yield.

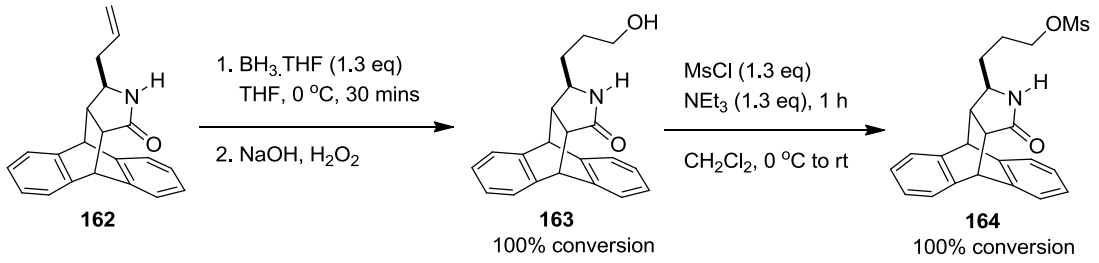
The forward synthesis started from treatment of methoxy cycloadduct **107** with allyl trimethylsilane in the presence of boron trifluoride which gave the allyl substituted lactam **161** as a single diastereomer in 74% yield.[69] It was expected that the anthracene would cause the attack of the nucleophilic allyl moiety to come from the *Re*-face, producing the (3*R*)-isomer of the *N*-PMP allyl lactam. From the ^{1}H NMR spectrum of the compound obtained after purification, the NC*H* proton and the C-4 proton have a coupling constant of J = 3.0, which is close to that observed with the *N*-PMP methoxy compound **107** suggesting a (3*R*)-isomer of the *N*-PMP allyl product. From here the amide was cleanly deprotected using CAN, giving the deprotected amide **162** as a single diastereomer in 81% yield.[96] Although the NC*H* proton in this compound appears as a multiplet around δ_H 3.08 – 3.12 ppm, the C-4 proton coupled with the NC*H* proton has a coupling constant, J = 3.2, showing a (3*R*)-stereochemistry (Scheme 60).



Scheme 60. Formation of allyl cycoadduct 161 and lactam 162

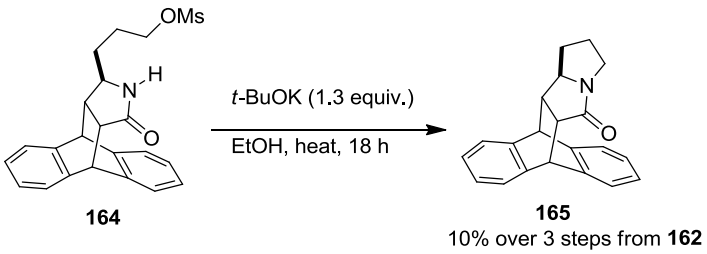
The deprotected lactam **162** was hydroborated by treatment with BH_3.THF followed by NaOH / H_2O_2 to yield the hydroxy-cycloadduct **163**. Previous work showed that this compound was very difficult to purify by both flash chromatography and recrystallisation.[76] Hence, the material was taken forward without purification. The ^{1}H NMR spectrum of the crude material showed 100% conversion of the lactam **162**. The absence of a terminal methyl signal expected to appear as a doublet around δ_H 1.10 ppm shows the complete regioselectivity of the hydroboration oxidation, producing selectively the primary alcohol. The hydroxy-cycloadduct **163** was mesylated by treatment with methane sulfonyl chloride and triethylamine to give the mesylated cycloadduct **164**. Although there was 100%

conversion from the ^{1}H NMR spectrum of the crude material the compound was again taken forward due to difficulties in purification (Scheme 61).



Scheme 61. Formation of hydroxy compound 163 and mesyl compound 164

Cyclisation of the crude mesylated compound **164** was achieved by the use of excess potassium *t*-butoxide in ethanol at reflux to give the cyclic compound **165**.[76] Although report from the previous work showed 36% yield of the bicyclic lactam **165** was achieved over the 3 steps, only 10% yield of the compound was repeatedly obtained over 3 steps using these reaction conditions (Scheme 62).

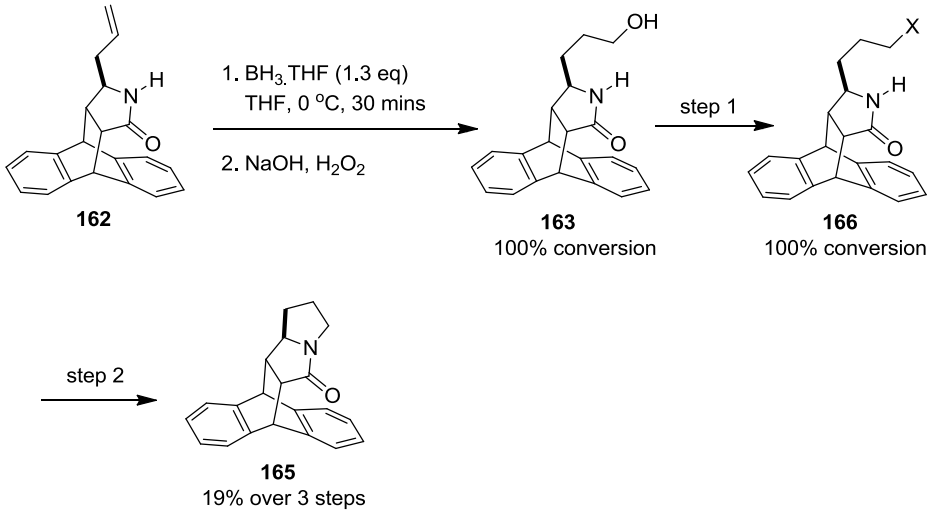


Scheme 62. Formation of bicyclic compound 165

Optimisation experiments were carried out on the last 2 steps in an effort to increase the yield of the bicyclic product **165**. Tosylation of the crude alcohol **163** was carried out in the presence of NEt_3 under the same conditions applied previously, and then cyclised using *t*-BuOK, applying conditions used as previously. Unfortunately only 5% of the bicyclic compound was obtained (Table 12, entry 2). Another tosylation of compound **163** was repeated using NEt_3 / DMAP followed by cyclisation of the crude product with DABCO and DBU, respectively. No conversion of the tosylated compound was observed with DABCO while an improved yield of 17% over 3 steps was obtained with DBU (Scheme 63; Table 12, entries 3 and 4).

When the crude hydroxy compound **163** was mesylated using NEt_3 / DMAP followed by cyclisation of the crude product with DABCO and DBU, a yield of 20% over 3 steps was recorded with DBU, while again no conversion of the mesylated compound was observed from the ^{1}H NMR spectrum when treated with DABCO (Table 12, entries 5 and 6).

In another optimisation attempt, the alcohol **163** was converted to the corresponding iodide compound using Appel reaction conditions and the crude iodo compound was treated with *t*-BuOK, DABCO and DBU respectively. Cyclisation with DBU gave a yield of 15% over 3 steps. The other two bases gave lower yields than that recorded for DBU (Table 12, entries 7, 8 and 9). Single diastereoselectivity was observed in all cases of the optimization.



Scheme 63. Optimisation experiment

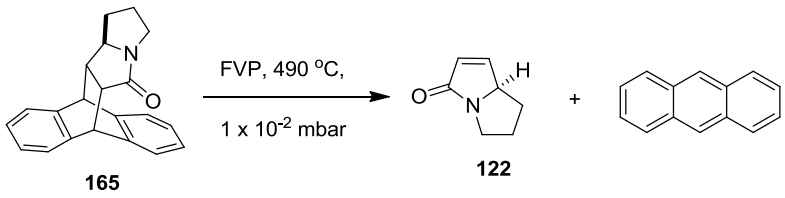
Table 12. Optimisation experiments for bicyclic compound 165

Entry	Step 1[a]	Step 2[b]	Yield of **165** over 3 steps (%)
1.	MsCl (1.3 eq), NEt_3 (2.5 eq)	*t*-BuOK (1.3 eq.), EtOH	10
2.	TsCl (1.3 eq), NEt_3 (2.5 eq),	*t*-BuOK (1.3 eq), EtOH	5
3.	TsCl (1.3 eq), NEt_3 (2.5 eq), DMAP (10 mol%)	DABCO (1.3 eq), EtOH	-
4.	TsCl (1.3 eq), NEt_3 (2.5 eq), DMAP (10 mol%)	DBU (1.3 eq), EtOH	17
5.	MsCl (1.3 eq), NEt_3 (2.5 eq) DMAP (10 mol%)	DABCO (1.3 eq), EtOH	-
6.	MsCl (1.3 eq), NEt_3 (2.5 eq) DMAP (10 mol%)	DBU (1.3 eq), EtOH	20
7.	PPh_3 (1.25 eq), I_2 (1.25 eq), imidazole (1.25 eq)	*t*-BuOK (1.3 eq), EtOH	12
8.	PPh_3 (1.25 eq), I_2 (1.25 eq), imidazole (1.25 eq)	DABCO (1.3 eq), EtOH	-
9.	PPh_3 (1.25 eq), I_2 (1.25 eq), imidazole (1.25 eq)	DBU (1.3 eq)	15

a. CH_2Cl_2, 1 h, -10 °C. b. reflux, 18 h.

To form pyrrolam A **122** from the bicyclic lactam **165**, a retro [4 + 2] cycloaddition was required. To achieve this, a flash vacuum pyrolysis (FVP) technique was utilised (Scheme 64).[77] This process involves the vapourisation of the cycloadduct in an oven under reduced

pressure, followed by further heating in a furnace where the retro Diels-Alder reaction occurs. Finally, the vapourised material is quickly cooled by passing through a Vigreux column where the anthracene is expected to be trapped, and then further cooled via liquid nitrogen in the product trap where pyrrolam A **122** is expected to be collected (Figure 14).



Scheme 64. Retro Diels-Alder to provide pyrrolam A

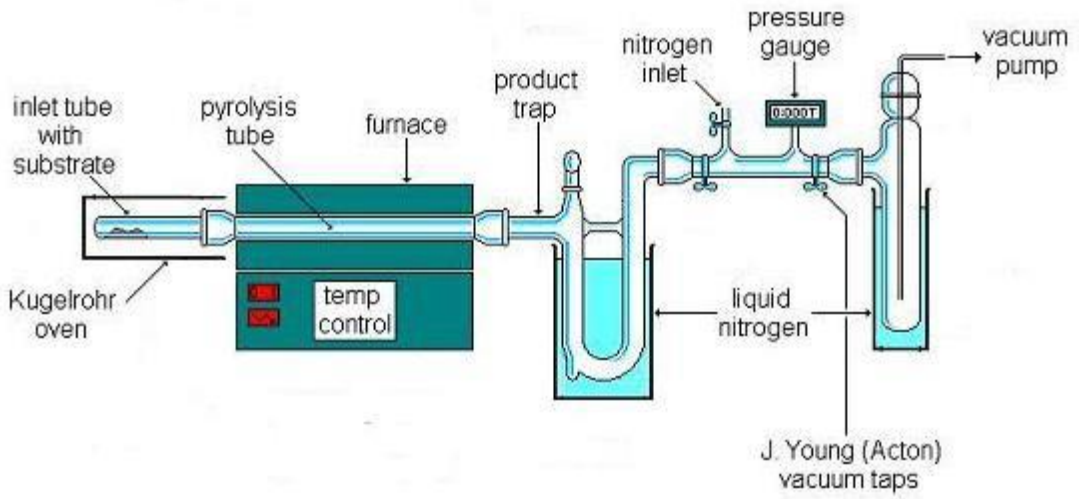


Figure 14. Flash vacuum pyrolysis apparatus (courtesy of Hamish M^{c}Nab)

Conditions were tested for flash vacuum pyrolysis of the cycloadduct **165**. The inlet temperature was kept at 226 ^{o}C (melting point of the cycloadduct) since temperatures below that resulted in an inefficient vapourisation of the material and the pressure set at 1 × 10^{-2} mbar. The initial temperature of the furnace was set at 560 ^{o}C which initiated the retro Diels-Alder producing 43 mg of anthracene in the u-tube from 100 mg of starting material. However this temperature led to the decomposition of the remainder of the material. A similar observation was made when the temperature was lowered to 520 ^{o}C (Table 13, entries 1 & 2). At a temperature of 510 ^{o}C a mixture of anthracene and starting material was obtained alongside some decomposed material in the u-tube. Although some peaks of pyrrolam A were observed in the crude ^{1}H NMR spectrum, the pure material was not successfully isolated (Table 13, entry 3). The best result was obtained when the furnace temperature was set at 490 ^{o}C which led to the isolation of the pure material in 70% yield and no decomposition of material was observed. A similar result was obtained when the FVP was repeated at the same

temperature with different weight of the starting material (Table 13, entries 4 & 5). When the temperature was further lowered to 470 ^{o}C a retro Diels-Alder failed to occur returning only the starting material in the u-tube, indicating the narrow range of temperature at which the retro-Diels would occur.

To obtain the racemic product needed for optimizing the HPLC conditions, the synthesis was repeated with the racemic methoxy compound prepared from the racemic version of the catalyst. Both the racemic and the enantiomeric pyrrolam A materials were successfully separated by chiral phase HPLC analysis, giving the enantiomeric product in a 94% ee.

Table 13. Flash vacuum pyrolysis of cycloadduct 165

Entry	Wt. of material (mg)	Furnace temp. (^{o}C)	Time (min)	Recovered crude (mg)	Starting material (mg)	Wt. of anthracene (mg)	Wt. of pyrrolam A (mg)
1.	100	560	20	74	-	43	Decomposition
2.	300	520	30	288	-	107	Decomposition
3.	177	510	20	151	88	12	Decomposition
4.	150	490	30	124	33	45	43 (70% Yield)
5.	200	490	30	195	60	81	56 (69% Yield)
6.	150	470	40	130	130	-	-

Inlet temperature of 226 ^{o}C at a pressure of 1×10^{-2} mbar. Reactions performed over a period of 20–40 mins until no further sublimation of the starting material was observed.

3.3 Conclusion

The total synthesis of (-)-(*R*)-pyrrolam A **122** was accomplished in six steps from the desymmetrised material **107** in 8.4% overall yield and 94% ee. The slight drop in the ee of product compared to starting material (94% from 99%) is probably due to the stability of the product as reported in previous isolation and synthetic studies on this molecule.[97] The overall yield is also hampered by the low yield obtained in the cyclisation step which is probably due to competing reactions. This illustrates the synthetic potentials of the desymmetrisation of *meso*-imides.

Chapter 4

Desymmetrisation of glutarimides

4.1 Background

The desymmetrisation of glutarimides is relatively unexplored. Although there have been many reports on the use of the oxazaborolidines derived from *cis*-1-aminoindan-2-ol for the desymmetrisation of five-membered *meso*-imides from the Jones research group, this work is the first attempt to extend such investigations to glutarimides. The excellent results obtained so far with five membered ring *meso*-imides had been a source of inspiration to explore the synthesis and desymmetrisation of these simple compounds that would open avenues for the synthesis of important natural products and pharmaceuticals.

4.2 Synthesis of glutarimides

For this investigation a variety of 3-substituted glutarimides was required, possessing different steric and electronic effects and accessible from commercially available starting materials. Previous work from the Jones research group on five-membered ring imides had shown that *N*-aryl versions gave good yields and excellent enantioselectivity compared to their *N*-alkyl counterparts.[74] The synthesis, therefore, focused on the *N*-*p*-methoxyphenyl (*N*-PMP) and *N*-benzyl (*N*-Bn) derivatives **167** – **170** (Figure 15). Earlier work on five-membered ring imides also revealed that the *N*-Bn derivatives showed higher yields of the desymmetrised products than the *N*-aryl imides, however with a slight decrease in selectivity.[74] Thus it was hoped that modifying the benzyl group would increase the selectivity without compromising the yields.

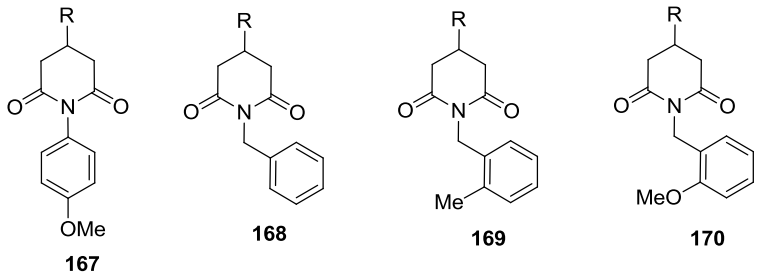
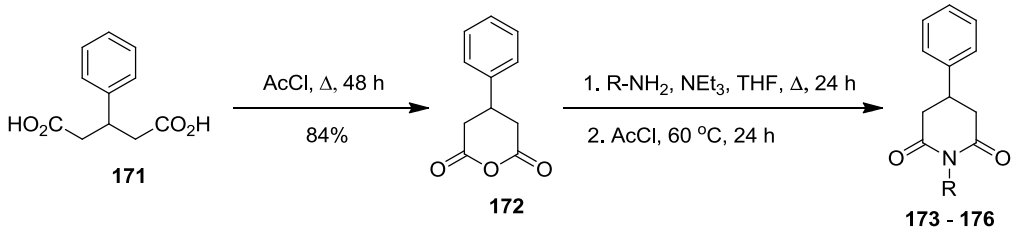


Figure 15. Glutarimdes targeted

4.2.1 Synthesis of 3-phenyl glutarimides

The commercially-available and inexpensive 3-phenylglutaric acid **171** was used as the starting material for the initial investigation of the route to the synthesis of glutarimides. The

3-phenylglutarimides **173** – **176** were accessed following literature procedures by first converting the 3-phenylglutaric acid to the corresponding anhydride **172** by the dehydrative cyclisation in acetyl chloride for 48 hours to give the anhydride in 84% yield after recrystallisation from ethyl acetate / hexane mixture. Condensation of the respective amines with the glutaric anhydride gave the corresponding glutarimides in excellent yields after recrystallisation from ethyl acetate / hexane mixture (Scheme 65, Table 14).[67]



Scheme 65. Synthesis of 3-phenylglutarimides

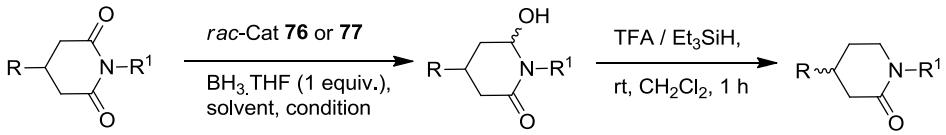
Table 14. Yields of 3-phenylglutarimides obtained according to Scheme 65

Entry	R		Yield (%)
1.	4-$MeOC_6H_4$	**173**	80
2.	Benzyl	**174**	85
3.	2-methylbenzyl	**175**	71
4.	2-methoxybenzyl	**176**	60

4.3 Desymmetrisation of glutarimides

The initial investigation for the desymmetrisation experiments started with the four glutarimides readily obtained from the commercially-available 3-phenylglutaric acid. It has been established by the Jones research group that BH_3.THF is the optimal borane source for the desymmetrisation of five membered *meso*-imides as there was no competing background reaction and the optimal catalyst loading was 10 mol%.[73] Hence BH_3.THF was employed as the hydride source and a catalyst loading of 10 mol% was used throughout this research work. Furthermore reduction of the *N*-PMP-3-phenyl glutarimide **173** and *N*-Bn-3-phenyl glutarimde **174** were separately performed with BH_3.THF and the result showed no background reaction in both cases after 24 hour reaction time. The desymmetrisation process therefore involved reduction of a glutarimide with 1 equivalent of BH_3.THF in the presence of 10 mol% catalyst at room temperature to give the corresponding hydroxy-lactam. The hydroxy-lactam was further reduced to the corresponding lactam by reaction with Et_3SiH / TFA for ease of analysis.

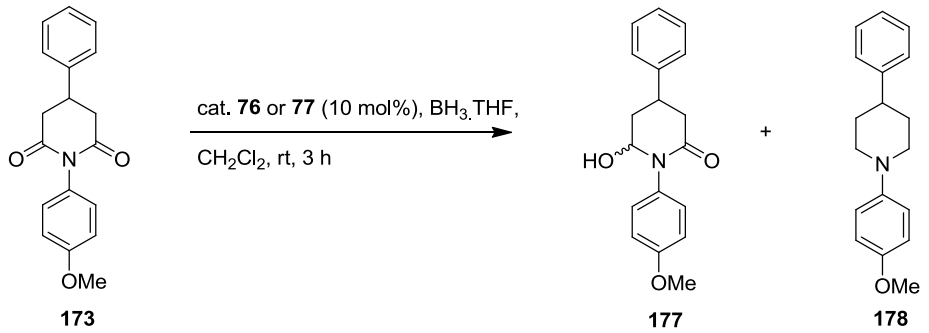
The corresponding racemic lactams needed for optimising chiral phase HPLC conditions were prepared by reduction of glutarimides with 1 equivalent of BH_3.THF in the presence of 10 mol% of racemic oxazaborolidine **76** or **77**, which was prepared by reacting racemic *cis*-1-aminoindan-2-ol with trimethyl boroxine in the case of *B*-Me catalyst **76** or trimethyl borate in the case of *B*-OMe catalyst **77** to furnish the corresponding hydroxylactams which were further reduced to the target lactams by reduction using TFA and triethylsilane (Scheme 66).



Scheme 66. Desymmetrisation of *meso*-imides with racemic catalysts

4.3.1 Desymmetrisation of N-PMP glutarimide

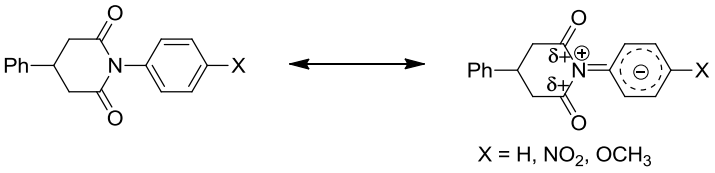
The initial screening for the best desymmetrisation conditions was first carried out on *N*-PMP protected 3-phenylglutarimide **173** using both *B*-Me catalyst **76** and *B*-OMe catalyst **77** employing BH_3.THF as borane source and reduction monitored by TLC. Careful monitoring of the reaction by TLC showed a build-up in the concentrations of both the hydroxy-lactam intermediate **177** and the over-reduced piperidine product **178** through a 3-hour reaction period. Beyond 3 hours the concentration of the hydroxy-lactam started to diminish with an increase in the concentration of the over-reduced piperidine product, suggesting a rapid conversion of the hydroxy-lactam to the undesired product **178** (Scheme 67).



Scheme 67. Initial reduction of *N*-PMP *meso*-glutarimide

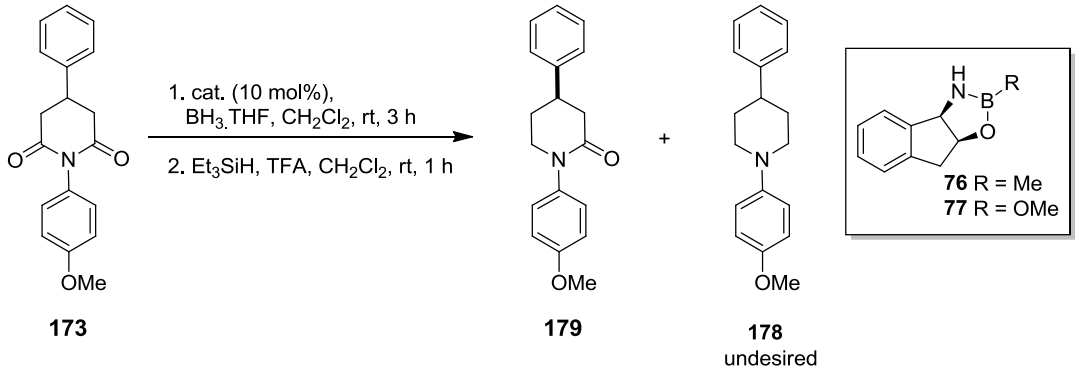
This rapid formation of the doubly reduced product confirmed the earlier observation made on the *N*-PMP five membered imides by the research group, which was attributed to the electronics of the aryl ring system directly bonded to the nitrogen atom of the imide. As the aryl ring is electron withdrawing, the nitrogen lone pair becomes engaged with the aryl ring

system rather than with carbonyl groups making both carbonyls more electropositive, hence susceptible to nucleophilic attack (Scheme 68). [74]



Scheme 68. Electron withdrawing of *N*-aryl substituents

The reaction was therefore repeated stopping the reduction after 3 hours and taking the hydroxy-lactam to the more stable 2-piperidinone **179** (Scheme 69)**.** Two methods of preparing the catalysts were employed. The first involved preparing the catalyst *in situ* at room temperature and using it straight away while the second way involved repeated distillations to azeotropically remove borate impurities before the final stock solution of the catalyst was made. The results are summarised in table 15.



Scheme 69. Desymmetrisation of *N*-PMP-3-phenylglutarimide using *B*-Me and *B*-OMe catalysts

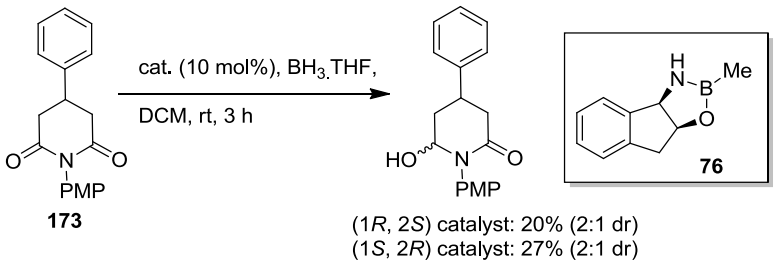
Table 15. Screening catalysts for desymmetrisation process of *N*-PMP glutarimide

Entry	Catalyst	Method	Starting Material (%)	179 (% Yield)	ee (%)	178 (% Yield)
1.	*B*-Me	*in situ*	66	18	53	10
2.	*B*-Me	distilled	28	33	95	30
3.	*B*-OMe	*in situ*	20	48	99	21
4.	*B*-OMe	distilled	37	43	>99	15

in situ: A 5 cm^3 stock solution of the *B*-OMe or *B*-Me catalyst in dry THF was prepared under N_2 atmosphere at room temperature. A solution of the glutarimide in dry DCM was treated with 10 mol% of the catalyst and BH_3.THF at rt for 3 hours, followed by treatment of a solution of the crude hydroxy-lactam in DCM with Et_3SiH / TFA for 1 hour to give the lactam product.
distilled: A 5 cm^3 solution of the *B*-OMe or *B*-Me catalyst in dry toluene was prepared under N_2 atmosphere at room temperature. It was distilled until approximately 2 cm^3 of solvent remained. 5 cm^3 of dry toluene was added and distilled as above. The distillation procedure was repeated twice before the final 5 cm^3 stock solution of the catalyst was made. The reduction of the glutarimide was then carried out as above.

In both cases and for both catalysts a desymmetrisation product was isolated together with an undesired over reduced product **178** at a reaction time of 3 hours. For the *B*-Me catalyst **76**, a significant difference in both yield and enantioselectivity was observed from the two methods of preparing the catalyst. Only 18% yield and 53% ee of the desired product was obtained when the catalyst was prepared *in situ* at room temperature with a significant mass return of the starting material (66%), while for the method involving distillation at elevated temperature, 33% yield of the desired product was obtained with a remarkable increase in enantioselectivity (95% ee). The undesired over reduced product also increased from 10% yield to 30% yield (Table 15, entries 1 & 2). For the *B*-OMe catalyst **77**, both methods gave excellent ee's, however the *in situ* method produced the 2-piperidinone in a 48% yield and the undesired piperidine was isolated in a 21% yield (Table 15, entry 3) while the distillation method gave 43% yield of the desired product and 15% of the undesired product (Table 15, entry 4). Generally, excellent selectivities were obtained with both catalysts; however the yields of the desymmetrised products were greatly hampered by the formation of the over-reduced product which is characteristic of *N*-PMP imide substrates.

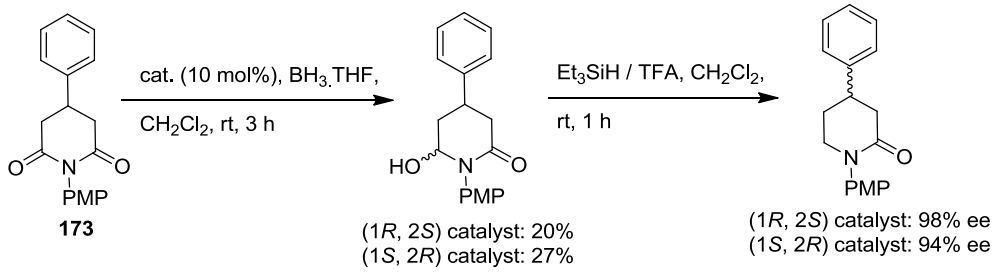
The relationship between excellent enantioselectivity and formation of over-reduced piperidine product **178** in the *N*-PMP substrate **173** was investigated by performing an experiment similar to the one carried out on the *N*-PMP anthracene-maleimide counterpart. The *B*-Me catalyst was chosen for the investigation, employing repeated distillation procedure since the highest yield of the over reduced compound with a significant change in selectivity was observed in that case. Firstly, an attempt was made to isolate pure samples of hydroxy-lactams by reducing the *N*-PMP glutarimide substrate **173** using both versions of the *B*-Me catalyst **76** under standard conditions. The two enantiomers of the hydroxy-lactam were obtained, both in 2:1 dr, in 20% yield for (1*R*, 2*S*) catalyst and 27% yield for (1*S*, 2*R*) catalyst, respectively (Scheme 70).



Scheme 70. Reduction of *N*-PMP substrate to hydroxy-lactam

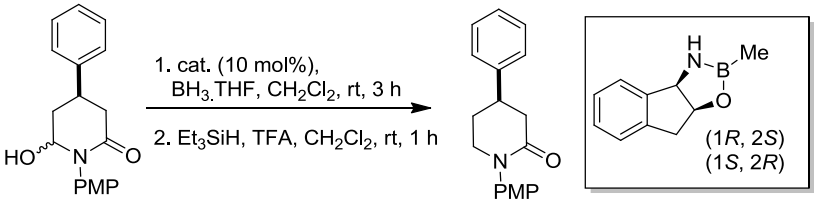
The poor yield of hydroxy-lactams obtained may be attributed to poor yields of the desymmetrisation products earlier observed with both *B*-OMe and *B*-Me catalysts for the *N*-

PMP substrate (Table 14). To confirm the high selectivity of both versions of the catalyst on the *N*-PMP glutarimide, a portion of each enantiomer of the hydroxy-lactam was converted to the corresponding lactam by treatment with TFA / Et_3SiH under standard conditions, giving quantitative yields of the lactams in 98% ee and 94% ee respectively (Scheme 71).



Scheme 71. Testing selectivity of both versions of *B*-Me catalyst on *N*-PMP substrate

A scalemic homogenous mixture of the two enantiomers of the hydroxy-lactam was then prepared in a 2:1 ratio (1*R*, 2*S*:1*S*, 2*R*). A portion of the scalemic mixture was quantitatively converted to the lactam and the ee of the resultant scalemic lactam compound was obtained. A sample of the scalemic mixture was then subjected to reduction with (1*R*, 2*S*) version of the *B*-Me catalyst followed by further reduction to the corresponding lactam under standard reaction conditions. The same procedure was repeated with the (1*S*, 2*R*) version of the catalyst. The yield and ee of the *N*-PMP lactam compounds were recorded. The results are summarised in table 16.



Scheme 72. Stereoablation experiment on *N*-PMP glutarimide

Table 16. Results from stereoablation experiment

Entry	Scalemic hydroxy-lactam ee (%)[a]	Catalyst	Yield (%)	ee (%)
1.	31	1*R*, 2*S*	73	60
2.	31	1*S*, 2*R*	75	14

[a] Based on derivatisation of a sample of scalemic hydroxy-lactam to the lactam and HPLC analysis of this compound.

A solution of the scalemic mixture of the hydroxy-lactam was treated with the catalyst (10 mol%), then BH_3.THF and allowed to stir at room temperature for 3 hrs. After standard work up, the crude product was treated with Et_3SiH / TFA at room temp. for 1 hr. The resultant *N*-PMP lactam was purified by flash column chromatography.

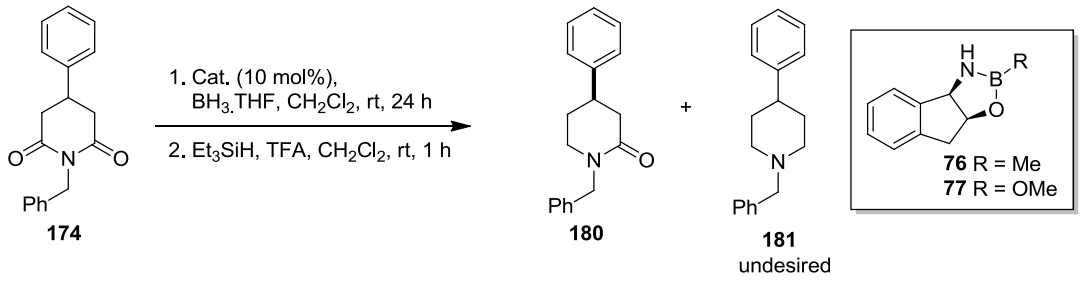
When a representative sample from the scalemic hydroxy-lactam (31% ee) was subjected to reduction with (1*R*, 2*S*) enantiomer of the *B*-Me catalyst **76** followed by subsequent reduction with Et_3SiH, the lactam was obtained in 73% yield and 60% ee (Table 16, entry 1). This result showed that a portion of the scalemic hydroxy-lactam was converted to the over reduced piperidine product by the BH_3.THF in presence of the (1*R*, 2*S*) catalyst. As observed with the anthracene-maleimide, there was an upgrade in the ee of the scalemic hydroxy-lactam from 31% to 60%, showing a stereoablative reduction of one enantiomer of the hydroxy-lactam by the (1*R*, 2*S*) catalyst (presumably the minor enantiomer) to the piperidine compound.

On the other hand, when the reaction was repeated with (1*S*, 2*R*) version of the catalyst, a near identical yield of 75% of the lactam compound was obtained. However, unlike in the anthracene-maleimide case where the ee of the scalemic hydroxy-lactam remained the same with this version of the catalyst, the ee of the scalemic hydroxy-lactam in this case eroded to 14% (Table 16, entry 2). This shows that the (1*S*, 2*R*) catalyst selectively reduces the opposite enantiomer of the hydroxy-lactam, the major enantiomer this time around, to the piperidine compound; thereby diminishing the ee of the scalemic hydroxy-lactam. Thus a double stereo-differentiation process was shown to be operative whereby matched and mismatched cases were observed in the two versions of the *B*-Me catalyst. The upgrade in selectivity observed in the former case could be regarded as the matched case where the (1*R*, 2*S*) enantiomer of the catalyst selectively eliminated the minor enantiomer of the hydroxy-lactam thus leading to enantio-enrichment of the product, while the downgrade in selectivity observed in the latter case might be because of the same process on the major enantiomer of the hydroxy-lactam (mismatched case) by the (1*S*, 2*R*) version of the *B*-Me catalyst. The near identical yields of the lactam products obtained (73% & 75%) under the same experimental condition suggests similar reaction rates of the two catalysts in the stereoablation reaction.

4.3.2 Desymmetrisation of N-Bn glutarimides

To investigate the performances of the two catalysts under these conditions further, the nitrogen protecting group was switched from *p*-(methoxy)phenyl to benzyl. It was hoped that a better yield of the product would be obtained with the *N*-benzyl imide while keeping the ee's high. The desymmetrisation of *N*-benzyl glutarimide analogue **174** was thus examined using both *B*-Me and *B*-OMe catalysts applying conditions employed earlier for the *N*-PMP counterpart. Again, the reduction step was monitored by TLC. An important observation made was a very slow build-up in the concentration of the over reduced product **181** even

after 3 hours. This allowed the reaction time to be extended to as long as 24 hours. The result of the desymmetrisation experiment is summarised in table 17.



Scheme 73. Desymmetrisation of *N*-Bn-3-phenylglutarimide using *B*-Me and *B*-OMe catalysts

Table 17. Screening catalysts for desymmetrisation process of *N*-Bn glutarimide

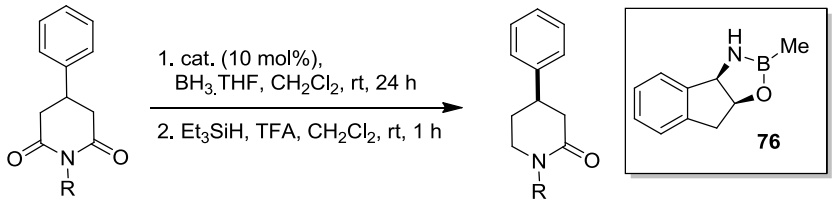
Entry	Catalyst	Method	Starting Material (%)	Yield 180 (%)	ee (%)	Undesired Product 181 (% Yield)
1.	*B*-Me	*in situ*	62	20	80	9
2.	*B*-Me	distilled	20	60	90	12
3.	*B*-OMe	*in situ*	60	34	85	5
4.	*B*-OMe	distilled	59	30	92	5

in situ: A 5cm^3 stock solution of the *B*-Me or *B*-OMe catalyst in dry THF was prepared under N_2 atmosphere at room temperature. A solution of the glutarimide in dry DCM was treated with 10 mol% of the catalyst and BH_3.THF at rt for 24 hours, followed by treatment of a solution of the crude hydroxy-lactam in DCM with Et_3SiH / TFA for 1 hour to give the lactam product.
distilled: A 5cm^3 solution of the *B*-Me or *B*-OMe catalyst in dry toluene was prepared under N_2 atmosphere at room temperature. It was distilled until approximately 2 cm^3 of solvent remained. 5cm^3 of dry toluene was added and distilled as above. The distillation procedure was repeated twice before the final 5cm^3 stock solution of the catalyst was made. The reduction of the glutarimide was then carried out as above.

As was expected, a slight decrease in selectivity was observed in both catalysts showing consistency with observations from earlier work on five-membered *meso*-imides. The *B*-OMe catalyst gives a rather disappointing result with *N*-benzyl imide as there was a decrease in both yields and selectivity. However, a remarkable change was observed with *B*-Me catalyst. Although the yield of the desired product obtained from the *in situ* preparation of the catalyst remains approximately the same as obtained in the *N*-PMP substrate, the enantioselectivity remarkably increased from 53% to 80% ee. Encouragingly, repeated distillation in the preparation of *B*-Me catalyst led to significant increase in the yield of the desymmetrised product, from 33% (Table 15, entry 2) to 60% with a slight decrease in enantioselectivity (Table 17, entry 2). In an effort to increase the yield of the product, the reduction was repeated with *B*-Me catalyst, employing repeated distillation procedure but extending the reaction time to 48 hours. However, only 50% of the lactam product was obtained.

Results from these optimization studies of the two oxazaborolidine catalysts using *N*-PMP and *N*-Bn imides show that both the *in situ* and the distilled methods are the optimal methods of preparing the *B*-OMe catalyst while the *B*-Me catalyst works best with successive azeotropic distillations. As observed earlier, the *B*-alkylated CBS oxazaborolidines are sensitive to any residual water which therefore needs complete removal by azeotropic distillations. Furthermore any trace of unreacted amino alcohol or borate decreases the enantioselectivity which may account of the significant difference in enantioselectivity observed in *B*-Me catalyst between the two methods of preparation. Overall, catalyst **76** gives the best result with *N*-benzyl-3-phenylglutarimde making it a better candidate than its *B*-OMe counterpart. The overall low yield observed in *B*-OMe catalyst was thought to be due to donation of the oxygen lone pairs from the methoxy group in to the empty *p*-orbital of the boron atom. This reduces the Lewis acidity of the boron atom which hinders the binding of the catalyst to the carbonyl group of the imide.[74]

Modification of the benzyl protecting group to 2-methylbenzyl and 2-methoxybenzyl and reduction with *B*-Me catalyst using repeated distillation procedure led to a significant decrease in yield (25% and 21%, respectively) but kept the ee's high (Table 17, entries 3 & 4). This further proves the delicate nature of the *N*-protecting groups in influencing the yield and / or selectivity of the oxazaborolidine catalysts in desymmetrisation of imide substrates. A summary of the results of desymmetrisation of 3-phenylglutarimides using *B*-Me catalyst employing the repeated distillation procedure is shown in table 18. Hence *N*-benzyl was chosen as the protecting group for the rest of the glutarimide synthesis and the *B*-Me catalyst **76** was used for the remaining desymmetrisation processes.



Scheme 74. Desymmetrisation of achiral 3-phenylglutarimides using *B*-Me catalyst (see Table 18 next page)

Table 18. Result of desymmetrisation of achiral 3-phenylglutarimides using *B*-Me catalyst (see Scheme 74 on the preceeding page)

Entry	Imide		Yield of product	ee
1.	*N*-PMP*	**173**	(**179**) 33%	95%
2.	*N*-Benzyl	**174**	(**180**) 60%	90%
3.	*N*-(2-MethylBn)	**175**	(**182**) 25%	88%
4.	*N*-(2-MethoxyBn)	**176**	(**183**) 21%	90%

A 5cm^3 solution of the *B*-Me catalyst in dry toluene was prepared under N_2 atmosphere at room temperature. It was distilled until approximately 2 cm^3 of solvent remained. 5cm^3 of dry toluene was added and distilled as above. The distillation procedure was repeated twice before the final 5cm^3 stock solution of the catalyst was made. A solution of the glutarimide in dry DCM was treated with 10 mol% of the catalyst and BH_3.THF at rt for 24 hours, followed by treatment of a solution of the crude hydroxy-lactam in DCM with Et_3SiH / TFA for 1 hour to give the lactam product.

* Reaction time of 3 h in the first step.

Although the stereoablation process has not been investigated at this time in the *N*-Bn substrates used in this research work, an additional reason to account for the difference in the selectivity of the products from *N*-aryl and *N*-Bn imides might be in the mode of catalyst binding to the two substrates which was explained by the transition state model put forward by Speckamp for desymmetrisation of imides using prolinol catalyst.[70] In this system the small substituent is considered to be the cyclic backbone of the imide and the large group is considered to be the nitrogen substituent (Figure 16). Using this model the sense of enantioselectivity can be broadly explained as the substituent size is increased from benzyl (*N*-CH_2-) to *p*-methoxyphenyl (*N*-Ph) there is an increase in enantioselectivity. Furthermore the limited rotation about the C-N bond in *N*-PMP substrate allows the substituent to adopt a conformation where the substituent presents a large group towards the oxazaborolidine **76**, without compromising binding (Figure 16, intermediate A). This results in a large energy difference between the two transition states giving access to only one enantiomer of the corresponding lactam. However as the rotation about the C-N bond becomes easier in *N*-Bn case (Figure 16, intermediate B), the catalyst has a better chance of approaching the substrate and binding with it from the two faces making the energy difference between the two diastereomeric transition states to decrease. The net result is higher yield and a decrease in selectivity. In fact, *N*-methyl substrate was observed to give comparable yield of the desymmetrised product with *N*-benzyl counterpart in desymmetrisation of five membered imides using oxazaborolidines employed in this work.[74]

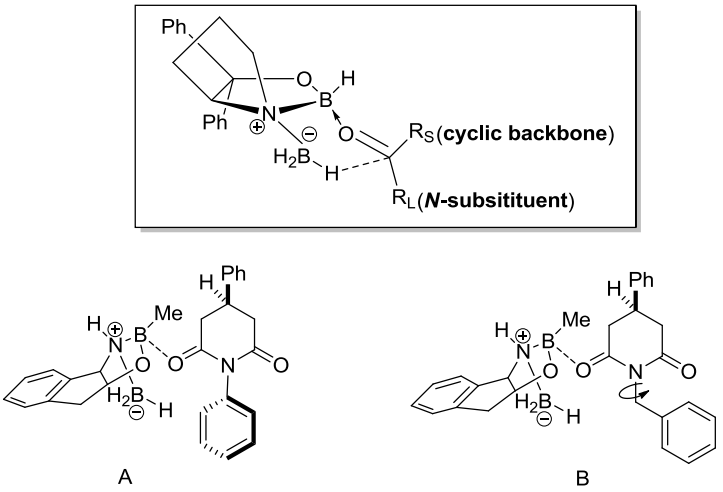
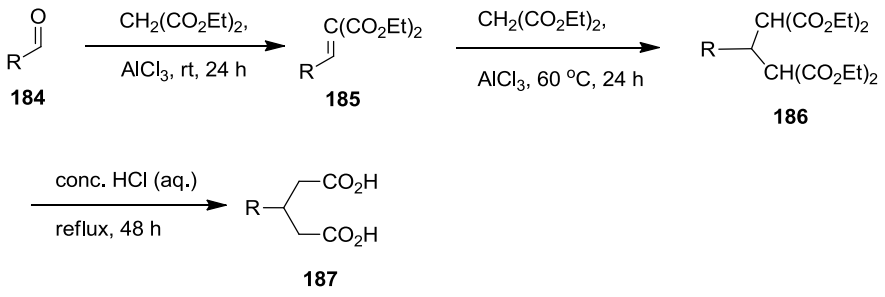


Figure 16. Transition state adopted by aryl and benzyl imides

4.4 Synthesis and desymmetrisation of 3-substituted glutarimides

Having synthesised the 3-phenylglutarimides from the diacid **171** in a short number of steps and in good yields, attention now focused on the synthesis of aryl and substituted aryl glutaric acids that could provide direct access to the corresponding aryl and substituted aryl glutarimides. The *o*-substituted phenyl glutaric acids **188** and **190** and 1-naphthyl glutaric acid **192** (Table 19) were synthesised from the corresponding aldehydes, using literature procedures. The aldehydes starting materials **184** were first converted to the corresponding benzylidenemalonates **185** through a solvent-free Knoevenagel condensation with diethyl malonate in the presence of $AlCl_3$, and the benzylidenemalonates were then made to undergo Michael addition by further reaction (neat) with diethylmalonate at 60 ^oC in the presence of $AlCl_3$ to yield dimalonates **186**. The resultant dimalonates **186** were subjected to acid hydrolysis and decarboxylation in one pot to obtain the corresponding glutaric acids, without further purification, in 51%, 52% and 60% yields, respectively, over 3 steps (Scheme 75, Table 19, entries 1, 3 & 5).[98]



Scheme 75. Synthesis of 3-Arylglutaric acids

Table 19. Summary of yields of 3-substituted glutaric acids

Entry	Method	R		Yield of Glutaric acid (%) (over 3 steps)
1.	A	2-F-C_6H_4	**188**	51%
2.	B	4-F-C_6H_4	**189**	55%
3.	A	2-CH_3-C_6H_4	**190**	52%
4.	B	4-CH_3-C_6H_4	**191**	57%
5.	A	1-Naphthyl	**192**	60%
6.	-	*CH_3-	**193**	-
7.	C	$(CH_3)_2CH$-	**194**	34%
8.	D	$(CH_3)_3C$-	**195**	58%

*commercially available

Method A: Solvent-free Knoevenagel condensation of the aldehyde starting material with diethyl malonate / $AlCl_3$ at room temperature followed by solvent-free Michael addition with diethyl malonate at 60 ^oC temperature to give corresponding tetracarboxylate, which underwent acid hydrolysis and decarboxylation at reflux to the diacid.

Method B: Drop-wise addition of the solution of aldehyde starting material in toluene to diethyl malonate / $AlCl_3$ solution in toluene at room temperature followed by solvent-free Michael addition with diethyl malonate at 60 ^oC temperature to give corresponding tetracarboxylate, which underwent acid hydrolysis and decarboxylation at reflux to the diacid.

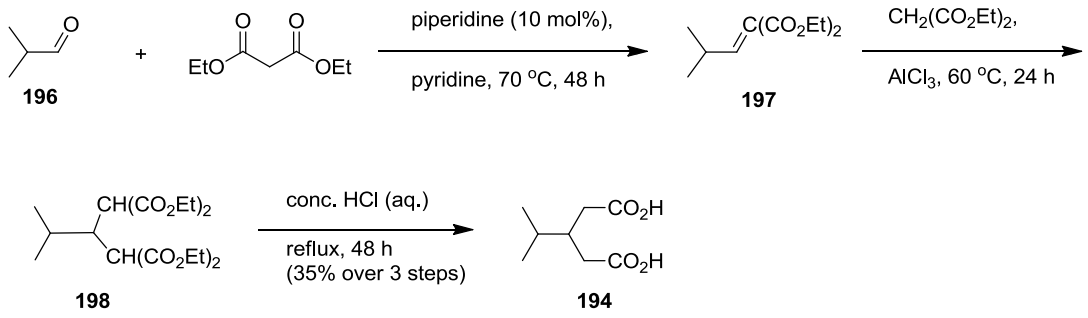
Method C: Knoevenagel condensation of the aldehyde starting material with diethyl malonate / piperidine (0.1 equiv.) in pyridine at 70 ^oC temperature followed by solvent-free Michael addition with diethyl malonate at 60 ^oC temperature to give corresponding tetracarboxylate, which underwent acid hydrolysis and decarboxylation at reflux to the diacid.

Method D: Knoevenagel condensation of the aldehyde starting material with ethylcyanoacetate / piperidine in toluene at reflux followed by Michael addition with dimethylsodiomalonate at reflux to give corresponding tetracarboxylate, which underwent acid hydrolysis and decarboxylation at reflux to the diacid.

However, in the case of more reactive *p*-fluoro and *p*-methylbenzaldehyde starting materials, the solvent-free conditions repeatedly led to the isolation of a white solid in the Knoevenagel condensation step (instead of the usual oily liquid product), which was identified by ^1H NMR and ^{13}C NMR analysis as the corresponding benzoic acid in 47% and 42% yields, respectively. It was thought that the electron donating effect of the methyl and fluoro substituents may change the course of the reaction by causing an intermolecular hydride transfer between two molecules of aldehydes leading to a self-redox (Cannizzaro) reaction.

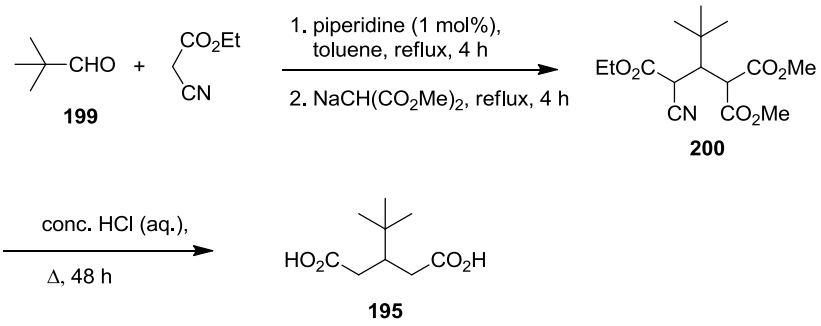
Pleasingly, a drop-wise addition of a solution of the aldehyde in toluene to the mixture of diethyl malonate and $AlCl_3$ in toluene at room temperature led to the formation of the required benzylidenemalonate products. The dimalonates **186** were then accessed using the procedure described for *o*-substituted benzaldehydes. A one pot acid hydrolysis and decarboxylation of the dimalonates led to the synthesis of the *p*-substituted glutaric acids **189** and **191** in 55% and 57% over 3 steps, respectively (Scheme 75, Table 19, entries 2 & 4). All efforts to synthesise 9-anthracyl glutaric acid using the procedures described above proved unsuccessful. The reason for the unreactivity of 9-anthraldehyde is most likely attributed to steric repulsion by the bulky anthracene moiety.

The synthesis of alkyl glutaric acids using the developed conditions gave extremely low yields of the Knoevenagel products. Hence, for the preparation of isopropyl malonate **197**, a modified procedure was employed by reacting the isobutyraldehyde **196** with the diethyl malonate in the presence of piperidine (0.1 equiv.) in pyridine at 70 ^oC for 48 h which gave the crude isopropyl malonate in appreciable quantities, and this was taken forward using the method described in scheme 76 to yield the isopropyl glutaric acid **194** in 34% yield over three steps (Table 19, entry 7).



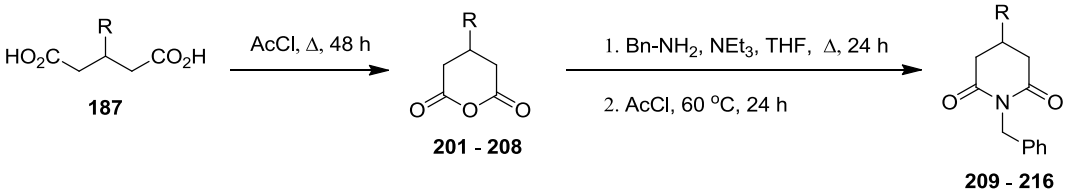
Scheme 76. Synthesis of 3-*iso*propylglutaric acid 194

Unfortunately, trimethylacetaldehyde **199** did not give the corresponding Knoevenagel product even with the above modification. Hence the method of Theisen and Heathcock was adopted for the synthesis of *tert*-butylglutaric acid **195**.[52] A solution of the aldehyde in toluene was reacted with ethyl cyanoacetate in presence of piperidine (0.01 equiv.) at elevated temperature for 4 hours to give the Knoevenegel product which underwent the Michael addition with sodium dimethylmalonate at reflux temperature for 17 h to yield the *tert*-butyl cyanotricarboxylate **200**. The cyanotricarboxylate obtained was then converted to *tert*-butyl glutaric acid **195** in 58% yield over 3 steps (Scheme 77, Table 19, entry 8). Methylglutaric acid **193** was commercially available and used as purchased.



Scheme 77. Synthesis of 3-*tert*-butylglutaric acid 195

The synthesised glutaric acids were then smoothly taken to the corresponding *N*-benzyl-3-substituted glutarimides using the method described earlier for the synthesis of 3-phenyl glutarimides (Scheme 78).[67] The anhydrides were accessed in 70 – 93% yield, after recrystallisation from ethyl acetate / hexane mixture, by heating at reflux the corresponding glutaric acids in acetyl chloride for 48 hours (Table 20). The isopropyl anhydride **207** and *tert*-butyl anhydride **208** were obtained as brown liquids which were purified by vacuum distillation. However, they were found to be slightly unstable under the distillation conditions. Hence, some minor peaks of the corresponding diacids were noticed in both the ^{1}H and ^{13}C NMR spectra showing a small portion of the anhydrides might have been converted back to the corresponding diacids. The anhydrides were converted to the corresponding *N*-Bn glutarimides over two steps by reacting them with benzylamine in THF under reflux in the presence of NEt_3 for 24 h and the resultant amido-carboxylic acids heated in acetyl chloride at 60 ^{o}C temperature for an additional 24 h to obtain the glutarimides in 52 – 89% yields after recrystallisation from ethyl acetate / hexane mixture, except isopropyl and *tert*-butyl glutarimides **215** and **216** which were purified by flash column chromatography (Table 20).



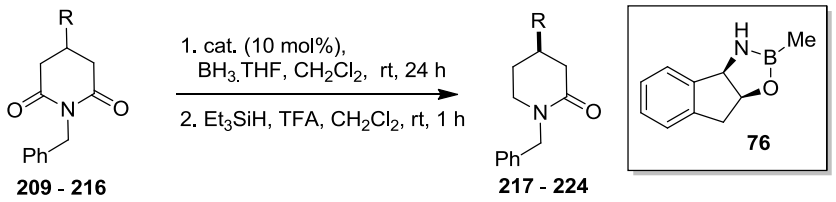
Scheme 78. Synthesis of *N*-Bn 3-substituted glutarimides

Table 20. Summary of yields of 3-subsitituted glutaric anhydrides and imides

Entry	R	Anhydride Yield (%)		Imide Yield (%)	
1.	2-F-C_6H_4	73	**201**	60	**209**
2.	4-F-C_6H_4	85	**202**	67	**210**
3.	2-CH_3-C_6H_4	75	**203**	87	**211**
4.	4-CH_3-C_6H_4	93	**204**	71	**212**
5.	1-Naphthyl	80	**205**	52	**213**
6.	CH_3-	79	**206**	70	**214**
7.	$(CH_3)_2CH$-	76	**207**	67	**215**
8.	$(CH_3)_3C$-	70	**208**	57	**216**

Desymmetrisation of the *N*-benzyl glutarimides **209** – **216** was explored using *B*-Me catalyst **76** employing BH_3.THF as the hydride source. The resultant hydroxy-lactam was converted to the 4-substituted 2-piperidinone for ease of analysis. Under the reaction conditions, the *N*-Bn-4-aryl substrates **209** – **212** furnished the chiral 2-piperidinones **217** – **220** in moderate yields (51 – 61%) and good enantioselectivities of 82 – 92% ee (Table 21, entries 1– 4). A change of substitution around the phenyl group does not seem to affect much the overall yield or enantioselectivity.

A switch from 4-substituted aryls to 4-substituted alkyls **222** – **224** surprisingly kept the selectivity at high level, although the yields of the products dropped (Table 21, entries 6 – 8).



Scheme 79. Desymmetrisation of *N*-Bn glutarimides using *B*-Me catalyst

Table 21. Desymmetrisation of *N*-benzyl-3-substituted glutarimides using *B*-Me catalyst

Entry	R		Yield (%)	ee (%)
1.	2-F-C_6H_4	**217**	51	82
2.	4-F-C_6H_4	**218**	54	92
3.	2-CH_3-C_6H_4	**219**	61	86
4.	4-CH_3-C_6H_4	**220**	51	88
5.	1-Naphthyl	**221**	20	54
6.	CH_3-	**222**	46	90
7.	$(CH_3)_2CH$-	**223**	41	86
8.	$(CH_3)_3C$-	**224**	46	87

A solution of the glutarimide in dry DCM was treated with 10 mol% of the catalyst at rt for 24 h, followed by treatment of a solution of the crude hydroxy-lactam in DCM with Et_3SiH / TFA for 1 hour. Purification by flash column chromatography after a standard work up gave the lactam product.

Notable is the significant change observed when the aryl group was changed to 1-naphthyl which resulted in sharp decrease in both yield and ee (Table 21, entry 5). This shows that steric hindrance at the stereogenic centre in question may affect the catalyst binding ability as well as its approach to the substrate despite it been distant from the binding site.

4.5 Establishing stereochemistry

The absolute configuration of the stereogenic centre for *N*-PMP-4-phenylpiperidin-2-one **179** (Table 22, entry 1) was assigned as (4*R*) by comparison of its optical property with that of a closely related known compound, *N*-PMP-4-(4-fluorophenyl)piperidin-2-one (Table 22, entry 2). The *N*-benzyl-4-phenyl lactam **180** (Table 22, entry 3) and *N*-benzyl-4-(4-fluorophenyl) lactam **218** (Table 22, entry 7) have their optical properties matching with known compounds in the literature and are also assigned as (4*R*). The rest of the chiral desymmetrisation products have their optical properties comparable to compounds **180** and **218** (Table 22), hence are assigned the same configurations. The only exception is the *N*-benzyl-4-(1-naphthyl) lactam **221** which has small negative alpha-D value (Table 22, entry 10).

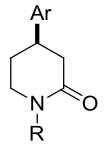
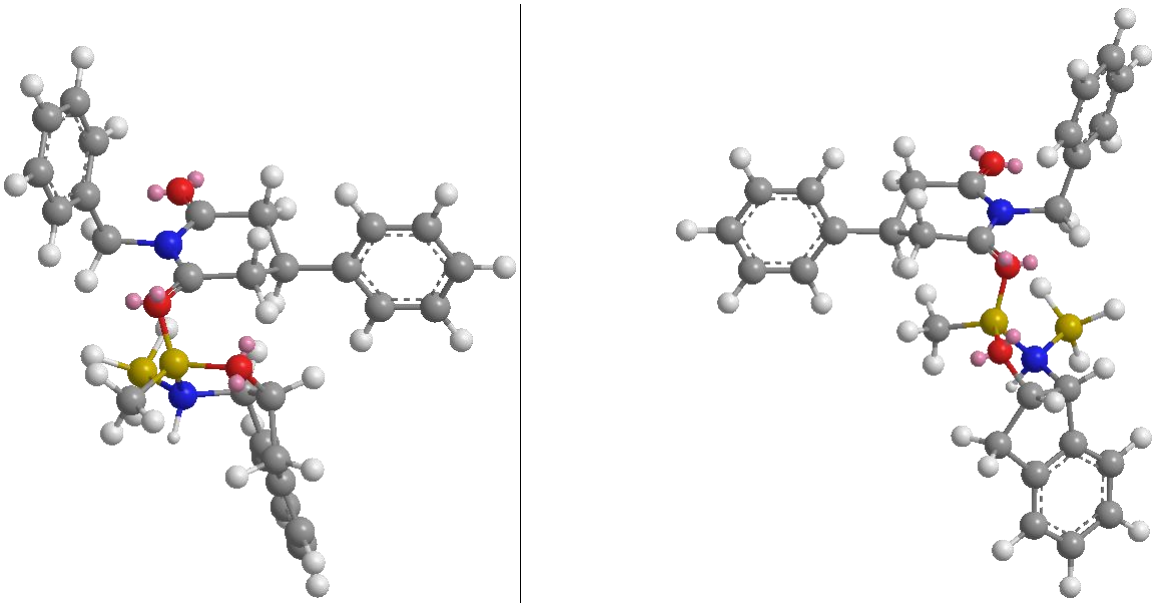


Table 22. Comparing optical properties of some representative chiral lactams

Entry	Ar	R	Measured $[\alpha]_D^{20}$	Literature $[\alpha]_D^{20}$
1.	C_6H_5-	PMP (**179**)	+6.0 (*c* 1.3, $CHCl_3$)	unknown
2.	(4*R*)-F-C_6H_4-	PMP	-	+8.0 (*c* 1.3, $CHCl_3$)[99]
3.	(4*R*)-C_6H_5-	Bn (**180**)	+33.0 (*c* 1.1, $CHCl_3$)	+35.0 (*c* 1.1, $CHCl_3$)[100]
4.	C_6H_5-	2-MeBn (**182**)	+ 26.6 (*c* 0.8, $CHCl_3$)	unknown
5.	C_6H_5-	2-OMeBn (**183**)	+ 21.7 (*c* 1.0, $CHCl_3$	unknown
6.	2-F-C_6H_4	Bn (**217**)	+ 20.1 (*c* 2.1, $CHCl_3$)	unknown
7.	(4*R*)-4-F-C_6H_4	Bn (**218**)	+30.0 (*c* 1.1, $CHCl_3$)	+33.0 (*c* 1.1, $CHCl_3$)[100]
8.	2-CH_3-C_6H_4	Bn (**219**)	+ 39.4 (*c* 0.3, $CHCl_3$)	unknown
9.	4-CH_3-C_6H_4	Bn (**220**)	+ 33.6 (*c* 1.1, $CHCl_3$)	unknown
10.	1-Naphthyl	Bn (**221**)	-13.3 (*c* 0.5, $CHCl_3$)	unknown
11.	CH_3-	Bn (**222**)	+ 46.6 (*c* 3.3, $CHCl_3$)	unknown
12.	$(CH_3)_2CH$-	Bn (**223**)	+ 44.3 (*c* 1.9, $CHCl_3$)	unknown
13.	$(CH_3)_3C$-	Bn (**224**)	+ 36.8 (*c* 1.4, $CHCl_3$)	unknown

Specific rotations were performed on an Optical Activity Ltd. AA-10 automatic polarimeter at 589nm (Na D-Line) and measured at 20 ^oC.

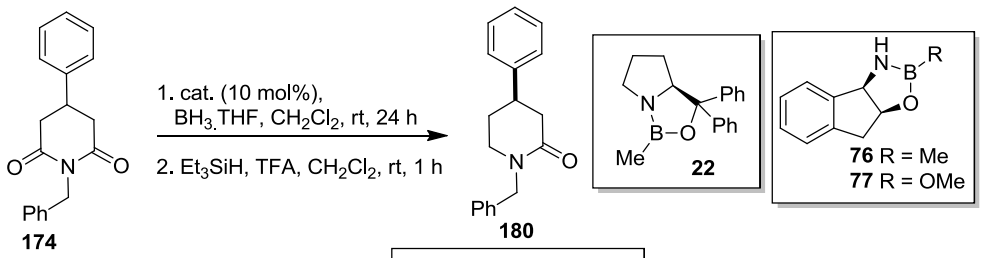
To explain the stereochemical outcome, two possible transition states A and B involving the imide and the oxazaborolidine catalyst were proposed using Chem3D after simple molecular mechanics minimisation of the pre-transition state intermediate (Figure 17). Two important assumptions play a key role in selecting such an intermediate with the least energy; i) the catalyst is co-ordinated to the least hindered carbonyl lone pair and ii) the phenyl group of the 2-piperidinone ring occupies the equatorial position. In intermediate A, there is clearly severe steric hindrance between the oxazaborolidine and the phenyl moiety and is therefore not favoured. The intermediate B on the other hand, has less steric hindrance between the oxazaborolidine and the equatorial C-4 phenyl of the 2-piperidinone ring. This is therefore the most likely intermediate giving the (4*R*) enantiomer of the product (Figure 17).



A (unfavoured) B (favoured)

Figure 17. Transition states for asymmetric reduction of imides

Comparison of the performance of the *B*-Me oxazaborolidine catalysts **76** and **77** with CBS catalyst **22** was conducted. The desymmetrisation of *N*-benzyl-4-phenylpiperidin-2,5-dione **174** was carried out with CBS catalyst **22** prepared *in situ* from (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol **20** using similar conditions employed for *B*-Me catalyst. The hydroxy-lactam was further reduced to the corresponding lactam **180**. Results from the desymmetrisation experiment showed only 13% yield and 14% ee of the lactam product (Scheme 80). Comparison of the results obtained from desymmetrisation of the same substrate with *B*-Me catalysts **76** and *B*-OMe catalyst **77** (Table 17) shows the remarkable superiority of both catalysts derived from *cis*-1-amino-indan-2-ol over the traditional CBS catalyst derived from (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol in desymmetrisation of glutarimides.



cat.	yield (%)	ee (%)
22	13	14
76	60	90
77	30	92

Scheme 80. Comparison of performance of catalysts

4.6 Conclusion

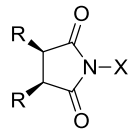
By adapting existing literature methodology, and some modifications where possible, various *N*-benzyl glutarimides have been successfully synthesised. This route could equally serve for the synthesis of 3-substituted glutaric acids and anhydrides. Anhydrides in particular are highly used for desymmetrisation processes.[51, 101, 102, 103, 104, 105]

The work has also shown that oxazaborolidines **76** and **77** gave excellent selectivity but a low yield in the desymmetrisation of *N*-PMP-3-phenyl glutarimide. The low yield was attributed to the formation of over reduced piperidine product. Investigation into correlation between high selectivity and formation of the over reduced product revealed that a stereoablative process is partly responsible for upgrade of ee in both versions of *B*-Me oxazaborolidine catalyst. A double stereo-differentiation process with strong matched and mismatched catalytic reductions in the two enantiomers of the catalyst was noted with *N*-PMP-3-phenyl glutarimide substrate.

Switching the nitrogen protecting group from *N*-PMP to *N*-benzyl, the *B*-Me catalyst **76** was shown to give a superior yield of the desymmetrised product than the *B*-OMe counterpart. The same catalyst was also shown to be effective in the desymmetrisation of various 3-substituted-*N*-benzyl glutarimides, giving good yield and excellent enantioselectivity of the chiral lactam products. The work also revealed that sterics at position-3 of the glutarimide can affect the catalyst performance as 3-(1-naphthyl) glutarimide **213** gave both poor yield and enantioselectivity of the desymmerised product.

4.7 Future work

The effect on structure for the desymmetrisation of 5 membered *meso*-imides **225** using oxazaborolidines as catalysts for the reduction has been fully investigated. The result showed that to obtain excellent stereocontrol the nitrogen protecting group has to be aryl and where R is a cyclic backbone, the *meso*-imide has to be based on a fused cyclohexyl group (Figure 18).

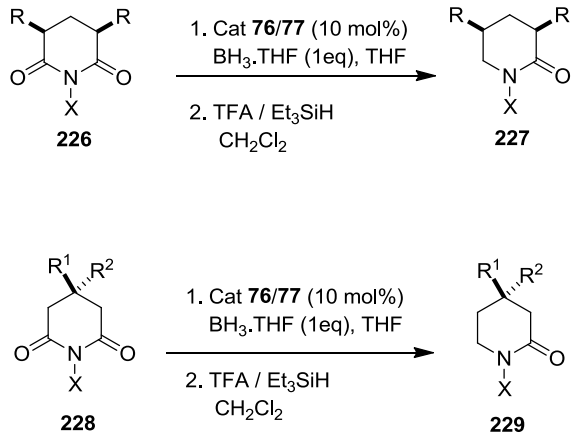


225

X = Bn, Ar, Alkyl

Figure 18. Five membered ring *meso* imides

Prior to this work, the desymmetrisation of six membered imides using oxazaborolidines has not been explored. An extension of this work would be to investigate the catalyst structure by using various oxazaborolines for the desymmetrisation process. Optimisation of the reaction conditions to minimize over reduction of the imide which could lead to higher yield of the product could also be performed. *meso* Glutarimides **226** and glutarimides **228** could also be targeted for desymmetrisation, assessing what controls the desymmetrisation of such systems. Variation of the functionalisation at the nitrogen atom and the stereogenic positions could be investigated (Scheme 81).



Scheme 81. Desymmetrisation of disubstituted imides

Further investigation on the stereoablative properties of both versions of *B*-Me and *B*-OMe catalysts on *N*-benzyl substrates could be investigated.

Chapter 5

Preparation of piperidine-containing structures

5.1 Background

Having successfully utilised desymmetrisation methodology for the synthesis of enantio-enriched 4-substituted lactams, investigations were directed towards functionalisation of the chiral lactams to 3,4-disubstituted 2-piperidinones that could give access to chiral piperidines.

Piperidines and their derivatives have become increasingly popular building blocks in a vast array of synthetic protocols because they are very important sub-units in natural products and synthetic pharmaceuticals.[106] During a recent 10-year period, several thousand piperidine compounds have been mentioned in clinical and preclinical studies.[107] Besides their interesting structural features, these compounds are also of pharmaceutical interest as they exhibit a wide range of biological activities.[107] Piperidinones serve a role as advanced intermediates prior to their conversion to piperidines.[108] Examples of natural products containing the piperidine ring include quinine **230**, hirsuteine **231** and dienomycin C **232**, all of which have potent biological activity (Figure 19).[109, 110, 111]

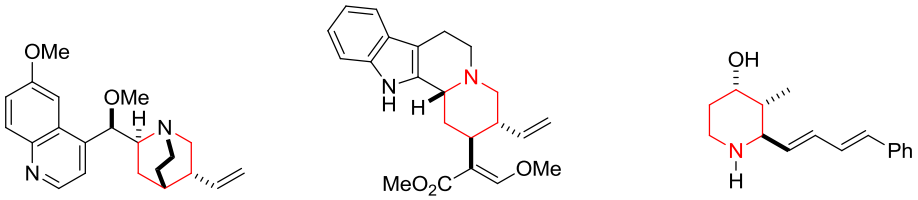


Figure 19. Some important natural products containing piperidine moiety

Pharmaceuticals containing piperidine moiety include psychotrine **236**, an HIV-1 reverse transcriptase inhibitor, paroxetine **233** and femoxitine **234**, which are selective serotonin uptake inhibitors and used as antidepressants.[112, 113] Paroxetine is also used in the treatment of Parkinson's disease (Figure 20).[114]

The absolute configurations at the C-3 and C-4 positions of the piperidine ring are critical for the activity of these compounds and 4-arylpiperidine in particular is an important structural motif in many biologically active compounds including paroxetine **233**, femoxetine **234** or Roche-1 **235** and psychotrine **236**.[114]

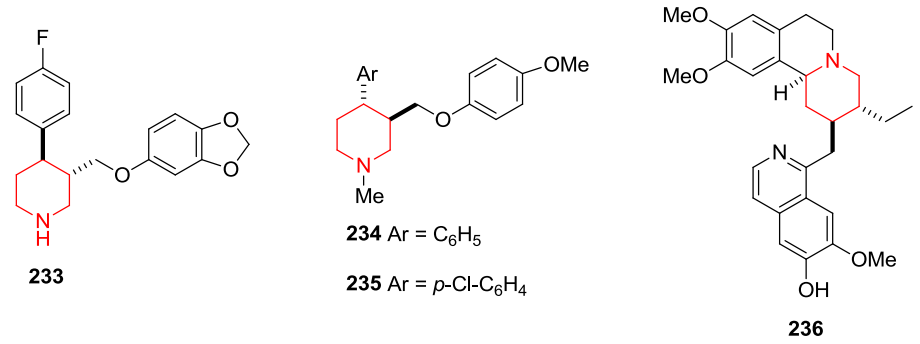
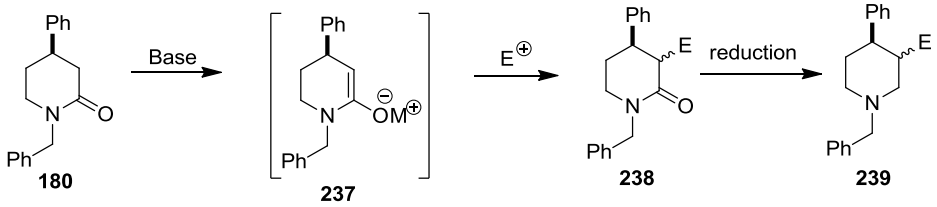


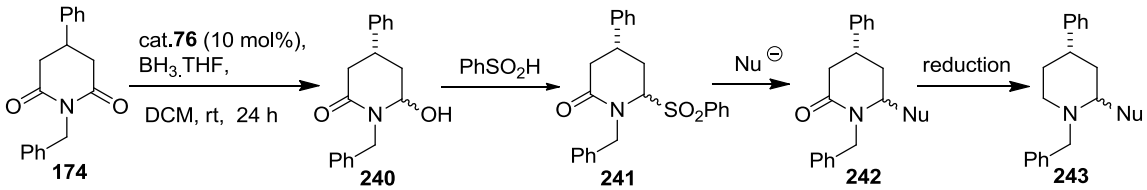
Figure 20. Some important pharmaceuticals containing piperidine moiety

In this work, the *N*-benzyl-4-phenyl lactam **180** was chosen as the representative compound for the functionalisation reactions. The first strategy was to attempt enolate chemistry by base abstraction of the acidic α-proton of the chiral lactam. The resultant enolate intermediate **237** generated *in situ* would then be reacted with an appropriate electrophile to generate a second stereogenic centre, thus giving a 3,4-disubstituted lactam **238**. The lactam could then be reduced to the corresponding 3,4-disubstituted piperidine **239** (Scheme 82).



Scheme 82. Substitution on position-3

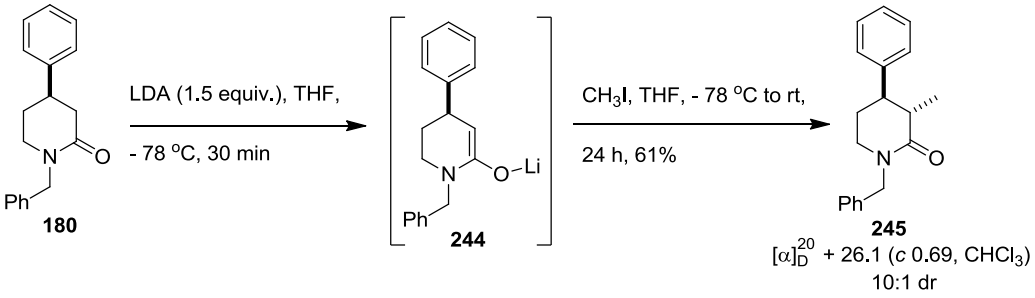
The second strategy was to try functionalisation at C-2. This could be accomplished by first performing an enantioselective desymmetrisation on the representative imide **174** using the *B*-Me catalyst **76**, employing conditions used for desymmetrisation. The resultant hydroxy-lactam **240** would then be reacted with phenylsulfinic acid to give the sulfone compound **241**, which would be made to undergo nucleophilic substitution on C-2 to give 2,4-disubstituted lactam **241**. Reduction of the lactam **241** would give the 2,4-disubstituted piperidine **243** (Scheme 83).



Scheme 83. Substitution on position-2

5.2 Enolate chemistry

The representative chiral lactam **180** was first reacted with LDA at –78 ^{o}C for 30 minutes to generate the enolate intermediate **244** *in situ*. Then methyl iodide was added as the electrophile (Scheme 85). After work-up the ^{1}H NMR spectrum of the crude material showed the formation of the 3-methyl substituted lactam product in 10:1 diastereomeric ratio. Purification by column chromatography led to isolation of the chiral 3-methyl lactam compound **245** as a single diastereomer in 61% yield (Scheme 84).



Scheme 84. α-Methylation of a representative chiral lactam

The C-3 configuration was established by COSY and nOe experiments. The nOe analysis showed a direct relationship of the C-3 methyl group with H_a and H_b protons (Figure 21). Irradiation of the methyl protons appearing as doublet at δ_H 2.20 led to enhancement in the signals of H_a as well as H_b protons. No enhancement was observed in any of the aromatic protons. This result suggests a *trans*-relationship between the C-3 methyl and the phenyl group on position-4 (Figure 21).

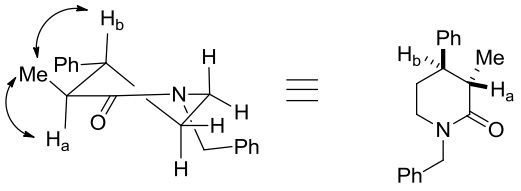


Figure 21. *trans*-Relationship between 3-methyl & 4-phenyl observed

A *cis*-relationship would have resulted in an enhancement in H_a proton signal due to gem-relationship with the irradiated methyl group, but should produce no effect on H_b proton which is distant to the methyl group. Furthermore, some of the C-4 phenyl protons would be affected (Figure 22).

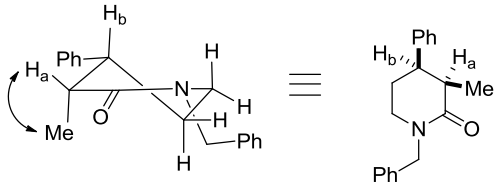


Figure 22. No *cis*-relationship between 3-methyl & 4-phenyl observed

The C-3 configuration may be explained as a result of the nucleophilic attack of the enolate ion on the electrophile from the opposite face of the phenyl on position-4 to avoid steric interactions (Figure 23).

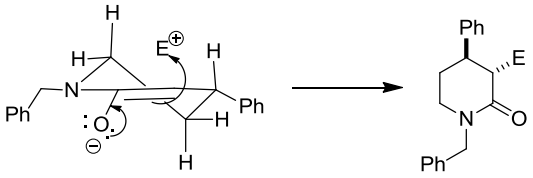
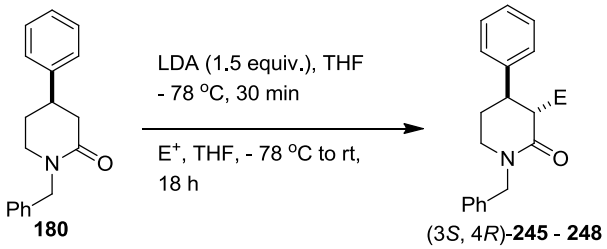


Figure 23. Attack of electrophile from opposite face of phenyl

5.2.1 Synthesis of piperidines

Having successfully transformed the 4-phenyl lactam **180** to the 3-methyl-4-phenyl lactam **245** in good yield, the versatility of the method was tested by deprotonating the representative lactam **180** and quenching with various electrophiles. The 3,4-disubstituted lactams **246** – **248** were isolated in good yields and excellent diastereoselectivity (Table 23). The 3-allyl lactam **246** and 3-benzyl lactam **247** were obtained as single diastereomers as observed by crude ^{1}H NMR spectra, while 3-methyl lactam **245** and 3-ethyl carboxylate lactam **248** were obtained as a 10:1 dr as observed in crude ^{1}H NMR spectra but only the major diastereomer was isolated (Table 23). The configuration of the 3-allyl-4-phenyldisubstituted lactam **246** was assigned as (3*S*, 4*R*) based on the configuration assigned for the 3-methyl-4-phenyl lactam **245**. The 3-benzyl-4-phenyl derivative **247** is a known compound, however the optical rotation was not given in the literature but the coupling constant for C*H*Ph proton (J = 9.7) matches closely with the literature value (J = 9.6) [115], and was therefore assigned (3*S*, 4*R*).



Scheme 85. Preparation of chiral 3-substituted-4-phenyl lactams

Table 23. Yields and optical properties of chiral 3-substituted-4-phenyl lactams

Entry	Electrophile	Yield (%)	dr (crude)	$[\alpha]_D^{20}$
1.	CH_3I	61 (**245**)	10:1	+26.1 (*c* 0.7 $CHCl_3$)
2.	CH_2=$CHCH_2MgBr$	62 (**246**)	100:0	+37.2 (*c* 1.2 $CHCl_3$)
3.	$PhCH_2Br$	57 (**247**)	100:0	-4.6 (*c* 4.0 $CHCl_3$)
4.	$ClCO_2Et$	71 (**248**)	10:1	+3.0 (*c* 0.1 $CHCl_3$)

A solution of LDA (1.5 equiv.) was added drop-wise to the solution of the substrate in dry THF at - 78 °C and stirred for 20 minutes. Then the electrophile (1.0 equiv.) was slowly added and the mixture stirred at - 78 °C for 2 h, allowed to warm to room temperature slowly and further stirred for 18 h. The product was purified by flash column chromatography

For the 3-ethyl carboxylate lactam **248**, the relative configuration of the major diastereomer was also confirmed as *trans* by COSY and nOe experiments. Irradiation of the H_a proton appearing as doublet around δ_H 3.66 (J = 11.0) led to enhancement in the signal of the two aromatic protons appearing as $(AX)_2$ around δ_H 7.22, showing a *trans*-relationship between the phenyl on position-4 and the carboxylate group on position-3 (Figure 24). Furthermore, the coupling constant for H_a (J = 11.0) matches the literature value for the closely-related compound (3*S*)-methylcarboxylate-(4*R*)-phenyl lactam **249** (J = 11.6) (Figure 24).[115]

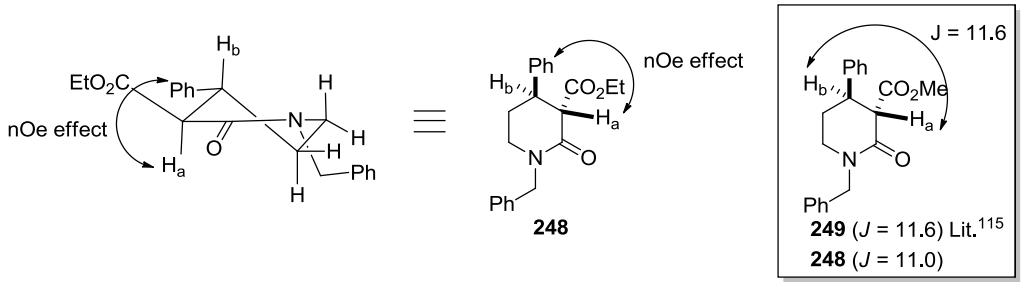
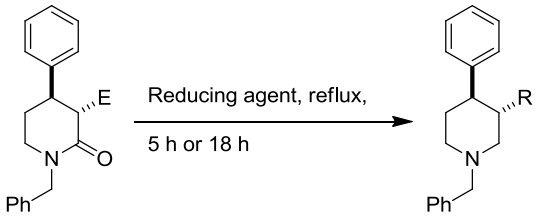


Figure 24. *trans*-relationship between 3-ethylcarboxylate & 4-phenyl observed

The chiral 3-substituted-4-phenyl lactams **245** – **248** were reduced to the corresponding piperidines by heating at reflux in the presence of lithium aluminium hydride as reducing agent for 18 hours. In the case of 3-methyl substituted lactam **245** and the 3-carboxylate lactam **248**, the reduction products could not be isolated in a reasonable yield when reduced with $LiAlH_4$. However, they were smoothly reduced by BH_3.THF to give the corresponding piperidines in moderate yields (Table 24). The methyl piperidine **249** was surprisingly obtained in a 10:1 diastereomeric ratio, due to epimerisation during the reaction (Table 24, entry 1). All the piperidines have their C*H*Ph proton coupling constant around J = 11.0, showing a 3,4-*trans* relationship. The exception is the 3-benzyl derivative **251** in which the proton merges with another proton to give a multiplet.



(3*S*, 4*R*)-**249** - **252**

Scheme 86. Preparation of chiral 3-phenyl-4-substituted piperidines

Table 24. Yields and optical properties of chiral 3-substituted 4-phenyl piperidines

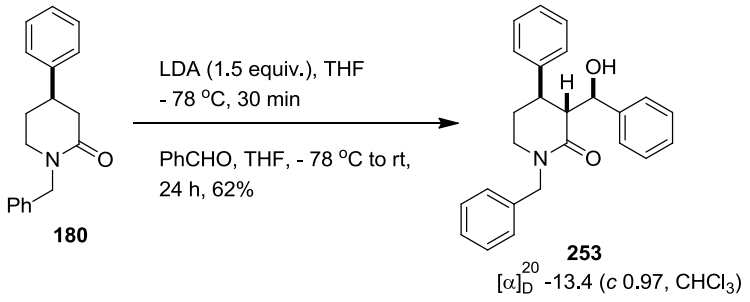
Entry	R		Reducing agent	Yield (%)	dr	$[\alpha]_D^{20}$
1.	$-CH_3$	(**249**)	BH_3.THF	65	10:1	-24.5 (*c* 1.8 $CHCl_3$)
2.	CH_2=$CHCH_2$-	(**250**)	$LiAlH_4$	52	100%	-15.0 (*c* 0.4 $CHCl_3$)
3.	$PhCH_2$-	(**251**)	$LiAlH_4$	61	100%	-16.6 (*c* 2.9 $CHCl_3$)
4.	$-CH_2OH$	(**252**)	BH_3.THF	55	100%	-22.2 (*c* 0.2 $CHCl_3$)

BH_3.THF (3 equiv.) or $LiAlH_4$ (3 equiv.) was added to a solution of the piperidin-2-one in dry THF. The mixture was heated at reflux for 5 hours (BH_3.THF) or 24 hours ($LiAlH_4$) and cooled to room temperature. The product was purified by flash column chromatography.

5.3 Aldol Reaction

Another important reaction in organic synthesis that utilizes enolate chemistry is the aldol condensation. The aldol addition reaction is a useful tool for the synthesis of biologically important natural products and considerable attention has been paid to the development of aldol methodology.[116]

In an effort to widen the scope of the lactam enolate chemistry, the representative lactam **180** was deprotonated using the standard procedure and the *in situ* generated enolate was quenched with benzaldehyde. After the normal work up, purification by flash column chromatography led to the isolation of the aldol adduct **253** in 62% yield as a single diastereomer (Scheme 87).



Scheme 87. Aldol reaction of the lactam 180

Although efforts to obtain crystals of the compound for a single crystal structure analysis failed, the configuration of the newly formed hydroxy benzylic stereogenic centre in the molecule was assigned as [(*R*)-hydroxyphenylmethyl] based on comparison of the coupling constants of a compound containing similar stereochemistry in the literature. The aldol product **253** is assumed to exist as intramolecularly H-bonded six-membered ring structure (Figure 25) as observed with comparable compound in the reference literature.[117] The proton (H_a) on position-3 of the piperidin-3-one ring appeared at δ 3.44 as a double doublet retaining its *trans* coupling (J = 11.7) with the H_b proton on position-4 [δ 2.66 (1H, td, J 11.7, 4.4] as observed in the 3-ethyl carboxylate lactam **248** and the rest of the piperidines, demonstrating a (3*S*, 4*R*) stereochemistry (Figure 25). The benzylic proton (H_c) appeared at δ 4.61 as a doublet coupled with H_a with J = 4.4 (Figure 25, Table 25). This matches closely with a similar proton of the *erythro*-isomer of a comparable compound **254** reported by House *et al*. (Figure 26, Table 25).[117] Furthermore, a Newman projection of the benzylic stereochemistry suggests a dihedral angle of 60° between H_a and H_c which according to Karplus relationship will have a J value between 2 – 5 Hz (Figure 25).

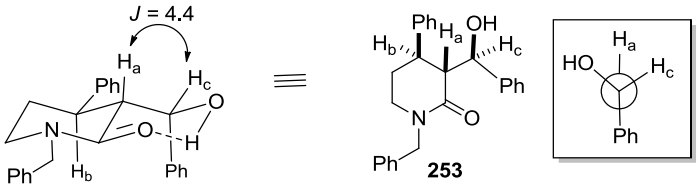


Figure 25. Comparing protons coupling constants in the aldol product 253

Table 25. Reference protons coupling constants

Entry	Proton	δ	Multiplicity	Coupling constant (*J*)
1	H_a	3.44	dd	11.7, 4.4
2	H_b	2.66	td	11.7, 4.4
3	H_c	4.61	d	4.4

Spectrum measured in $CDCl_3$ using 400 MHz spectrometer

In the reference work, the coupling constants of benzylic protons of the *threo* and *erythro* isomers of the aldol product **254**, existing as intramolecularly H-bonded six-membered ring structures, were compared in different solvents (Figure 26).[117] The coupling constant of the benzylic proton in the *threo*-isomer **254**(a) was found to be higher, at around J = 8.4 in all the three solvents (Table 26). The coupling constant of the benzylic proton in the e*rythro*-isomer **254**(b) on the other hand has a coupling constant of J = 2.4 – 4.3, which is comparable with the observed coupling constant of the H_c proton of the aldol adduct **253** in this work (Figure 26).

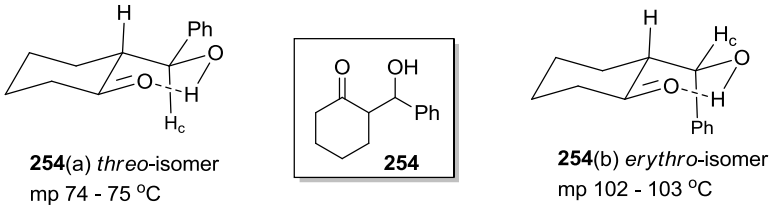


Figure 26. *Threo* and *erythro* isomers of the ketone 254

Table 26. Reference benzylic protons in the aldol adduct 254

Entry	Solvent	Benzylic proton H_c	
		254(a)	**254**(b)
1	D_2O	δ 4.68 (d, *J* 8.4)	δ 5.30 (d, *J* 2.4)
2	C_6D_6	δ 4.80 (d, *J* 8.4)	δ 5.38 (m)
3	CH_3OD	δ 4.95 (d, *J* 8.5)	δ 5.25 (d, *J* 4.3)

The transition state of the aldol reaction can therefore be pictured as a six-membered ring in a chair conformation with the electropositive lithium chelated between the two oxygen atoms of the two reacting molecules (Figure 27). The approaching benzaldehyde is oriented such that the large phenyl moiety is directed away from the C-4 phenyl substituent in the 2-piperidinone ring to minimise steric interaction. This makes the phenyl group in the aldehyde to adopt a *pseudo*-axial conformation in the six-membered transition state, thereby favouring the formation of the *erythro*-diastereomer.

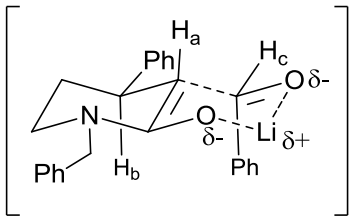


Figure 27. Proposed transition state for the aldol reaction

5.4 Formal synthesis of (-)-paroxitine and (-)-femoxetine

(-)-Paroxetine hydrochloride **233** marketed as Paxil/Seroxat, and (-)-femoxetine **234** (Figure 28) are selective serotonin reuptake inhibitors used in the treatment of depression, obsessive compulsive disorder, and panic. (-)-Paroxetine hydrochloride was reported to have generated sales in excess of over $1.0 billion/year.[112]

There have been a number of reported syntheses of these two pharmaceuticals showing different ways of enantioselective constructions of the (3*S*)- and (4*R*)-stereogenic centres.[113]

These ways include kinetic resolutions,[118, 119] chiral auxiliaries,[120] chiral bases,[121, 115] the use of chiral pool,[122] enantioselective catalysis,[100, 123] and enzymatic asymmetrisations.[112]

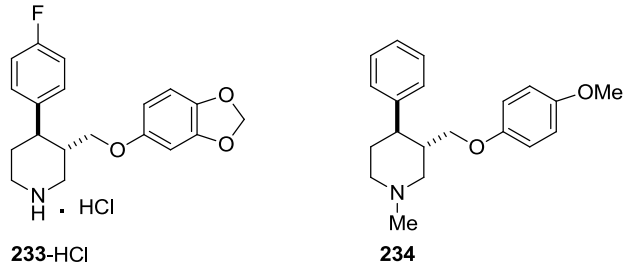


Figure 28. (3*S*, 4*R*) (-)-paroxetine hydrochloride and (-)-femoxetine

The desymmetrisation methodology has also been employed as an effective way of constructing these two stereogenic centres in paroxetine by some research groups. Various asymmetric desymmetrisations of a variety of achiral substrates (Figure 29) have been employed for that purpose. Yu *et al*. employed a porcine liver esterase (PLE) mediated asymmetric desymmetrisation of glutaric acid bis methyl ester **255**,[112] Liu *et al*. used desymmetrisation of 3-substituted glutaric anhydride **202** with (*S*)-methylbenzylamine.[103] Desymmetrisation of glutarimides have also been employed for the synthesis of (-)-paroxetine. Ikariya *et al*. used ruthenium catalysed asymmetric hydrogenation of glutarimide **256**[124] while Simpkins and co-workers employed a chiral lithium amide base desymmetrisation of glutarimide **210**[68] all for the synthesis of (-)-paroxetine.

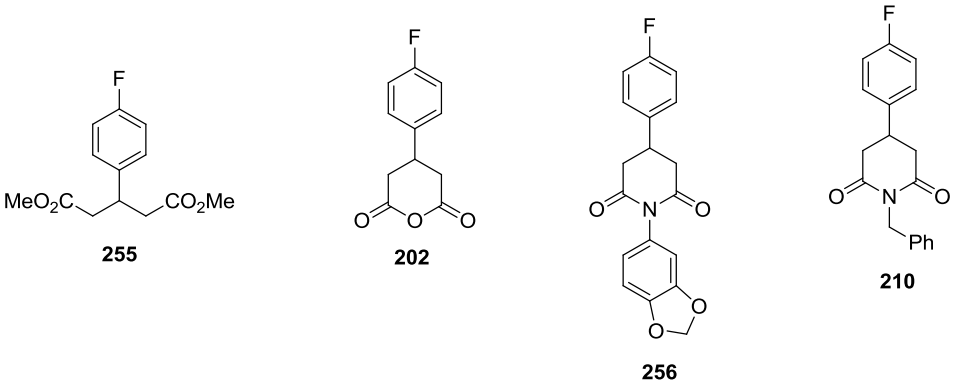
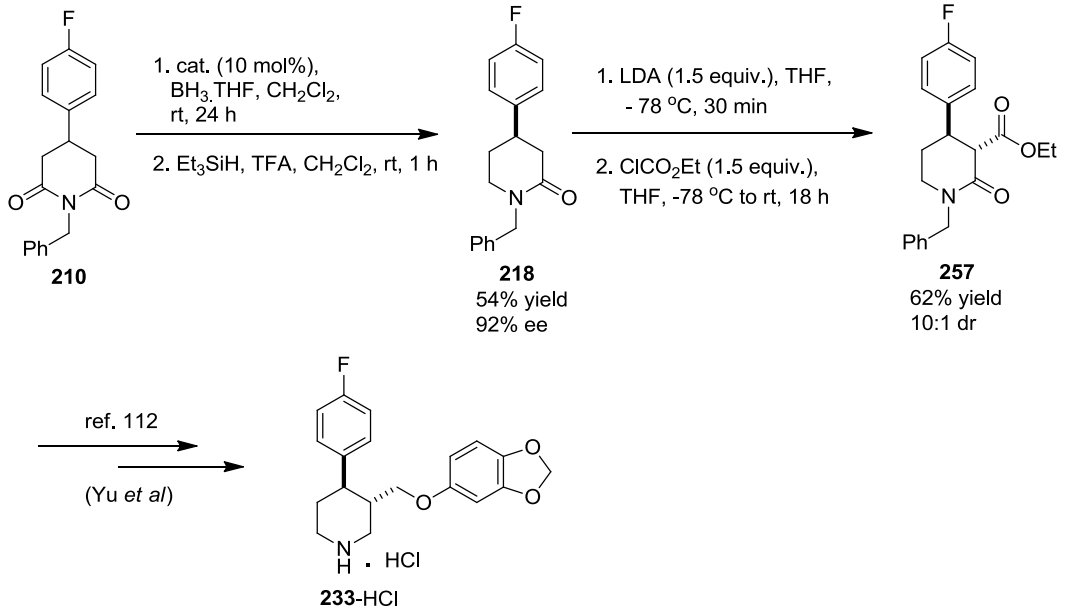


Figure 29. Substrates used for desymmetrisation methodology in the synthesis of (-)-paroxetine

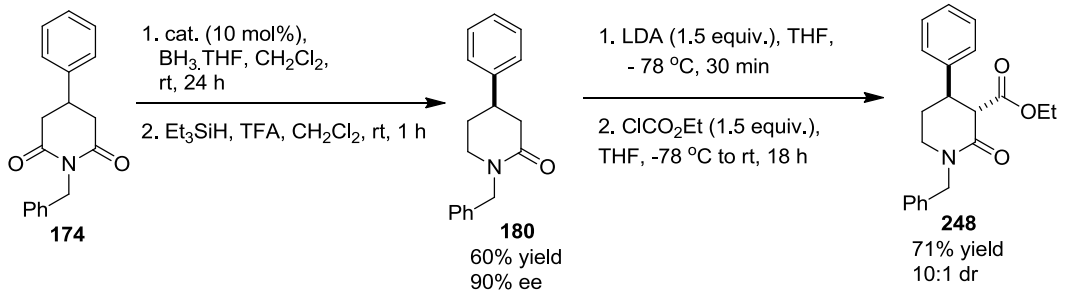
The desymmetrisation of glutarimides and their subsequent functionalisation to (3*S*, 4*R*) lactams carried out in this research work provides yet another convenient route to the construction of the two important stereogenic centres in these important pharmaceuticals. The 4-(*p*-fluorophenyl) lactam **218** obtained as the desymmetrisation product from the corresponding glutarimide **210** in 54% yield and 92% ee could serve as an important intermediate for (-)-paroxetine. Deprotonation of the lactam and quenching with ethyl chloroformate provided the corresponding carboxylate **257** in 62% and 10:1 diastereomeric

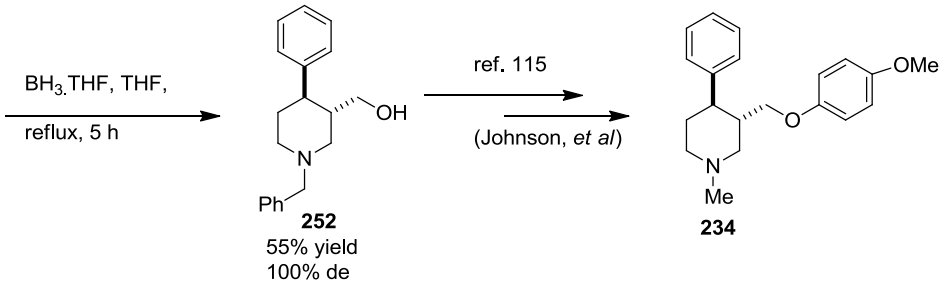
ratio (Scheme 89). The carboxylate intermediate **257** could be converted to (-)-paroxetine **233**-HCl in four steps by the method of Yu *et al*.[112] (Scheme 88).



Scheme 88. Formal synthesis of (3*S*, 4*R*) (-)-paroxetine

In the same way, the desymmetrised product **180** obtained in 60% yield and 90% ee from the corresponding glutarimide **174** could provide direct access to (-)-femoxetine **234**. The carboxylate intermediate **248** from the C-3 functionalisation of *N*-Bn lactam **180** was obtained in 71% yield and 10:1 dr. Subsequent borane reduction of the carboxylate compound gave the alcohol **252** in 55% yield as a single diastereomer (Scheme 89). The alcohol intermediate **252** could be converted to (-)-femoxetine in four steps by the method of Johnson, T. A *et al*.[115]

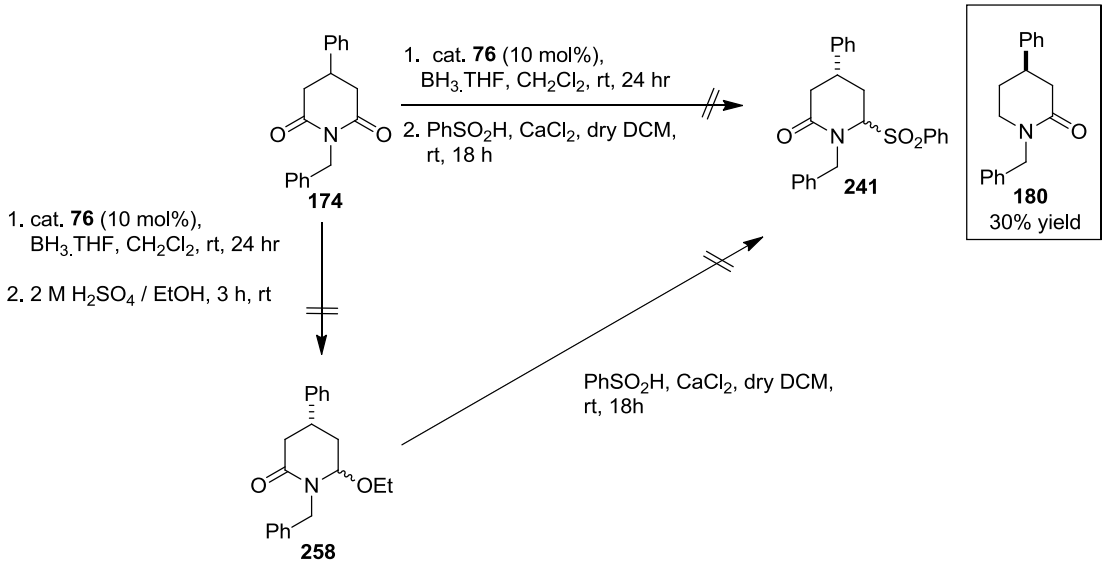




Scheme 89. Formal synthesis of (3*S*, 4*R*) (-)-fermoxetine

5.5 Substitution on carbon-2

Having achieved success in the enolate chemistry, attention was focused on C-2 functionalisation. The initial attempt was the synthesis of the 2-benzenesulfonyl compound **241** that could provide access to other C-2 functions. The representative imide **174** was subjected to reduction under standard conditions followed by treatment of the resultant crude hydroxy-lactam with phenylsulfinic acid in presence of $CaCl_2$ at room temperature for 18 hours. After standard work up and purification by flash column chromatography, the 4-phenyl lactam **180** was isolated in 30% yield instead of the expected sulfonyl compound (Scheme 90). Another attempt still led to isolation of the lactam **180**. An alternative route to the sulfonyl compound **241**, using literature procedure, was the conversion of the imide to the ethoxy lactam **258** which would then be converted to the sulfonyl compound **241** (Scheme 91).[125] Reduction of the phenyl imide **174** under standard conditions followed by treatment of the crude mixture with 2 M H_2SO_4 / EtOH for 3 hours at room temperature did not lead to the isolation of the ethoxy product **258**. The reaction was repeated and the crude product was treated with phenylsulfinic acid in presence of $CaCl_2$ at room temperature for 18 hours. Purification of the product surprisingly led to isolation of the phenyl lactam **180**, again in 30% yield, instead of the required C-2 substituted compound (Scheme 90).



Scheme 90. Attempted substitution of phenyl sulfonyl on C-2

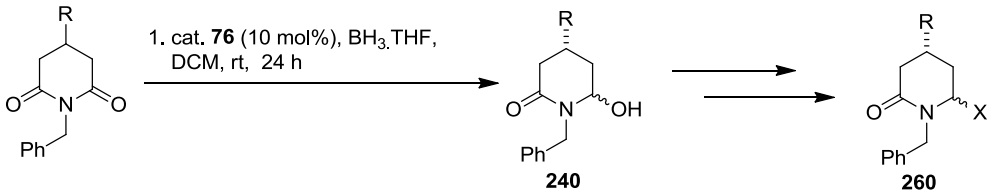
5.6 Conclusion

Functionalisation of a representative chiral desymmetrised product led to the synthesis of various (3*S*, 4*R*)-disubstituted 2-piperidinones in good yield and excellent diastereoselectivity. Reduction of the 2-piperidinones gave (3*S*, 4*R*)-disubstituted piperidines which are important structural motifs in many biologically active natural products and pharmaceuticals. Two of the piperidines could provide direct access to (3*S*, 4*R*)-(-)-paroxetine and (-)-femoxetine which are important antidepressants.

Attempts on the functionalisation of a representative hydroxy-lactam intermediate on carbon-2 persistently led to isolation of the corresponding 2-piperidinone.

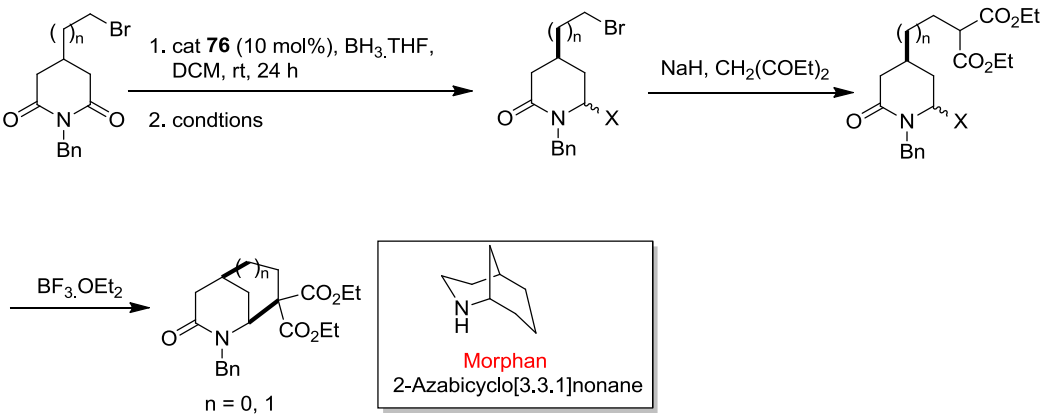
5.7 Future work

Functionalisation of the chiral lactams on C-3 applying an enolate methodology was found to occur readily. Functionalisation on C-2, however was more challenging. Investigation in to the optimised conditions that could convert the unstable hydoxy-lactam **240** to a more stable lactam which would then be converted to various C-2 functions could be carried out (Scheme 91).



Scheme 91. Substitution on C-2

The optimised functionalisation methodologies could be applied to the construction of 2-azabicyclo[3.3.1]nonane ring system, which is a core skeleton of biologically active alkaloid natural products (Scheme 92).



Scheme 92. Route to the construction of 2-azabicyclo[3.3.1]nonane

Chapter 6

Experimental

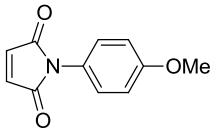
6.1 General

All solvents were obtained dry from a Grubbs dry solvent system and glassware was flame dried and cooled under vacuum before use. All dry reactions were carried out under nitrogen. TLC was carried out using Merck aluminium TLC sheets (silica gel 60 F_{254}), visualisation of TLC plates was performed using a UV lamp or by dipping in $KMnO_4$ then exposure to heat. Flash column chromatography was carried out with silica gel 40-63μ 60Å (Fluorochem Limited). ^{1}H and ^{13}C NMR spectra were measured using $CDCl_3$ as solvent unless otherwise stated, on a Brüker 250 or 400 MHz machine with an automated sample changer (unless otherwise stated). Chemical shifts for carbon and hydrogen are given on the δ scale relative to TMS (tetramethylsilane, δ = 0 ppm). Coupling constants were measured in Hz. ^{13}C NMR spectra were recorded using the JMOD method. Specific rotations were performed on an Optical Activity Ltd. AA-10 automatic polarimeter at 589nm (Na D-Line) and measured at 20 ^{o}C unless otherwise stated. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR machine using 0.5mm NaCl cells and mass spectra were recorded on a Kratos instrument using electrospray technique unless otherwise stated. HPLC was carried out on a Gilson analytical system using a Chiralcel (4.8 mm × 250 mm) column with 10% or 20% IPA in hexane as the solvent. The flow rate was 1.00 cm^3 per minute and the detector was set at 220 nm or 254 nm. All chemicals were used as received without further purification except (1*R*, 2*S*)-*cis*-1-amino-2-indanol, (1*S*, 2*R*)-*cis*-1-amino-2-indanol and anthracene which were recrystallised from hot toluene prior to use. Borane-THF was used as a 1M solution in THF.

Where compounds have been previously reported in the literature citing full analytical data, LRMS instead of HRMS is recorded and elemental analysis may not be carried out. However if a compound has been reported lacking data, the missing information has been recorded. Also, if elemental analysis is carried out LRMS instead of HRMS may be recorded.

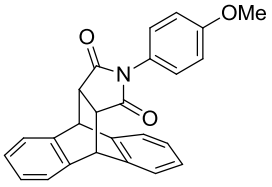
6.2 Experimental for the synthesis and desymmetrisation of meso-malimides

_N_-(_p_-Methoxyphenyl)-maleimide 100[126]



A solution of maleic anhydride (11.15 g, 0.114 mol) in toluene (200 cm^3) was treated with *p*-anisidine (14.00 g, 0.114 mol) and allowed to stir at room temperature for 1 hr. Dry zinc (II) chloride (15.49 g, 0.114 mmol) was added, the reaction warmed to 80 ^oC and hexamethyldisilazane (35.00 cm^3, 0.168 mol) was added portion-wise over a 40 min period. The reaction was heated at reflux for a further 4 hr, allowed to cool to room temperature and added to 1M HCl (130 cm^3). The product was extracted with EtOAc (3 × 50 cm^3) and the combined organic extracts were washed with saturated $NaHCO_3$ (3 × 50 cm^3), brine (3 × 50 cm^3) and dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* to afford the pure imide as a green crystalline solid (16.11 g, 70%). Mpt 134 – 136 ^oC (lit.[127] 136 – 138 ^oC); ν_{max} (ATR)/cm^{-1} 1703, 1510; ^1H NMR (250 MHz; $CDCl_3$) δ_H 3.85 (3H, s, OC*H*$_3$), 6.85 (2H, s, 2 × C*H*), 6.98 [2H, $(AX)_2$, ArC*H*], 7.23 [2H, $(AX)_2$, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 55.5 (*C*H$_3$), 114.5 (2 × Ar*C*H), 123.8 (Ar*C*), 127.6 (2 × Ar*C*H), 134.2 (2 × *C*=*C*H), 159.2 (Ar*C*), 169.8 (2 × *C*=O); *m*/*z* (TOF MS ES$^+$) 204 (100%, MH^+ $C_{11}H_{10}NO_3$). All data was in accordance with the literature.

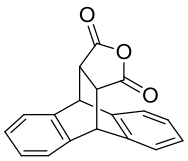
_N_-(_p_-Methoxyphenyl)-9,10-dihydro-9,10-ethanoanthracene-1',2'-dicarboximide 101[128]



Recrystallised anthracene (8.70 g, 49 mmol) and *N*-(*p*-methoxyphenyl)-maleimide **100** (10.0 g, 49 mmol) were suspended in toluene (350 cm^3). The suspension was heated at reflux for 5 hrs, cooled and the solvent was removed *in vacuo* to give a pale brown powder. The pure cycloadduct was obtained via recrystallisation from EtOAc to give the title compound as white powder (17.5 g, 94%). Mpt 240 – 242 ^oC (lit.[128] 258 ^oC); ν_{max} (ATR)/cm^{-1} 2362, 1708, 1608, 1511; ^1H NMR (400 MHz; $CDCl_3$) δ_H 3.39 [2H, $(AX)_2$, 2 × C*H*CO], 3.77 (3H, s, OC*H*$_3$), 4.92 [2H, $(AX)_2$, 2 × C*H*], 6.43 (2H, d, *J* 8.9, ArC*H*), 6.83 (2H, d, *J* 8.9, ArC*H*), 7.22 – 7.25 (4H, m, ArC*H*), 7.37 [2H, $(AX)_2$, ArC*H*], 7.45 [2H, $(AX)_2$, ArC*H*]; ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 45.9 (2 × *C*H), 47.0 (2 × *C*HCO), 55.4 (OCH_3), 114.5 (2 × Ar*C*H), 124.0 (Ar*C*), 124.4 (2 × Ar*C*H), 125.2 (2 × Ar*C*H), 126.9 (2 × Ar*C*H), 127.1 (2 × Ar*C*H), 127.6 (2

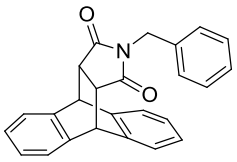
× Ar*C*H), 138.8 (Ar*C*), 141.3 (2 × Ar*C*), 159.6 (2 × Ar*C*), 176.4 (2 × *C*=O); *m/z* (TOF MS ES^+) 382.1437 (100%, MH^+ $C_{25}H_{20}NO_3$ requires 382.1443). All data was in accordance with the literature.

9,10-Dihydro-9,10-ethano-anthracene-11,12-dicarboxylic acid anhydride 102[128]



Maleic anhydride (11.0 g, 0.11mol) and anthracene (20.0 g, 0.11 mol) were suspended in toluene (500 cm^3) and heated at reflux for 6 hrs. Once cooled to rt, the solvent was removed *in vacuo* to yield a white powder. This was purified by recrystallisation from CH_2Cl_2 : petroleum ether (60-80) to give the title compound as white crystals (29.5 g, 97%). Mpt 256 – 258 ^oC (lit.[129] 261^oC); ν_{max} (ATR)/cm^{-1} 3069, 3021, 2977, 2161, 2032, 1834, 1768; ^1H NMR (400 MHz; $CDCl_3$) δ_H 3.55 [2H, $(AX)_2$, 2 × C*H*CO], 4.86 [2H, $(AX)_2$, 2 × C*H*], 7.20 – 7.26 (4H, m, ArC*H*), 7.36 (2H, dd, *J* 5.4, 3.2, ArC*H*), 7.42 (2H, dd, *J* 5.4, 3.2, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 45.4 (2 × *C*HCO), 48.0 (2 × *C*H), 124.4 (2 × Ar*C*H), 125.2 (2 × Ar*C*H), 127.2 (2 × Ar*C*H), 127.8 (2 × Ar*C*H), 138.1 (2 × Ar*C*), 140.6 (2 × Ar*C*), 170.5 (2 × *C*=O); *m/z* (TOF MS ES^-) 275.0697 [100%, M^- ($-H^+$) $C_{18}H_{11}O_3$ requires 275.0708], 293 (50), 302 (40). All data was in accordance with the literature.

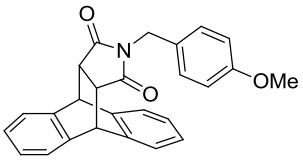
***N*-(Benzyl)-9,10-dihydro-9,10-ethanoanthracene-1',2'-dicarboximide 103**



Cycloadduct **102** (15.0 g, 53.4 mmol) was suspended in acetic acid (175 cm^3) followed by the addition of *N*-benzylamine (5.80 cm^3, 53.4 mmol). The resulting white suspension was heated at reflux overnight. Once cooled to RT the solution was added to an ice water mixture (200 cm^3) and stirred vigorously. The white precipitate formed was collected, and identified as the title compound that required no further purification (17.4 g, 89%). Mpt 221 – 223 ^oC; ν_{max} (ATR)/cm^{-1} 3062, 3034, 2966, 1770, 1690; ^1H NMR (400 MHz; $CDCl_3$) δ_H 3.25 [2H, $(AX)_2$, 2 × C*H*CO), 4.31 (2H, s, NCH_2), 4.80 [2H, $(AX)_2$, 2 × C*H*], 6.71 [2H, $(AX)_2$, ArC*H*], 7.02 [2H, $(AX)_2$, ArC*H*], 7.15 – 7.22 (7H, m, ArC*H*), 7.15 – 7.22 (2H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 42.1 (NCH_2), 45.4 (2 × *C*HCO), 46.9 (2 × *C*H), 124.2 (2 × Ar*C*H), 124.9 (2 × Ar*C*H), 126.7 (2 × Ar*C*H), 127.1 (2 × Ar*C*H), 127.3 (Ar*C*H), 127.7 (2 × Ar*C*H), 128.4 (2 ×

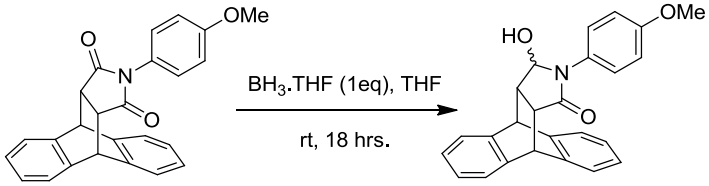
Ar*C*H), 134.9 (Ar*C*), 138.5 (2 × Ar*C*), 141.7 (2 × Ar*C*), 176.5 (2 × *C*=O); *m/z* (TOF MS ES$^+$) 366.1478 (100%, MH$^+$ $C_{25}H_{20}NO_2$ requires 366.1494).

***N*-(*p*-Methoxybenzyl)-9,10-dihydro-9,10-ethanoanthracene-1',2'-dicarboximide 104**[130]



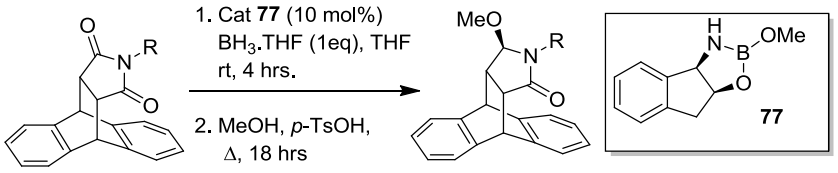
Cycloadduct **102** (15.0 g, 41.1 mmol), was suspended in acetic acid (175 cm^3) followed by addition of *p*-methoxy benzylamine (5.40 cm^3, 41.1 mmol). The resulting white suspension was heated at reflux overnight. Once cooled to rt the solution was added to an ice water mixture (200 cm^3) and stirred vigorously. The white precipitate was collected, which was identified as the title compound that required no further purification (14.3 g, 88%). Mpt 221 – 223 ^{o}C (lit.[130] 224 – 226 ^{o}C); ν_{max} (ATR)/cm^{-1} 3034, 2970, 2939, 2838, 1775, 1702, 1618, 1516; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.22 [2H, $(AX)_2$, 2 × C*H*CO], 3.79 (3H, s, OC*H*$_3$), 4.23 (2H, s, NC*H*$_2$), 4.79 [2H, $(AX)_2$, 2 × C*H*], 6.68 [4H, $(AX)_2$, ArC*H*], 7.00 [2H, $(AX)_2$, ArC*H*], 7.18 [4H, $(AX)_2$, ArC*H*], 7.38 [2H, $(AX)_2$, ArC*H*]; ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 41.6 (N*C*H$_2$), 45.4 (2 × *C*H), 46.9 (2 × *C*H), 55.3 (*C*H$_3$), 113.8 (2 × Ar*C*H), 124.2 (2 × Ar*C*H), 124.8 (2 × Ar*C*H), 126.7 (2 × Ar*C*H), 127.0 (2 × Ar*C*H), 127.3 (Ar*C*), 129.4 (2 × Ar*C*H), 138.5 (2 × Ar*C*), 141.7 (2 × Ar*C*), 158.8 (Ar*C*), 176.6 (2 × *C*=O). *m/z* (TOF MS ES$^+$) 396.1586 (100%, MH$^+$ $C_{26}H_{22}NO_3$ requires 396.1600). All data was in accordance with the literature.

Background reaction of *N*-(*p*-Methoxyphenyl)-9,10-dihydro-9,10-ethanoanthracene-1',2'-dicarboximide 101 with BH_3.THF



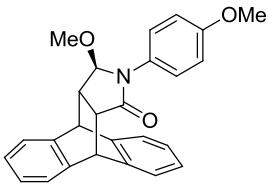
N-(*p*-Methoxyphenyl)-9,10-dihydro-9,10-ethanoanthracene-1',2'-dicarboximide **101** (0.18 mg, 0.50 mmol) was dissolved in THF (4 cm^3), treated with BH_3.THF (0.50 cm^3, 0.50 mmol) and allowed to stir at rt for 18 hrs. The reaction was quenched by addition of 1M HCl (1 cm^3) and H_2O (1 cm^3), the product was extracted with CH_2Cl_2 (3 × 5 cm^3) and the organic extracts dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* to give a white powder. ^{1}H NMR analysis showed only 2% conversion to the corresponding hydroxy-lactam.

General Procedure A for the asymmetric reduction of imide cycloadducts using *B*-OMe catalyst 77 followed by conversion to the corresponding -OMe aminal



A solution of (1*R*,2*S*)-*cis*-1-aminoindan-2-ol (0.19 g, 1.25 mmol) in THF (3 cm^3) was treated with trimethylborate (0.30 cm^3, 1.25 mmol) and allowed to stir for 45 mins. The solution was then diluted to 5 cm^3 by further addition of THF, to give the catalyst **77** as a stock solution. The cycloadduct (2.5 mmol) was dissolved in dry THF (20 cm^3) under a nitrogen atmosphere and this solution was treated with the catalyst stock solution (1 cm^3, 10 mol%) then BH_3.THF (2.50 cm^3, 2.50 mmol), and allowed to stir at rt for 4 hrs. The reaction was quenched by the addition of MeOH (5 cm^3) and 1M HCl (5 cm^3), and extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give the crude hydroxy-lactam as a white powder. The crude hydroxy-lactam was then dissolved in MeOH (150 cm^3), treated with *p*-TsOH.H_2O (0.1 equiv. of the crude hydroxy-lactam) and heated at reflux until no hydroxy-lactam remained via TLC (approximately 17 hrs). The reaction mixture was allowed to cool to room temperature and quenched with saturated aqueous $NaHCO_3$ (15 cm^3). The mixture was then extracted with CH_2Cl_2 (3 × 15 cm^3), the combined organic extracts dried over $MgSO_4$, filtered and solvent removed *in vacuo* to give a crude brown solid, which was purified via flash column chromatography eluting with EtOAc : petroleum ether (40-60) (3:7).

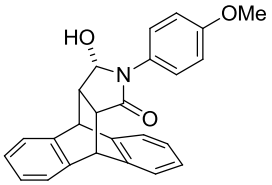
(3*R*,3a*S*,9a*R*)-2,3,3a,4,9,9a-Hexahydro-3-methoxy-2-(4-methoxyphenyl)-4,9[1',2']-benzeno-1*H*-benz[*f*]isoindol-1-one 107



The title compound was obtained as a white powder from 0.95 g (2.5 mmol) of cycloadduct **101** using general procedure **A** (0.60 g, 61% over 2 steps). $[\alpha]_D^{20}$ - 86 (*c* 0.07, $CHCl_3$; > 99% ee); Mpt. 102 – 104 ^oC; ν_{max} (ATR)/cm^{-1} 3036, 2954, 2833, 1693, 1608, 1510; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.73 (1H, ddd, *J* 9.2, 3.2, 1.2, C*H*), 3.24 – 3.27 (4H, m, OCH_3 + C*H*CO), 3.75 (3H, s, ArOCH_3), 4.48 (1H, d, *J* 3.2, C*H*), 4.63 (1H, app s, NC*H*), 4.83 (1H, d, *J* 3.6,

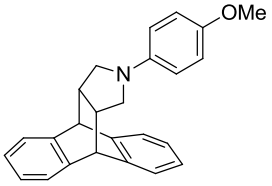
C*H*), 6.49 [2H, $(AX)_2$, ArC*H*], 6.73 [2H, $(AX)_2$, ArC*H*], 7.17 – 7.21 (4H, m, ArC*H*), 7.33 – 7.43 (4H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 43.3 (*C*H), 46.1 (*C*H), 47.5 (*C*H), 48.7 (*C*H), 52.8 (CH_3), 55.4 (CH_3), 95.2 (*C*H), 114.2 (2 × Ar*C*H), 123.8 (Ar*C*H), 124.3 (Ar*C*H), 124.6 (Ar*C*H), 125.4 (Ar*C*H), 126.4 (Ar*C*H), 126.5 (Ar*C*H), 126.7 (2 × Ar*C*H), 126.8 (2 × Ar*C*H), 129.8 (Ar*C*), 139.1 (Ar*C*), 140.6 (Ar*C*), 141.8 (Ar*C*), 142.4 (Ar*C*), 158.5 (Ar*C*), 173.7 (*C*=O); *m/z* (TOF MS ES$^+$) 398.1768 (100%, MH$^+$ $C_{26}H_{24}NO_3$ requires 398.1756). Chiral HPLC, CELLULOSE-1, 10% IPA in hexane @ 1.0 mL min^{-1}, t_R (major) 20.6 min and (minor) 23.7 min.

(3*S*,3a*S*,9a*R*)-2,3,3a,4,9,9a-Hexahydro-3-hydroxy-2-(4-methoxyphenyl)-4,9[1',2']-benzeno-1*H*-benz[*f*]isoindol-1-one 106



Using general procedure **A** with imide **101** (0.95 g, 2.5 mmol), *but purifying the crude hydroxy-lactam before conversion to the methoxy aminal* gave the title compound as a white powder (0.57 g, 60%). $[\alpha]_D^{20}$ -105.7 (*c* 2.54 $CHCl_3$); Mpt 218 – 220 ^oC; ν_{max} (ATR)/cm^{-1} 3318, 3018, 2938, 2834, 1663, 1609, 1587; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.56 (1H, app d, *J* 11.3, O*H*), 3.06 (1H, ddd, *J* 9.9, 7.9, 2.8, C*H*), 3.27 (1H, dd, *J* 9.9, 3.7, C*H*CO), 3.76 (3H, s, OCH_3), 4.81 (1H, d, *J* 2.8, C*H*), 4.91 (1H, d, *J* 3.7, C*H*), 5.63 (1H, dd, *J* 11.3, 7.9, NC*H*), 6.72 [2H, $(AX)_2$, ArC*H*], 6.82 [2H, $(AX)_2$, ArC*H*], 7.19 – 7.24 (4H, m, ArC*H*), 7.36 – 7.48 (4H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 42.1 (*C*H), 44.3 (*C*H), 46.1 (*C*H), 49.7 (*C*H), 55.4 (*C*H), 84.5 (OCH_3), 114.3 (2 × Ar*C*H), 123.7 (Ar*C*H), 124.3 (Ar*C*H), 124.4 (Ar*C*H), 126.2 (Ar*C*H), 126.3 (Ar*C*H), 126.5 (Ar*C*H), 126.6 (2 × Ar*C*H), 126.7 (Ar*C*H), 127.1 (Ar*C*H), 128.4 (Ar*C*), 140.9 (Ar*C*), 141.8 (Ar*C*), 142.4 (Ar*C*), 143.0 (Ar*C*), 158.3 (Ar*C*), 171.5 (*C*=O); *m/z* (TOF MS ES$^+$) 384.1600 (100%, MH$^+$ $C_{25}H_{22}NO_3$ requires 384.1600).

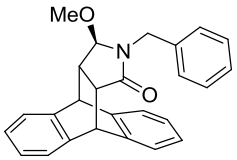
2-(4-Methoxyphenyl)octahydro-4,9[1',2']-benzeno-1*H*-benz[*f*]isoindole 111



Using general procedure **A** the title compound, a white powder, was obtained as a side product from 0.95 g (2.5 mmol) of cycloadduct **101** (0.17 g, 19% over 2 steps). Mpt. 100 –

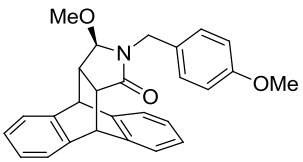
102 °C; ν_{max} (ATR)/cm^{-1} 2947, 2823, 2495, 2161, 2033, 1978, 1512; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.48 – 2.51 (2H, m, 2 × CH*H*), 2.92 – 2.94 (2H, m, 2 × CH*H*), 3.49 – 3.53 (2H, m, 2 × C*H*), 3.73 (3H, s, ArOC*H*$_3$), 4.26 [2H, (AX)$_2$, 2 × C*H*], 6.44 [2H, (AX)$_2$, ArC*H*], 6.76 [2H, (AX)$_2$, ArC*H*], 7.03 – 7.07 (2H, m, ArC*H*), 7.10 – 7.14 (2H, m, ArC*H*), 7.23 – 7.27 (2H, m, ArC*H*), 7.31 – 7.33 (2H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 44.2 (2 × *C*H), 47.8 (2 × *C*H), 52.1 (2 × *C*H$_2$), 55.8 (*C*H$_3$), 114.2 (2 × Ar*C*H), 114.6 (2 × Ar*C*H), 123.7 (2 × Ar*C*H), 125.6 (2 × Ar*C*H), 125.9 (2 × Ar*C*H), 126.0 (2 × Ar*C*H), 136.6 (Ar*C*), 141.0 (2 × Ar*C*), 143.8 (2 × Ar*C*), 151.5 (Ar*C*); *m/z* (TOF MS ES$^+$) 354.1866 (100%, MH$^+$ $C_{25}H_{23}NO$ requires 354.1858).

(3*R*,3a*S*,9a*R*)-2,3,3a,4,9,9a-Hexahydro-3-methoxy-2-benzyl-4,9[1',2']-benzeno-1*H*-benz[*f*]isoindol-1-one 108



Using general procedure **A** with imide **103** (0.91 g, 2.50 mmol) gave the title compound as a white powder (0.71 g, 75%). $[\alpha]_D^{20}$ - 50.2 (*c* 0.1, $CHCl_3$; 95% ee). Mpt 159 – 160 °C; ν_{max} (ATR)/cm^{-1} 3030, 2953, 2915, 1692; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.67 (1H, ddd, *J* 9.9, 3.5, 1.6, C*H*), 3.20 (3H, s, OC*H*$_3$), 3.23 (1H, d, *J* 3.5, C*H*CO), 3.66 (1H, d, *J* 14.8, NCH*H*), 4.24 (1H, app s, NC*H*), 4.31 (1H, d, *J* 3.5, C*H*), 4.75 (1H, d, *J* 14.8, NCH*H*), 4.79 (1H, d, *J* 3.5, C*H*), 6.34 (2H, app d, *J* 7.2, ArC*H*), 7.06 – 7.25 (9H, m, ArC*H*), 7.37 – 7.42 (2H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 43.1 (N*C*H$_2$), 42.6 (*C*H), 43.1 (*C*H), 45.5 (*C*H), 47.3 (*C*H), 50.0 (O*C*H$_3$), 90.5 (*C*HN), 123.6 (Ar*C*H), 124.1 (Ar*C*H), 124.8 (Ar*C*H), 125.2 (Ar*C*H), 126.2 (Ar*C*H), 126.4 (Ar*C*H), 126.7 (Ar*C*H), 126.8 (Ar*C*H), 127.0 (Ar*C*H), 127.8 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 134.7 (Ar*C*), 139.2 (Ar*C*), 140.6 (Ar*C*), 142.3 (Ar*C*), 142.9 (Ar*C*), 173.3 (*C*=O); *m/z* (TOF MS ES$^+$) 382.1812 (100%, MH$^+$ $C_{26}H_{24}NO_2$ requires 382.1807), 368 (10), 350 (20); Chiral HPLC, KROMASIL 3-CELLUCOAT, 10% IPA in hexane @ 1.0 mL min^{-1}, t_R (major) 8.1 min and (minor) 9.7 min.

(3*R*,3a*S*,9a*R*)-2,3,3a,4,9,9a-Hexahydro-3-methoxy-2-(4-methoxybenzyl)-4,9[1',2']-benzeno-1*H*-benz[*f*]isoindol-1-one 109

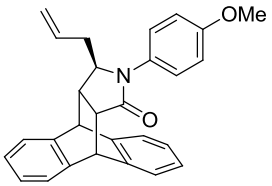


Using general procedure **A** with imide **104** (0.99 g, 2.50 mmol) gave the title compound as a white solid (0.40 g, 39%). $[\alpha]_D^{20}$ - 63.7 (*c* 0.2, $CHCl_3$; 97% ee). Mpt 189 – 192 °C; ν_{max}

(ATR)/cm^{-1} 2956, 2838, 1685, 1608, 1583; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.64 (1H, ddd, *J* 9.8, 3.1, 1.5, C*H*), 3.18 – 3.21 (4H, m, OCH_3 and C*H*), 3.58 (1H, d, *J* 14.7, NCH*H*), 3.82 (3H, s, OCH_3), 4.21 (1H, app s, NC*H*), 4.29 (1H, d, *J* 3.1, C*H*), 4.67 (1H, d, *J* 14.7, NCH*H*), 4.78 (1H, d, *J* 3.1, C*H*), 6.31 [2H, $(AX)_2$, ArC*H*], 6.66 [2H, $(AX)_2$, ArC*H*], 7.07 – 7.41 (8H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 42.5 (NCH_2), 43.0 (*C*H), 45.5 (*C*H), 47.3 (*C*H), 49.0 (*C*H), 51.9 (OCH_3), 55.3 (ArOCH_3), 90.4 (*C*HN), 113.8 (2 × Ar*C*H), 123.6 (Ar*C*H), 124.1 (Ar*C*H), 124.8 (Ar*C*H), 125.2 (Ar*C*H), 126.2 (Ar*C*H), 126.4 (Ar*C*H), 126.6 (Ar*C*H), 126.7 (Ar*C*H), 126.8 (Ar*C*), 129.2 (2 × Ar*C*H), 139.2 (Ar*C*), 140.6 (Ar*C*), 142.3 (Ar*C*), 142.9 (Ar*C*), 158.6 (Ar*C*), 173.2 (*C*=O); *m/z* (TOF MS ES$^+$) 412.1896 (100%, MH$^+$ $C_{27}H_{26}NO_3$ requires 412.1913), 398 (20), 380 (10); Chiral HPLC, KROMASIL 3-CELLUCOAT, 10% IPA in hexane @ 1.0 mL min^{-1}, t_R (major) 8.6 min and (minor) 16.6 min.

6.3 Experimental for the synthesis of pyrrolam A

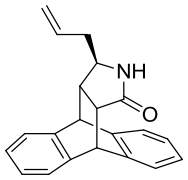
(3*R*,3a*S*,9a*R*)-2,3,3a,4,9,9a-Hexahydro-3-allyl-2-(*p*-methoxyphenyl)-4,9[1',2']-benzeno-1*H*-benz[*f*]isoindol-1-one 161



Methoxylactam **107** (2.30 g, 5.79 mmol) was dissolved in dry CH_2Cl_2 (30 cm^3) and cooled to -78 ^{o}C. $BF_3.OEt_2$ (1.45 cm^3, 11.6 mmol) and allyltrimethylsilane (1.84 cm^3, 11.6 mmol) in CH_2Cl_2 (5 cm^3) were added drop-wise, the solution was allowed to stir at -78 ^{o}C for 1 hr then allowed to warm to rt and stirred for a further 18 hrs. The reaction was quenched by addition of cold saturated $NaHCO_3$ (20 cm^3), extracted with CH_2Cl_2 (3 × 15 cm^3) and organic extracts dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* to give a brown powder, which was purified by flash column chromatography eluting with 50% EtOAc : petroleum ether (40 - 60), yielding the title compound as white crystals (1.75 g, 74%); $[\alpha]_D^{20}$ -61.0 (*c* 0.36, $CHCl_3$); Mpt 184 – 185 ^{o}C; ν_{max} (ATR)/cm^{-1} 2933, 1687, 1511; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.14 – 2.21 (1H, m, CH*H*), 2.30 – 2.36 (1H, m, CH*H*), 2.62 (1H, dt, *J* 9.8, 3.0, C*H*), 3.17 (1H, dd, *J* 9.8, 3.0, C*H*CO), 3.43 (1H, dt, *J* 7.5, 3.0, NC*H*), 3.75 (3H, s, OCH_3), 4.29 (1H, d, *J* 3.0, C*H*), 4.81 (1H, d, *J* 3.0, C*H*), 5.10 – 5.19 (2H, m, =CH_2), 5.74 (1H, ddt, *J* 17.0, 10.3, 7.0, =C*H*), 6.44 [2H, $(AX)_2$, ArC*H*], 6.76 [2H, $(AX)_2$, ArC*H*], 7.16 – 7.25 (4H, m, ArC*H*), 7.34 – 7.40 (4H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 38.4 (CH_2), 41.5 (*C*H), 46.0 (*C*HCO), 48.7 (*C*H), 49.6 (*C*H), 55.4 (OCH_3), 63.8 (N*C*H), 114.4 (2 ×

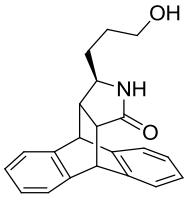
Ar*C*H), 119.5 (=*C*H_2), 123.7 (Ar*C*H), 124.2 (Ar*C*H), 124.8 (Ar*C*H), 125.4 (Ar*C*H), 126.1 (Ar*C*H), 126.2 (Ar*C*H), 126.3 (Ar*C*H), 126.8 (Ar*C*H), 127.3 (2 × Ar*C*H), 129.8 (Ar*C*), 132.4 (=*C*H), 139.7 (Ar*C*), 141.0 (Ar*C*), 142.2 (Ar*C*), 142.6 (Ar*C*), 158.4 (Ar*C*), 173.0 (*C*=O); *m/z* (EI) 407.1885 (17%, M^+ $C_{28}H_{25}NO_2$ requires 407.1903), 366 (7), 229 (6), 202 (4), 188 (100), 178 (89), 176 (10).

(3*R*,3a*S*,9a*R*)-2,3,3a,4,9,9a-Hexahydro-3-allyl-4,9[1',2']-benzeno-1*H*-benz[*f*]isoindol-1-one 162



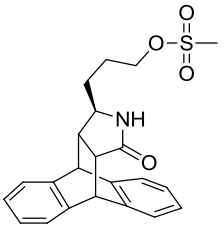
N-PMP amide **161** (1.41 g, 3.50 mmol) was dissolved in acetonitrile (100 cm^3), and cooled to 0 ^oC. Cerium (IV) ammonium nitrate (5.69 g, 10.5 mmol) in H_2O (100 cm^3) was added drop-wise over a 3 min period, and the resulting orange solution stirred vigorously at 0 ^oC for 30 mins. The acetonitrile was removed under reduced pressure and the aqueous layer extracted with EtOAc (3 × 25 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ (25 cm^3) and 10% sodium sulfite (20 cm^3 portions) was then added until the organic layer was colourless. The organic layer was washed with brine (20 cm^3), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a brown solid, which was purified via flash column chromatography on silica gel eluting with 70% EtOAc : petroleum ether (40-60), affording the title compound as a white powder (0.89 g, 84%). $[\alpha]_D^{20}$ - 40.0 (*c* 0.2, $CHCl_3$); Mpt 186 – 187 ^oC; ν_{max} (ATR)/cm^{-1} 3192, 3071, 2934, 1674, 1511; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.15 – 2.22 (1H, m, CH*H*), 2.31 – 2.38 (1H, m, CH*H*), 2.58 (1H, dt, *J* 10.1, 3.2, C*H*), 3.02 (1H, dd, *J* 10.1, 3.2, C*H*CO), 3.08 – 3.12 (1H, m, NC*H*), 4.27 (1H, d, *J* 3.2, C*H*), 4.70 (1H, d, *J* 3.2, C*H*), 5.10 – 5.16 (2H, m, =CH_2 and N*H*), 5.71 (1H, dddd, *J* 16.9, 10.4, 7.8, 6.5, =C*H*), 7.12 – 7.18 (4H, m, ArC*H*), 7.30 – 7.39 (4H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 41.9 (*C*H_2), 45.2 (*C*H), 45.4 (*C*HCO), 48.3 (*C*H), 48.5 (*C*H), 56.0 (NCH), 119.1 (=*C*H_2), 123.7 (Ar*C*H), 124.0 (Ar*C*H), 125.0 (Ar*C*H), 125.1 (Ar*C*H), 126.2 (Ar*C*H), 126.2 (Ar*C*H), 126.3 (Ar*C*H), 126.6 (Ar*C*H), 133.0 (=*C*H), 139.6 (Ar*C*), 140.6 (Ar*C*), 142.4 (Ar*C*), 142.7 (Ar*C*), 175.6 (*C*=O); *m/z* (TOF MS ES^+) 302 (100%, MH^+ $C_{21}H_{20}NO$), 324 (10, $M + Na^+$).

(3*R*,3a*S*,9a*R*)-2,3,3a,4,9,9a-Hexahydro-3-(3-hydroxypropyl)-4,9[1',2']-benzeno-1*H*-benz[*f*]isoindol-1-one 163



Alkene **162** (1.41 g, 4.6 mmol) was dissolved in dry THF (10 cm^3) and cooled to 0 ^oC, before BH_3.THF (7.0 cm^3, 7.0 mmol) was added drop-wise. The solution was allowed to warm to rt and stirred for a further 1 hr. H_2O (2 cm^3) was added to quench any residual borane, followed by addition of 1M NaOH (4 cm^3) and 30% H_2O_2 (4 cm^3) and left to stir vigorously for 1 hr. The reaction was quenched by addition of saturated $NaHCO_3$ (5 cm^3) and the product extracted using CH_2Cl_2 (3 × 10 cm^3). The organic extracts were washed with brine (10 cm^3), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give the crude material as a white crystalline solid (1.45 g). Full conversion of starting material was observed in the ^1H NMR spectrum. However, due to difficulties encountered during using silica gel the crude material was taken through to the next synthetic step without further purification. Selected data; ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.53 – 1.70 (4H, m, 2 × C*H*$_2$), 2.52 (1H, ddd, *J* 10.0, 3.2, 3.1, C*H*), 2.99 (1H, dd, *J* 10.0, 3.3, C*H*CO), 3.04 – 3.11 (1H, m, NC*H*), 3.65 – 3.68 (2H, m, C*H*$_2$OH), 4.25 (1H, d, *J* 3.1, C*H*), 4.67 (1H, d, *J* 3.3, C*H*), 5.54 (1H, br s, N*H*), 7.13 – 7.17 (4H, m, ArC*H*), 7.29 – 7.35 (4H, m, ArC*H*).

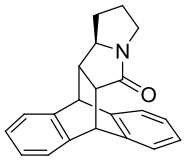
(3*R*,3a*S*,9a*R*)-2,3,3a,4,9,9a-Hexahydro-3-[3-(methylsulfonyloxy)propyl]-4,9[1',2']-benzeno-1*H*-benz[*f*]isoindol-1-one 164



Crude alcohol **163** (1.45 g, ~ 4.55 mmol) in dry CH_2Cl_2 (15 cm^3) was cooled to - 10 ^oC. NEt_3 (1.60 cm^3, 11.38 mmol) and DMAP (0.06 g, ~ 0.5 mmol) were added to the cold solution and the reaction left to stir for 10 mins. Methanesulfonyl chloride (0.50 cm^3, 5.92 mmol) was added and the solution was stirred for a further 1 hr at -10 ^oC. The reaction was quenched by careful addition of H_2O (5 cm^3) and 1M HCl (5 cm^3). The product was extracted with CH_2Cl_2 (3 × 10 cm^3), the organic extracts were washed with saturated $NaHCO_3$ (10 cm^3) and brine (10 cm^3), and dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* to give a brown powder 1.67 g. Full conversion of the starting material was observed in the ^1H NMR

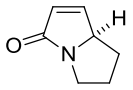
spectrum but this compound could not be purified on silica gel and it was taken forward to the next synthetic step without further purification. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.41 – 1.50 (1H, m, CH*H*), 1.63 – 1.81 (3H, m, CH*H* + CH_2), 2.52 (1H, ddd, *J* 10.1, 3.2, 3.1, C*H*), 2.97–3.12 (5H, m, C*H*CO + NC*H* + SO_3CH_3), 4.22 – 4.27 (3H, m, CH*H* + CH_2SO_3Me), 4.68 (1H, d, *J* 3.5, CH*H*), 5.43 (1H, br s, N*H*), 7.12 – 7.16 (4H, m, ArC*H*), 7.29 – 7.35 (4H, m, ArC*H*).

(3*R*,3a*S*,9a*R*)-2,3,3a,4,9,9a-Octahydro-(4*R*), 9-[1', 2']-benzeno-1*H*-benz-[*f*]-isoindolin-[2,3]-pyrrolidin-1-one 165



Crude mesylate **164** (1.67 g, ~ 4.21 mmol) was dissolved in EtOH (50 cm^3) and treated with DBU (0.80 cm^3, 5.47 mmol). The mixture was heated at reflux for 24 hrs, cooled to rt, after which 1M HCl (10 cm^3) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 cm^3), the combined organic extracts dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the product purified by flash column chromatography eluting with 70% EtOAc : petroleum ether (40-60). This gave the title compound as a white powder (0.21 g, 20% over three steps). $[\alpha]_D^{20}$ - 67.7 (*c* 0.16, $CHCl_3$); Mpt 226 – 228 ^{o}C; ν_{max} (ATR)/cm^{-1} 2955, 2868, 1688; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.14 – 1.25 (1 H, m, NC*H*H), 1.72 – 1.82 (1H, m, C*H*), 1.93 – 2.06 (2H, m, 2 × CH*H*), 2.65 – 2.71 (2H, m, 2 × CH*H*), 3.12 – 3.17 (2H, m, 2 × CH*H*), 3.45 (1H, dt, *J* 11.7, 8.3, 1 × NCH*H*), 4.35 (1H, d, *J* 3.2, C*H*), 4.71 (1H, d, *J* 3.2, C*H*), 7.11 – 7.17 (4H, m, ArC*H*), 7.30 – 7.37 (4H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 25.0 (*C*H_2), 31.6 (*C*H_2), 41.4 (N*C*H*H*), 42.9 (*C*H), 45.8 (*C*H), 48.3 (*C*H), 53.0 (N*C*H), 64.5 (*C*HCO), 123.7 (Ar*C*H), 123.9 (Ar*C*H), 125.0 (Ar*C*H), 125.1 (Ar*C*H), 126.0 (Ar*C*H), 126.1 (Ar*C*H), 126.2 (Ar*C*H), 126.6 (Ar*C*H), 140.1 (Ar*C*), 140.7 (Ar*C*), 142.7 (Ar*C*H), 142.8 (Ar*C*), 174.8 (*C*=O); *m/z* (TOF MS ES$^+$) 302 (100%, MH^+ $C_{21}H_{20}NO$), 324 (10, M + Na^+).

(5*R*)-Azabicyclo[3.3.0]oct-3-en-2-one [(*R*)-pyrrolam A] 112



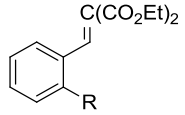
Lactam **165** (0.20 g, 0.66 mmol) was subjected to flash vacuum pyrolysis (inlet temperature 226 ^{o}C, furnace temperature 490 ^{o}C, pressure 1 × 10^{-2} mbar) for 30 mins. The crude material was collected in the u-tube (0.19 g). Purification by flash column chromatography eluting with 70% EtOAc : Petrol (40 - 60 ^{o}C) on silica gel gave the title compound as a white solid which slowly decomposes to yellow oily mixtures when left for 48 hours (0.06 mg, 69%

yield). Mpt 59 – 61 °C (Lit.[88] 59 °C); $[\alpha]_D^{20}$ - 23.3 (*c* 0.9, $CHCl_3$; 94% ee) lit.[88] -29.3 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3077, 2969, 2951, 2896, 2875, 1669; ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.14 – 1.23 (1H, m, 1 × C*H*), 2.08 – 2.15 (1H, m, 1 × C*H*), 2.23 – 2.41 (2H, m, CH_2), 3.31 (1H, ddd, *J* 11.0, 8.8, 2.3, 1 × CH*H*), 3.50 (1H, dt, *J* 11.0, 8.9, 1 × CH*H*), 4.29 (1H, dd, *J* 10.4, 6.0, C*H*), 6.06 (1H, dd, *J* 5.7, 1.6, =C*H*), 7.22 (1H, dd, *J* 5.7, 1.5, =C*H*) ; ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 29.0 (*C*H_2), 29.9 (*C*H_2), 41.9 (*C*H_2N), 67.8 (*C*HN), 128.5 (*C*H=C), 148.8 (C=*C*H), 175.6 (*C*=O) . *m*/*z* (TOF MS ES^+) 124 (100%, MH^+ $C_7H_{10}NO$), 146 (50 M + Na^+). Chiral HPLC, Lux 3u CELLULOSE-1, 10% IPA in hexane @ 1.0 mL min^{-1}, t_R (minor) 10.3 min and (major) 11.7 min. All data are in accordance with literature.[88]

6.4 Experimental for the synthesis of glutarimides

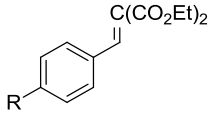
General Procedure B for the synthesis of 3-(substitutedphenyl)glutaric acids.[98]

B-1 Synthesis of benzylidenemalonate from 3-(o-Substituted)benzaldehydes



$AlCl_3$ (0.1 equiv.) was slowly added to a mixture of 2-substituted benzaldehyde and diethylmalonate (2 equiv.) and stirred at room temperature for 24 h. The mixture was poured into an ice-water / conc. HCl solution mixture (25 : 5 cm^3) and extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and excess diethylmalonate was removed by vacuum distillation (130 °C, 9.5 × 10^{-1} mbar) to give the crude diethyl 2-substitutedbenzylidenemalonate which was taken to next step (B-3) without further purification.

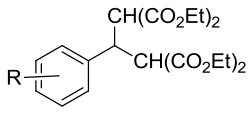
B-2 Synthesis of benzylidenemalonate from 3-(p-Substituted)benzaldehydes



A solution of *p*-substituted benzaldehyde in toluene (10 cm^3) was added drop-wise to a mixture of $AlCl_3$ (0.1 equiv.) and diethylmalonate (2 equiv.) in toluene (10 cm^3) and stirred at room temperature for 24 h. The mixture was poured into an ice-water / conc. HCl solution mixture (25 : 5 cm^3) and extracted with CH_2Cl_2 (3 × 25 cm^3). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and excess diethylmalonate was removed by vacuum distillation (130 °C, 9.5 × 10^{-1} mbar) to give crude

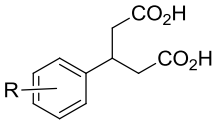
diethyl 4-substitutedbenzylidenemalonate as oily residue which was taken to next step (B-3) without further purification.

B-3 Synthesis of substitutedbenzylidene dimalonate



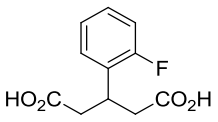
$AlCl_3$ (0.05 equiv.) was slowly added to a mixture of the crude benzylidenemalonate (obtained from procedure B-1 or B-2 above) and diethylmalonate (1 equiv.) and stirred at 60 ^oC for 24 h. Another portion of $AlCl_3$ (0.05 equiv.) was slowly added to the mixture and the reaction temperature was raised to 70 ^oC and further stirred for additional 24 h. The mixture was allowed to cool to room temperature, poured into an ice / conc. HCl solution mixture (25 : 5 cm^3) and extracted with CH_2Cl_2 (3 × 25 cm^3). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and excess diethylmalonate was removed by vacuum distillation (130 ^oC, 9.5 × 10^{-1} mbar) to give the crude tetraethyl 2-(*ortho* or *para* substituted phenyl)propane-1,1,3,3-tetracarboxylate as oily residue which was taken to the next synthetic step without further purification.

B-4 Synthesis of 3-(substitutedphenyl) glutaric acids



The crude benzylidene dimalonate (obtained in B-3 above) in conc. HCl (10 cm^3) was heated at reflux for 24 h. The conc. HCl was evaporated to about 4 cm^3 and fresh conc. HCl (10 cm^3) was added and further heated at reflux for additional 24 h. The mixture was allowed to cool to room temperature, the solid was filtered off and recrystallised from EtOAc / petrol (40 – 60 ^oC).

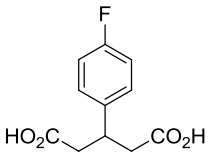
3-(2-Fluorophenyl)pentan-1,5-dioic acid 188



Using general procedure *B-1* starting with (8.250 g, 66.47 mmol) of 2-fluorobenzaldehyde and diethylmalonate (20.20 cm^3, 132.9 mmol), the crude diethyl 2-fluorobenzylidenemalonate (17.00 g) was obtained as a yellow liquid which was not purified. Selected data; ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.16 – 1.21 (6H, m, 2 × C*H*$_3$), 4.22 (4H, qd, *J* 7.1, 1.2, 4 × CH*H*), 7.00 – 7.07 (2H, m, ArC*H*), 7.28 – 7.34 (1H, m, ArC*H*), 7.38 [1H, $(AX)_2$,

ArC*H*], 7.83 (1H, s, =C*H*). This material was subjected to general procedure *B-3*, the tetraethyl 2-(2-fluorophenyl)propane-1,1,3,3-tetracarboxylate (23.29 g) was obtained as a yellow liquid. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.90 (6H, t, *J* 7.1, 2 × C*H*$_3$), 1.11 (6H, t, *J* 7.1, 2 × C*H*$_3$), 3.82 (4H, q, *J* 7.1, 2 × C*H*$_2$), 3.98 – 4.06 [6H, m, 2 × C*H*$_2$ and 2 × C*H*(CO)$_2$], 4.36 (1H, t, *J* 9.4, C*H*), 6.83 – 6.88 (1H, m, ArC*H*), 6.90 – 6.94 (1H, m, ArC*H*), 7.07 – 7.12 (1H, m, ArC*H*), 7.28 – 7.32 (1H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 13.7 (2 × *C*H$_3$), 13.9 (2 × *C*H$_3$), 38.3 (*C*H), 54.4 (2 × *C*H), 61.4 (2 × *C*H$_2$), 61.7 (2 × *C*H$_2$), 115.4 (d, *J* $_{C\text{-}F}$ 22.9, Ar*C*H), 123.8 (d, *J* $_{C\text{-}F}$ 3.3, Ar*C*H), 124.8 (d, *J* $_{C\text{-}F}$ 14.6, Ar*C*), 129.5 (d, *J* $_{C\text{-}F}$ 8.6, Ar*C*H), 131.6 (Ar*C*H), 161.2 (d, *J* $_{C\text{-}F}$ 248, Ar*C*), 167.4 (2 × *C*=O), 167.8 (2 × *C*=O). This material was subjected to procedure *B-4* to give a brown solid that was purified by recrystallisation from EtOAc / petrol (40 – 60 ^{o}C) giving the title compound as white crystals (7.660 g, 51% over 3 steps). Mpt 140 – 142 ^{o}C; (Found: C, 58.23; H, 4.96. $C_{12}H_{14}O_4$ requires C, 58.41; H, 4.90); υ_{max} (ATR)/cm^{-1} 2890 (broad), 1693, 1585; ^{1}H NMR (400 MHz; DMSO) δ_H 2.58 (2H, dd, *J* 15.9, 8.5, 2 × CH*H*), 2.66 (2H, dd, *J* 15.9, 6.6, 2 × CH*H*), 3.73 (1H, quintet, *J* 7.0, C*H*), 7.09 – 7.15 (2H, m, ArC*H*), 7.21 – 7.27 (1H, m, ArC*H*), 7.37 (1H, td, *J* 7.7, 1.5, ArC*H*), 12.16 (2H, s, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 31.8 (*C*H), 39.4 (2 × *C*H$_2$), 115.8 (d, *J* $_{C\text{-}F}$ 22.5, Ar*C*H), 124.7 (d, *J* $_{C\text{-}F}$ 2.9, Ar*C*H), 128.7 (d, *J* $_{C\text{-}F}$ 8.4, Ar*C*H), 129.5 (d, *J* $_{C\text{-}F}$ 4.5, Ar*C*H), 130.4 (d, *J* $_{C\text{-}F}$ 14.2, Ar*C*), 160.7 (d, *J* $_{C\text{-}F}$ 244.2, Ar*C*), 173.1 (2 × *C*=O); *m/z* (TOF MS ES^{+}) 227 (70%, MH^{+} $C_{11}H_{12}FO_4$), 209 (100).

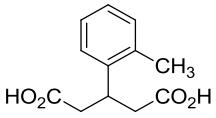
3-(4-Fluorophenyl)pentan-1,5-dioic acid 189



Using general procedure *B-2* starting with (10.00 g, 80.57 mmol) of 4-fluorobenzaldehyde and diethylmalonate (24.50 cm^3, 161.1 mmol), the crude diethyl 4-fluorobenzylidenemalonate (18.22 g) was obtained as a yellow liquid which was not purified. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.90 (3H, t, *J* 7.1, C*H*$_3$), 1.08 (3H, t, *J* 7.1, C*H*$_3$), 4.16 (2H, q, *J* 7.1, C*H*$_2$), 4.21 (2H, q, *J* 7.1, C*H*$_2$), 6.82 [2H, (AX)$_2$, ArC*H*], 7.35 [2H, (AX)$_2$, ArC*H*], 7.56 (1H, s, =C*H*). This material was subjected to general procedure *B-3*, and the crude tetraethyl 2-(4-fluorophenyl)propane-1,1,3,3-tetracarboxylate (23.29 g) was obtained as a yellow liquid which was not purified at this stage. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.89 (6H, t, *J* 7.1, 2 × C*H*$_3$), 1.08 (6H, t, *J* 7.1, 2 × C*H*$_3$), 3.82 (4H, q, *J* 7.1, 2 × C*H*$_2$), 3.94 – 4.02 (7H, m, 2 × C*H*$_2$ and 3 × C*H*), 6.80 (2H, app t, *J* 8.7, 2 × ArC*H*), 7.24 [2H, (AX)$_2$, ArC*H*]. This material was subjected to procedure *B-4*, to give a brown solid that

was purified by recrystallisation from EtOAc / petrol (40 – 60 ^{o}C) giving the title compound as white crystals (9.881 g, 55% over 3 steps). Mpt 145 – 147 ^{o}C (lit.[103, 131] 146 – 147 ^{o}C); (Found: 58.36; H, 4.65. $C_{11}H_{11}FO_4$ requires C, 58.41; H, 4.90); υ_{max} (ATR)/cm^{-1} 2914 (broad), 2672, 1708, 1604, 1509; ^{1}H NMR (400 MHz; DMSO) δ_H 2.51 (2H, dd, *J* 15.8, 8.8, 2 × CH*H*), 2.65 (2H, dd, *J* 15.8, 6.2, 2 × CH*H*), 3.37 – 3.45 (1H, m, C*H*), 7.10 (2H, app t, *J* 8.8, ArC*H*), 7.31 [2H, $(AX)_2$, ArC*H*], 12.11 (2H, bs, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 37.7 (*C*H), 40.6 (2 × *C*H_2), 115.3 (d, $J_{C\text{-}F}$ 21.0, 2 × Ar*C*H), 129.8 (d, $J_{C\text{-}F}$ 7.8, 2 × Ar*C*H), 140.0 (d, $J_{C\text{-}F}$ 2.6, Ar*C*), 161.3 (d, $J_{C\text{-}F}$ 241.9, Ar*C*), 173.2 (2 × *C*=O); *m*/*z* (TOF MS ES^{+}) 227 (30%, MH^{+} $C_{11}H_{12}FO_4$), 250 (20%, MH^{+} + Na), 209 (100). All data are in accordance with literature.

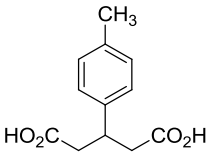
3-(2-Methylphenyl)pentan-1,5-dioic acid 190



Using general procedure *B-1* starting with (9.350 g, 77.82 mmol) of 2-methylbenzaldehyde and diethylmalonate (23.60 cm^{3}, 155.6 mmol), the crude diethyl 2-methylbenzylidenemalonate (17.00 g) was obtained as a yellow liquid, which was not purified. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.05 (3H, t, *J* 7.1, C*H*$_3$), 1.22 (3H, t, *J* 7.1, C*H*$_3$), 2.24 (3H, s, C*H*$_3$), 4.10 (2H, q, *J* 7.1, C*H*$_2$), 4.20 (2H, q, *J* 7.1, C*H*$_2$), 7.02 – 7.09 (2H, m, ArC*H*), 7.15 (1H, app td, *J* 7.5, 1.2, ArC*H*), 7.26 (1H, d, *J* 7.5, ArC*H*), 7.87 (1H, s, =C*H*). This material was subjected to procedure *B-3*, and the crude tetraethyl 2-(2-methylphenyl)propane-1,1,3,3-tetracarboxylate (15.90 g) was obtained as a yellow liquid which was not purified at this stage. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.89 (6H, t, *J* 7.1, 2 × C*H*$_3$), 1.17 (6H, t, *J* 7.1, 2 × C*H*$_3$), 2.42 (3H, s, C*H*$_3$), 3.80 (4H, q, *J* 7.1, 2 × C*H*$_2$), 3.96 [2H, d, *J* 9.5, 2 × C*H*$(CO)_2$], 4.03 – 4.11 (4H, m, 2 × C*H*$_2$), 4.51 (1H, t, *J* 9.5, C*H*), 7.00 – 7.06 (3H, m, ArC*H*), 7.18 (1H, d, *J* 6.8, ArC*H*). This material was subjected to general procedure *B-4* to give a brown solid that was purified by recrystallisation from EtOAc / petrol (40 – 60 ^{o}C) giving the title compound as white crystals (8.942 g, 52% over 3 steps). Mpt 154 – 156 ^{o}C; (Found: 64.71; H, 6.46. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35); υ_{max} (ATR)/cm^{-1} 2971 (broad), 1708; ^{1}H NMR (400 MHz; DMSO) δ_H 2.37 (3H, s, C*H*$_3$), 2.49 – 2.63 (4H, m, 2 × C*H*$_2$), 3.69 – 3.76 (1H, m, C*H*), 7.04 – 7.16 (3H, m, ArC*H*), 7.27 (1H, d, *J* 7.6, ArC*H*), 12.60 (2H, s, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 19.7 (*C*H$_3$), 33.2 (*C*H), 40.5 (2 ×

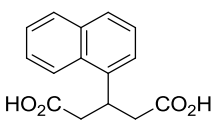
CH_2), 126.2 (Ar*C*H), 126.4 (Ar*C*H), 126.5 (Ar*C*H), 130.5 (Ar*C*H), 136.2 (Ar*C*), 142.3 (Ar*C*), 173.4 (2 × *C*=O); *m*/*z* (TOF ES^-) 221 (100%, $M\text{-}H^-$).

3-(4-Methylphenyl)pentan-1,5-dioic acid 191



Using general procedure *B-2* starting with (10.00 g, 83.23 mmol) of 4-methylbenzaldehyde and diethylmalonate (25.30 cm^3, 166.5 mmol), the crude diethyl 4-methylbenzylidenemalonate (17.23 g) was obtained as a yellow liquid, which was not purified. This material was subjected to procedure *B-3*, and the crude tetraethyl 2-(4-methylphenyl)propane-1,1,3,3-tetracarboxylate (25.20 g) was obtained as a yellow liquid which was not purified at this stage. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.98 (6H, t, *J* 7.1, 2 × C*H*$_3$), 1.18 (6H, t, *J* 7.1, 2 × C*H*$_3$), 2.22 (3H, s, C*H*$_3$), 3.90 (4H, q, *J* 7.1, 2 × C*H*$_2$), 4.02 – 4.15 (7H, m, 2 × C*H*$_2$ and 3 × C*H*), 7.0 (2H, d, *J* 8.0, 2 × ArC*H*), 7.17 (2H, d, *J* 8.0, 2 × ArC*H*). This material was subjected to general procedure *B-4* to give a brown solid that was purified recrystallisation from EtOAc / petrol (40 – 60 ^{o}C) giving the title compound as white crystals (10.55 g, 57% over 3 steps). Mpt 122 – 124 ^{o}C (lit.[132] 118 – 121 ^{o}C); (Found: 64.85; H, 6.13. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35); υ_{max} (ATR)/cm^{-1} 2925 (broad), 1704, 1515; ^{1}H NMR (400 MHz; DMSO) δ_H 2.25 (3H, s, C*H*$_3$), 2.48 (2H, dd, *J* 15.7, 8.7, 2 × CH*H*), 2.62 (2H, dd, *J* 15.7, 6.3, 2 × CH*H*), 3.34 – 3.41 (1H, m, C*H*), 7.07 (2H, d, *J* 8.0, 2 × ArC*H*), 7.14 (2H, d, *J* 8.0, 2 × ArC*H*), 12.06 (2H, s, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 21.1 (*C*H$_3$), 38.0 (*C*H), 40.7 (2 × *C*H$_2$), 127.8 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 135.8 (Ar*C*), 140.8 (Ar*C*), 173.3 (2 × *C*=O); *m*/*z* (TOF MS ES^+) 223 (10%, MH^+), 205 (100, MH^+ - H_2O). All data are in accordance with literature.

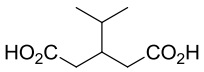
3-(1-Naphthyl)pentan-1,5-dioic acid 192



Using general procedure *B-1* starting with (10.35 g, 66.27 mmol) of 1-naphthaldehyde and diethylmalonate 20.12 cm^3 (132.5 mmol), the crude diethyl 1-naphthylidenemalonate (19.25 g) was obtained as a pale yellow liquid, which was not purified. Selected data; ^{1}H NMR (400

MHz; $CDCl_3$) δ_H ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.06 (3H, t, *J* 7.1, C*H*$_3$), 1.38 (3H, t, *J* 7.1, C*H*$_3$), 4.18 (2H, q, *J* 7.1, C*H*$_2$), 4.38 (2H, q, *J* 7.1, C*H*$_2$), 7.42 (1H, t, *J* 7.8, ArC*H*), 7.49 – 7.56 (2H, m, ArC*H*), 7.61 (1H, d, *J* 7.8, ArC*H*), 7.83 – 7.87 (2H, m, ArC*H*), 8.00 (1H, d, *J* 7.8, ArC*H*), 8.50 (1H, s, =C*H*). This material was subjected to procedure *B-3*, and the crude tetraethyl 2-(1-naphthyl)propane-1,1,3,3-tetracarboxylate (32.56 g) was obtained as dark brown liquid which was not purified at this stage. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.73 (6H, t, *J* 7.1, 2 × C*H*$_3$), 1.17 (6H, t, *J* 7.1, 2 × C*H*$_3$), 3.67 – 3.76 (4H, m, 2 × C*H*$_2$), 4.06 – 4.14 (4H, m, 2 × C*H*$_2$), 4.24 [2H, d, *J* 9.0, 2 × C*H*(CO)$_2$], 5.25 (1H, t, *J* 9.0, C*H*), 7.37 (1H, t, *J* 7.7, ArC*H*), 7.43 (1H, t, *J* 7.7, ArC*H*), 7.51 – 7.56 (2H, m, ArC*H*), 7.70 (1H, d, *J* 8.1, ArC*H*), 7.76 (1H, d, *J* 8.1, ArC*H*), 8.41 (1H, d, *J* 8.1, ArC*H*). This material was subjected to general procedure *B-4* to give a brown solid that was purified recrystallisation from EtOAc / petrol (40 – 60 ^{o}C) giving the title compound as white crystals (10.20 g, 60% over 3 steps). Mpt 185 – 187 ^{o}C (lit.[133] 181.5 ^{o}C); (Found: C, 69.64; H, 5.39. $C_{15}H_{14}O_4$ requires C, 69.76; H, 5.46); υ_{max} (ATR)/cm^{-1} 2904 (broad), 1707, 1599, 1511; ^{1}H NMR (400 MHz; DMSO) 2.76 (4H, d, *J* 7.2, 2 × C*H*$_2$), 3.39 (1H, quintet, *J* 7.2, C*H*), 7.46 – 7.62 (4H, m, ArC*H*), 7.80 (1H, d, *J* 7.8, ArC*H*), 7.93 (1H, d, *J* 8.1, ArC*H*), 8.21 (1H, d, *J* 8.6, ArC*H*), 12.17 (2H, s, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 38.0 (*C*H), 40.3 (2 × *C*H$_2$), 123.5 (Ar*C*H), 123.7 (Ar*C*H), 125.9 (Ar*C*H), 126.0 (Ar*C*H), 126.6 (Ar*C*H), 127.3 (Ar*C*H), 129.2 (Ar*C*H), 131.5 (Ar*C*), 134.0 (Ar*C*), 140.0 (Ar*C*), 173.4 (2 × *C*=O); *m*/*z* (TOF MS ES$^-$) 257 (100%, M-H$^-$ $C_{15}H_{13}O_4$).

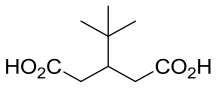
3-Isopropylpentan-1,5-dioic acid 194



Piperidine (1.180 g, 13.86 mmol) was added to a mixture of isobutyraldehyde (10.00 g, 138.7 mmol) and diethylmalonate (22.21 g, 138.7 mmol) dissolved in pyridine (25 cm^3) and stirred at 70 ^{o}C for 48 h. The mixture was cooled to room temperature and ethyl acetate (150 cm^3) was added, washed with 1M HCl (4 × 20 cm^3), then brine (20 cm^3), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give crude diethyl isopropylidenemalonate (21.53 g) as a yellow oily residue which was not purified. This material was subjected to procedure *B-3*, and the crude tetraethyl 2-isopropylpropane-1,1,3,3-tetracarboxylate (25.56 g) was obtained as an oily residue which was not purified at this stage. This material was subjected to general procedure *B-4* but the final acidic mixture, after allowing to cool to room temperature, was poured in to ice / water mixture (50 cm^3) and extracted with ether (4 × 30

cm^3). The combined ethereal portions were washed with water, dried over $MgSO_4$, filtered and solvent evaporated *in vacuo* to obtain a dark brown liquid which upon standing in fridge turned to brown solid. Purification by recrystallisation from EtOAc / petrol (40 – 60 ^oC) gave the title compound as white crystals (8.211 g, 34% over 3 steps). Mpt 94 – 96 ^oC (lit.[134] 100 – 101 ^oC); (Found: 55.14; H, 8.16. $C_8H_{14}O_4$ requires C, 55.16; H, 8.10); υ_{max} (ATR)/cm^{-1} 2966 (broad), 2160, 1692; ^1H NMR (400 MHz; DMSO) δ_H 0.82 (6H, d, *J* 6.9, 2 × C*H*$_3$), 1.70 (1H, pent d, *J* 6.9, 3.4, C*H*), 2.10 – 2.15 (3H, m, 2× CH*H* and C*H*), 2.19 – 2.26 (2H, m, 2 × CH*H*), 12.10 (2H, bs, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 19.2 (2 × *C*H$_3$), 29.9 (*C*H), 35.9 (2 × *C*H$_2$), 37.5 (*C*H), 174.5 (2 × *C*=O); *m*/*z* (TOF MS ES$^+$) 198 (40%, M + Na$^+$), 175 (30, MH$^+$ $C_8H_{15}O_4$), 157 (100). Only melting point and ^1H NMR were given in literature.

3-*tert*-Butylpentan-1,5-dioic acid 195



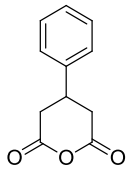
A mixture of trimethylacetaldehyde (10.00 g, 116.3 mmol), ethylcyanoacetate (13.14 g, 116.3 mmol) and piperidine (0.100 cm^3, 1.163 mmol) in toluene (40 cm^3) was heated at reflux for 4 hours and allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (30.00 cm^3), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give an orange oily residue (20.70 g) which was added to a solution of dimethylsodiomalonate [made from dimethylmalonate (15.35 g, 116.3 mmol) and sodium (0.268 g, 11.63 mmol) in dry MeOH (20 cm^3)]. The mixture was heated at reflux for 17 hours, allowed to cool to room temperature and acidified with 1M HCl (15 cm^3). The mixture was then extracted with ether (5 × 60 cm^3) and the combined ethereal fractions were washed with water (60 cm^3), dried over $MgSO_4$ and filtered. The ether was evaporated under reduced pressure to give the crude cyanotricarboxylate as orange oil (29.60 g). The crude cyanotricarboxylate (29.60 g, ~ 94.57 mmol) in conc. HCl (10 cm^3) was heated at reflux for 24 h. The conc. HCl was evaporated to about 4 cm^3 and fresh conc. HCl (10 cm^3) was added. The reaction mixture was again heated at reflux for additional 24 h. The mixture was allowed to cool to room temperature, poured in to ice / water mixture (50 cm^3) and extracted with ether (5 × 30 cm^3). The combined ethereal portions were washed with water, dried over $MgSO_4$, filtered and solvent evaporated *in vacuo* to obtain a dark brown liquid as crude which upon standing in fridge turned to brown solid. Purification by recrystallisation from EtOAc / hexane gave the title compound as white crystals (12.76 g, 58% over 3 steps). Mpt 146 – 148 ^oC (lit.[52] 144.5 – 145.5 ^oC); υ_{max} (ATR)/cm^{-1} 2966 (broad), 2671, 1704; ^1H NMR (400 MHz; $CDCl_3$) δ_H 0.96 (9H, s, 3 × C*H*$_3$), 2.15 – 2.22 (2H, m, 2 × CH*H*), 2.32 (1H, tt, *J*

9.7, 1.8, C*H*), 2.66 (2H, dd, *J* 14.2, 1.8, 2 × CH*H*), 12.36 (2H, bs, 2 × O*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 27.3 (3 × *C*H_3), 33.1 (*C*), 36.1 (2 × *C*H_2), 42.4 (*C*H), 180.9 (2 × *C*=O); *m*/*z* (TOF MS ES$^+$) 189.1130 (100%, MH^+ $C_9H_{17}O_4$ requires 189.1127). Only melting point and IR were provided in the literature.[52, 135]

General Procedure C for the synthesis of glutaric anhydrides.[67]

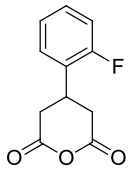
A mixture of glutaric acid in acetyl chloride (30 cm^3) was heated at reflux for 48 h. The mixture was cooled to room temperature and the acetyl chloride was removed *in vacuo* to give brown liquid which was purified by recrystallisation.

4-Phenyldihydropyran-2,6-dione 172



Using general procedure **C** starting with commercially available 3-phenylglutaric acid (4.10 g, 0.02 mol), the title compound was obtained as white crystals by recrystallisation from EtOAc / hexane (3.22 g, 84%). Mpt 104 – 106 ^{o}C (lit.[52, 136] 104 – 105 ^{o}C); υ_{max} (ATR)/cm^{-1} 1812, 1752; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.90 (2H, dd, *J* 17.5, 11.5, 2 × CH*H*), 3.11 (2H, dd, *J* 17.5, 4.3, 2 × CH*H*), 3.42 (1H, tt, *J* 11.5, 4.3 C*H*), 7.21 – 7.24 (2H, m, ArC*H*), 7.34 – 7.45 (3H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 34.1 (*C*H), 37.2 (2 × *C*H_2), 126.2 (2 × Ar*C*H), 128.2 (Ar*C*H), 129.4 (2 × Ar*C*H), 139.1 (Ar*C*), 165.8 (*C*=O); *m*/*z* (TOF MS ES$^+$) 191 (100%, MH^+ $C_{11}H_{11}O_3$). All data are in accordance with the literature.[52, 136, 105]

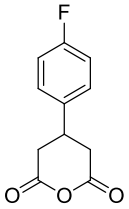
4-(2-Fluorophenyl)dihydropyran-2,6-dione 201



Using general procedure **C** starting with glutaric acid **188** (3.00 g, 13.3 mmol), the title compound was obtained as white crystals by recrystallisation from EtOAc / petrol (40 – 60 ^{o}C) (2.00 g, 73%). Mpt 84 – 86 ^{o}C; υ_{max} (ATR)/cm^{-1} 2914, 1812, 1754, 1710, 1586; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.99 (2H, dd, *J* 17.2, 11.2, 2 × CH*H*), 3.13 (2H, dd, *J* 17.2, 4.2, 2 × CH*H*), 3.66 – 3.73 (1H, m, C*H*), 7.11 – 7.21 (3H, m, ArC*H*), 7.33 – 7.38 (1H, m, ArC*H*); ^{13}C

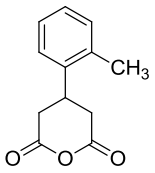
NMR (100 MHz; $CDCl_3$); δ_C 28.9 (*C*H), 35.5 (2 × *C*H_2), 116.3 (d, $J_{C\text{-}F}$ 21.8, Ar*C*H), 125.0 (d, $J_{C\text{-}F}$ 3.4, Ar*C*H), 126.0 (d, $J_{C\text{-}F}$ 13.3, Ar*C*), 127.2 (d, $J_{C\text{-}F}$ 3.8, Ar*C*H), 129.9 (d, $J_{C\text{-}F}$ 8.5, Ar*C*H), 160.7 (d, $J_{C\text{-}F}$ 246.6, Ar*C*), 165.7 (2 × *C*=O); *m*/*z* (EI^+) 208.0544 (30%, M^+ $C_{11}H_9FO_3$ requires 208.0536), 123 (25), 122 (100), 96 (20).

4-(4-Fluorophenyl)dihydropyran-2,6-dione 202



Using general procedure **C** starting with glutaric acid **189** (2.50 g, 11.1 mmol), the title compound was obtained as white crystals by recrystallisation from EtOAc / petrol (40 – 60°C) (1.96 g, 85%). Mpt 84 – 86 °C (lit.[103] 98.5 – 99 °C); (Found: C, 63.22; H, 4.08. $C_{11}H_9FO_3$ requires C, 63.46; H, 4.36); υ_{max} (ATR)/cm^{-1} 1806, 1755, 1717, 1606, 1512; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.86 (2H, dd, *J* 17.4, 11.4, 2 × CH*H*), 3.13 (2H, dd, *J* 17.4, 4.4, 2 × CH*H*), 3.45 (1H, tt, *J* 11.4, 4.4, C*H*), 7.09 – 7.14 (2H, m, ArC*H*), 7.18 – 7.23 (2H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$); δ_C 33.5 (*C*H), 37.3 (2 × *C*H_2), 116.4 (d, $J_{C\text{-}F}$ 21.6, 2 × Ar*C*H), 127.9 (d, $J_{C\text{-}F}$ 8.1, 2 × Ar*C*H), 134.8 (d, $J_{C\text{-}F}$ 3.2, Ar*C*), 162.3 (d, $J_{C\text{-}F}$ 248.5, Ar*C*), 165.6 (2 × *C*=O); *m*/*z* (EI^+) 208 (40%, M^+ $C_{11}H_9FO_3$), 123 (30), 122 (100). All data are in accordance with literature.[103, 124, 131]

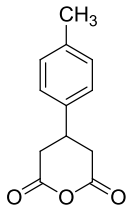
4-(2-Methylphenyl)dihydropyran-2,6-dione 203



Using general procedure **C** starting with glutaric acid **190** (3.00 g, 13.5 mmol), the title compound was obtained as white crystals by recrystallisation from EtOAc / hexane (2.07 g, 75%). Mpt 103 – 105 °C (lit.[137] 106 – 109 °C); υ_{max} (ATR)/cm^{-1} 1808, 1749, 1712; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.39 (3H, s, CH_3), 2.86 (2H, dd, *J* 17.4, 11.6, 2 × C*H*H), 3.08 (2H, dd, *J* 17.4, 4.4, 2 × C*H*H), 3.65 (1H, tt, *J* 11.6, 4.4, C*H*), 7.13 (1H, d, *J* 6.9, ArC*H*), 7.24 – 7.31 (3H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 19.3 (*C*H_3), 30.1 (*C*H), 36.6 (2 × *C*H_2), 124.1 (Ar*C*H), 127.1 (Ar*C*H), 127.9 (Ar*C*H), 131.4 (Ar*C*H), 135.6 (Ar*C*), 137.2 (Ar*C*), 166.1

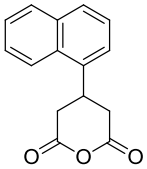
(2 × *C*=O). *m*/*z* (EI^+) 204.0792 (40%, MH^+ $C_{12}H_{13}O_3$ requires 204.0786), 144 (60), 118 (100), 117 (75). All data are in accordance with literature.

4-(4-Methylphenyl)dihydropyran-2,6-dione 204



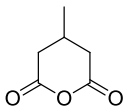
Using general procedure **C** starting with glutaric acid **191** (7.00 g, 31.5 mmol), the title compound was obtained as white crystals by recrystallisation from EtOAc / petrol (40 – 60°C) (6.0 g, 93%). Mpt 136 – 138 °C; υ_{max} (ATR)/cm^{-1} 1806, 1753, 1518; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.37 (3H, s, C*H*$_3$), 2.87 (2H, dd, *J* 17.4, 11.4, 2 × C*H*H), 3.12 (2H, dd, *J* 17.4, 4.5, 2 × C*H*H), 3.41 (1H, tt, *J* 11.4, 4.5, C*H*), 7.11 (2H, d, *J* 8.0, ArC*H*), 7.22 (2H, d, *J* 8.0, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$); δ_C 21.0 (*C*H$_3$), 33.7 (*C*H), 37.3 (2 × *C*H$_2$), 126.1 (2 × Ar*C*H), 130.0 (2 × Ar*C*H), 136.1 (Ar*C*), 138.0 (Ar*C*), 165.9 (2 × *C*=O); *m*/*z* (EI^+) 204.079550 (40%, M^+ $C_{12}H_{12}O_3$ requires 204.078644), 118 (100), 117 (40), 91 (20). No analytical data was given for the compound in the literature.[138]

4-(1-Naphthyl)dihydropyran-2,6-dione 205



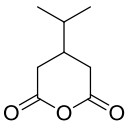
Using general procedure **C** starting with glutaric acid **192** (3.00 g, 0.01 mol), the title compound was obtained as white crystals by recrystallisation from EtOAc / petrol (40 – 60°C) (2.24 g, 80%). Mpt 148 – 150 °C; (Found: C, 74.64; H, 4.68. $C_{15}H_{12}O_3$ requires C, 74.99; H, 5.03); υ_{max} (ATR)/cm^{-1} 1808, 1753, 1599, 1508; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.05 (2H, dd, *J* 17.3, 10.5, 2 × CH*H*), 3.31 (2H, dd, *J* 17.3, 4.5, 2 × CH*H*), 4.28 (1H, tt, *J* 10.5, 4.5, C*H*), 7.31 (1H, d, *J* 7.2, ArC*H*), 7.49 – 7.53 (1H, m, ArC*H*), 7.57 – 7.66 (2H, m, ArC*H*), 7.87 (1H, d, *J* 8.2, ArC*H*), 7.94 – 7.98 (2H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 29.5 (*C*H), 36.8 (2 × *C*H$_2$), 121.8 (Ar*C*H), 122.0 (Ar*C*H), 125.5 (Ar*C*H), 126.3 (Ar*C*H), 127.1 (Ar*C*H), 128.9 (Ar*C*H), 129.5 (Ar*C*H), 130.6 (Ar*C*), 134.1 (Ar*C*), 134.8 (Ar*C*), 166.0 (2 × *C*=O); *m*/*z* (TOF MS ES^+) 241 (100%, MH^+ $C_{15}H_{13}O_3$).

4-Methyldihydropyran-2,6-dione 206



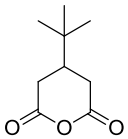
Using general procedure **C** starting with commercially available 3-methylglutaric acid (10.0 g, 63.5 mmol), the title compound was obtained as white crystals by recrystallisation from EtOAc / petrol (40 – 60^{o}C) (6.89 g, 79%). Mpt 44 – 46 ^{o}C, (Found: C, 56.27; H, 6.31. $C_6H_8O_3$ requires C, 56.24; H, 6.29); υ_{max} (ATR)/cm^{-1} 2977, 1806, 1757, 1744; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.16 (3H, d, *J* 6.4, C*H*$_3$), 2.29 – 2.37 (1H, m, C*H*), 2.39 – 2.46 (2H, m, 2 × CH*H*), 2.88 (2H, dd, *J* 17.1, 4.2, 2 × CH*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 20.0 (*C*H$_3$), 24.0 (*C*H), 37.7 (2 × *C*H$_2$), 166.4 (2 × *C*=O); *m*/*z* (TOF MS ES$^+$) 129 (100%, MH$^+$ $C_6H_9O_3$).

4-Isopropyldihydropyran-2,6-dione 207



Using general procedure **C** starting with glutaric acid **194** (5.74 g, 33.0 mmol), a brown liquid was obtained. This was vacuum distilled (temp. 110 ^{o}C, 85 × 10^{-2} mbar); bp lit.[52] 138 ^{o}C (0.5 Torr), to give a colourless liquid which solidified upon standing. The solid was recrystallised from hexane to give the title compound as white crystals (3.93 g, 76%). Mpt 25 – 26 ^{o}C (lit.[52] 25.5 – 26.5 ^{o}C); υ_{max} (ATR)/cm^{-1} 2967, 2878, 1798, 1757, 1702; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.97 (6H, d, *J* 6.8, 2 × C*H*$_3$), 1.62 (1H, octet, *J* 6.8, C*H*), 1.94 (1H, dtt, *J* 11.5, 6.8, 4.4, C*H*), 2.43 (2H, dd, *J* 17.3, 11.5, 2 × CH*H*), 2.88 (2H, dd, *J* 17.3, 4.4, 2 × CH*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 18.9 (2 × *C*H$_3$), 31.3 (*C*H), 34.0 (2 × *C*H$_2$), 35.0 (*C*H), 166.9 (2 × *C*=O); *m*/*z* (TOF MS ES$^+$) 157.0870 (100%, MH$^+$ $C_6H_8O_3$ requires 157.0865). All data are in accordance with literature.

4-*tert*-Butyldihydropyran-2,6-dione 208



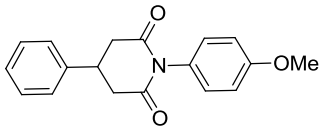
Using general procedure **C** starting with glutaric acid **195** (5.00 g, 26.6 mmol), a brown liquid was obtained. This was vacuum distilled (temp. 120 ^{o}C, 16 × 10^{-2} mbar); bp lit.[52] 146 – 148 ^{o}C (0.55 Torr), to give a colourless liquid which solidified upon standing to give the title

compound as a white solid (3.15 g, 70%). Mpt. 62 – 64 ^{o}C (lit.[52] 63.5 – 64.5 ^{o}C); υ_{max} (ATR)/cm^{-1} 2967, 1808, 1748; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.96 (9H, s, 3 × C*H*$_3$), 1.94 (1H, tt, *J* 12.9, 4.1, C*H*), 2.35 – 2.43 (2H, m, 2 × CH*H*), 2.90 (2H, dd, *J* 17.2, 4.1, 2 × CH*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 26.4 (3 × *C*H$_3$), 32.0 (*C*), 32.3 (2 × *C*H$_2$), 38.7 (*C*H), 167.2 (*C*=O); *m*/*z* (TOF MS ES$^+$) 171.1024 (100%, MH$^+$ $C_9H_{15}O_3$ requires 171.1021). All data are in accordance with literature.

General Procedure D for the synthesis of glutarimides.[67]

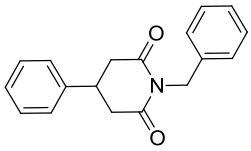
The corresponding amine (1.0 equiv.) was slowly added to a solution of the glutaric anhydride (1.0 equiv.) and triethylamine (1.0 equiv.) in dry THF (30 cm^3). The mixture was heated at reflux for 48 h, cooled to room temperature and concentrated under reduced pressure. Dichloromethane (15 cm^3) was added and the resulting solution was washed with 1M HCl (5 cm^3) and brine (5 cm^3), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was dissolved in acetyl chloride (30 cm^3), heated at 60 ^{o}C for 48 h and cooled to room temperature. The solvent was removed *in vacuo* to give a brown solid which was purified by recrystallisation.

***N*-(4-Methoxyphenyl)-4-phenylpiperidin-2,6-dione 173**



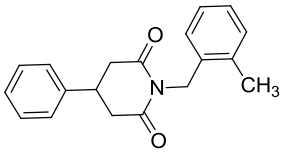
Using general procedure **D** starting with 3-phenylglutaric anhydride **172** (1.00 g, 5.26 mmol), *p*-anisidine (0.65 g, 5.26 mmol) and triethylamine (0.70 cm^3, 5.26 mmol), the title compound was obtained as white crystals by recrystallisation from EtOAc (1.23 g, 80%). Mpt 248 – 250 ^{o}C; (Found: C, 73.00; H, 5.52; N, 4.66. $C_{18}H_{17}NO_3$ requires C, 73.20; H, 5.80; N, 4.74); υ_{max} (ATR)/cm^{-1} 1731, 1672, 1610, 1511; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.02 (2H, dd, *J* 17.2, 11.4, 2 × C*H*H), 3.18 (2H, dd, *J* 17.2, 4.4, 2 × C*H*H), 3.58 (1H, tt, *J* 11.4, 4.4, C*H*), 3.85 (3H, s, OC*H*$_3$), 6.99 – 7.06 (4H, m, ArC*H*), 7.28 – 7.45 (5H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 34.7 (*C*H), 40.1 (2 × *C*H$_2$), 55.4 (*C*H$_3$), 114.7 (2 × Ar*C*H), 126.4 (2 × Ar*C*H), 127.3 (Ar*C*), 127.7 (Ar*C*H), 129.2 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 140.5 (Ar*C*) 159.5 (Ar*C*), 172.0 (*C*=O); *m*/*z* (TOF MS ES$^+$) 296 (100%, MH$^+$ $C_{18}H_{18}NO_3$), 270 (10), 249 (40), 241 (8).

1-(Phenylmethyl)-4-phenylpiperidin-2,6-dione 174



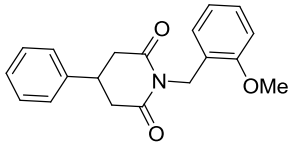
Using general procedure **D** starting with 3-phenylglutaric anhydride **172** (1.50 g, 7.89 mmol), benzylamine (0.85 g, 7.89 mmol) and triethylamine (1.10 cm^3, 7.89 mmol), the title compound was obtained as white crystals by recrystallisation from EtOAc : petrol (40 – 60) (1.87 g, 85%). Mpt 100 – 102 ^oC (lit.[139] 94 – 96 ^oC) ; υ_{max} (ATR)/cm^{-1} 3031, 1726, 1668, 1605; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.85 (2H, dd, *J* 17.2, 11.8, 2 × C*H*H), 3.05 (2H, dd, *J* 17.2, 4.3, 2 × C*H*H), 3.38 (1H, tt, *J* 11.8, 4.3, C*H*), 5.02 (2H, s, NCH_2), 7.21 [2H, $(AX)_2$, ArC*H*], 7.28 – 7.42 (8H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 34.6 (*C*H), 39.9 (2 × *C*H_2), 42.9 (*C*H_2), 126.3 (2 × Ar*C*H), 127.5 (Ar*C*H), 127.6 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.9 (2 × Ar*C*H), 129.1 (2 × Ar*C*H), 137.1 (Ar*C*) 140.6 (Ar*C*), 171.6 (2 × *C*=O). *m*/*z* (TOF MS ES^+) 280 (100%, MH^+). Only melting point and ^1H NMR were cited in the literature.[139, 124, 140]

1-(2-Methylphenylmethyl)-4-phenylpiperidin-2,6-dione 175



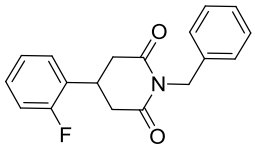
Using general procedure **D** starting with 3-phenylglutaric anhydride **172** (1.70 g, 8.95 mmol), 2-methylbenzylamine (1.09 g, 8.95 mmol) and triethylamine (1.25 cm^3, 8.95 mmol), the title compound was obtained as white crystals by recrystallisation from EtOAc : petrol (40 – 60) (1.87 g, 71%). Mpt 123 – 125 ^oC; (Found: C, 77.53, H, 6.51, N, 4.76. $C_{19}H_{19}NO_2$ requires C, 77.79; H, 6.53; N, 4.77); υ_{max} (ATR)/cm^{-1} 2973, 1727, 1667; ^1H NMR (250 MHz; $CDCl_3$) δ_H 2.44 (3H, s, CH_3), 2.91 (2H, dd, *J* 17.0, 11.5, 2 × CH*H*), 3.10 (2H, dd, *J* 17.0, 4.4, 2 × CH*H*), 3.46 (1H, tt, *J* 11.5, 4.4, C*H*), 5.01 (2H, s, NCH_2), 6.96 [1H, $(AX)_2$, ArC*H*], 7.08 – 7.18 (3H, m, ArC*H*), 7.23 – 7.27 (2H, m, ArC*H*), 7.32 – 7.44 (3H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 19.4 (*C*H_3), 34.6 (*C*H), 39.9 (2 × *C*H_2), 40.4 (*C*H_2), 126.0 (Ar*C*H), 126.0 (Ar*C*H), 126.4 (2 × Ar*C*H), 127.1 (Ar*C*H), 127.7 (Ar*C*H), 129.1 (2 × Ar*C*H), 130.3 (Ar*C*H), 134.7 (Ar*C*), 135.8 (Ar*C*), 140.5 (Ar*C*), 171.7 (2 × *C*=O); *m*/*z* (TOF MS ES^+) 294 (100%, MH^+ $C_{19}H_{20}NO_2$).

1-(2-Methoxyphenylmethyl)-4-phenylpiperidin-2,6-dione 176



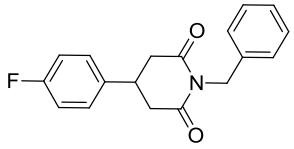
Using general procedure **D** starting with 3-phenylglutaric anhydride **172** (2.00 g, 10.5 mmol), 2-methoxybenzylamine (1.37 cm^3, 10.5 mmol) and triethylamine (1.47 cm^3, 10.5 mmol), the title compound was obtained as white crystals by recrystallisation from EtOAc : petrol (40 – 60) (1.97 g, 60%). Mpt 98 – 100 ^oC; (Found: C, 73.50, H, 6.06, N, 4.44. $C_{19}H_{19}NO_3$ requires C, 73.77; H, 6.19; N, 4.5); υ_{max} (ATR)/cm^{-1} 2960, 1728, 1671, 1603; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.91 (2H, dd, *J* 17.1, 11.5, 2 × CH*H*), 3.08 (2H, dd, *J* 17.1, 4.3, 2 × CH*H*), 3.44 (1H, tt, *J* 11.5, 4.3, C*H*), 3.86 (3H, s, OCH_3), 5.08 (2H, s, NCH_2), 6.88 – 6.96 (3H, m, ArC*H*), 7.22 – 7.28 (3H, m, ArC*H*), 7.31 – 7.35 (1H, m, ArC*H*), 7.38 – 7.40 (2H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 34.6 (*C*H), 38.5 (2 × *C*H_2), 39.9 (*C*H_2), 55.4 (*C*H_3), 110.4 (Ar*C*H), 120.3 (2 × Ar*C*H), 124.8 (Ar*C*), 126.5 (2 × Ar*C*H), 127.0 (Ar*C*H), 127.6 (Ar*C*H), 128.2 (Ar*C*H), 129.1 (Ar*C*H), 140.7 (Ar*C*) 157.1 (Ar*C*), 171.5 (2 × *C*=O); *m*/*z* (TOF MS ES^+) 310.1451 (100%, MH^+ $C_{19}H_{20}NO_3$ requires 310.1443).

1-(Phenylmethyl)-4-(2-fluorophenyl)piperidin-2,6-dione 209



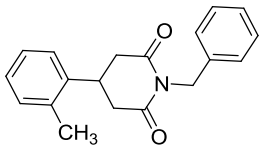
Using general procedure **D** starting with glutaric anhydride **201** (2.00 g, 9.62 mmol), benzylamine (1.10 cm^3, 9.62 mmol) and triethylamine (1.34 cm^3, 9.62 mmol), the title compound was obtained as white powder by recrystallisation from EtOAc : petrol (40 – 60) (1.7 g, 60%). Mpt 76 – 78 ^oC; (Found: C, 72.38; H, 5.26; N, 4.57. $C_{18}H_{16}FNO_2$ requires C, 72.71; H, 5.42; N, 4.71); υ_{max} (ATR)/cm^{-1} 3068, 2895, 1728, 1672, 1582; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.91 (2H, dd, *J* 16.9, 11.4, 2 × CH*H*), 3.04 (2H, dd, *J* 16.9, 4.0, 2 × CH*H*), 3.61 – 3.68 (1H, m, *CH*), 5.02 (2H, s, NCH_2), 7.07 – 7.13 (3H, m, ArC*H*), 7.27 – 7.34 (4*H*, m, ArC*H*), 7.42 (2H, d, *J* 7.0, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 29.1 (CH), 38.3 (2 × *C*H_2), 43.0 (*C*H_2), 116.1 (d, $J_{C\text{-}F}$ 22.1, Ar*C*H), 124.7 (d, $J_{C\text{-}F}$ 3.3, Ar*C*H), 127.2 (d, $J_{C\text{-}F}$ 4.0, Ar*C*H), 127.4 (Ar*C*), 127.6 (Ar*C*H), 128.5 (2 × Ar*C*H), 129.0 (2 × Ar*C*H), 129.3 (d, $J_{C\text{-}F}$ 8.5, Ar*C*H), 137.1 (Ar*C*), 160.8 (d, $J_{C\text{-}F}$ 246.6, Ar*C*), 171.4 (2 × *C*=O); *m*/*z* (TOF MS ES^+) 298 (100%, MH^+ $C_{18}H_{17}FNO_2$).

1-(Phenylmethyl)-4-(4-fluorophenyl)piperidin-2,6-dione 210



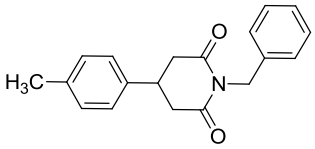
Using general procedure **D** starting with glutaric anhydride **202** (4.00 g, 19.20 mmol), benzylamine (2.10 cm^3, 19.2 mmol) and triethylamine (2.60 cm^3, 19.2 mmol), the title compound was obtained as white powder by recrystallisation from EtOAc : petrol (40 – 60) (1.20 g, 67%). Mpt 120 – 122 ^oC; (Found: C, 72.47; H, 5.31; N, 4.77. $C_{18}H_{16}FNO_2$ requires C, 72.71; H, 5.42; N, 4.71); υ_{max} (ATR)/cm^{-1} 3060, 2955, 1718, 1672, 1604, 1512; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.81 (2H, dd, *J* 17.1, 11.5, 2 × CH*H*), 3.00 (2H, dd, *J* 17.1, 4.3, 2 × CH*H*), 3.37 (1H, tt, *J* 11.5, 4.3, C*H*), 5.01 (2H, s, NCH_2), 7.02 – 7.07 (2H, m, ArC*H*), 7.13 – 7.17 (2*H*, m, ArC*H*), 7.28 – 7.32 (3H, m, ArC*H*), 7.38 – 7.41 (2*H*, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 33.9 (*C*H), 40.0 (2 × *C*H_2), 42.9 (CH_2), 115.9 (Ar*C*H), 116.1 (Ar*C*H), 127.6 (Ar*C*H), 127.9 (Ar*C*H), 128.0 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.9 (2× Ar*C*H), 136.3 (d, $J_{C\text{-}F}$ 3.0, Ar*C*), 137.0 (Ar*C*), 162.0 (d, $J_{C\text{-}F}$ 246.6, Ar*C*), 171.3 (2 × *C*=O); *m*/*z* (TOF MS ES^+) 298.1233 (100%, MH^+ $C_{18}H_{17}FNO_2$ requires 298.1243). Only ^1H NMR was cited in literature.[124]

1-(Phenylmethyl)-4-(2-methylphenyl)piperidin-2,6-dione 211



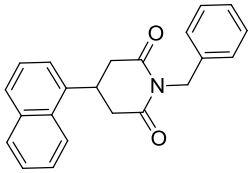
Using general procedure **D** starting with glutaric anhydride **203** (1.50 g, 7.35 mmol), benzylamine (0.81 cm^3, 7.35 mmol) and triethylamine (1.02 cm^3, 7.35 mmol), the title compound was obtained as white powder by recrystallisation from EtOAc : petrol (40 – 60) (1.88 g, 87%). Mpt 138 – 140 ^oC; υ_{max} (ATR)/cm^{-1} 3017, 2953, 1728, 1670, 1605; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.37 (3H, s, CH_3), 2.81 (2H, dd, *J* 17.2, 11.8, 2 × CH*H*), 2.98 (2H, dd, *J* 17.2, 4.3, 2 × CH*H*), 3.58 (1H, tt, *J* 11.8, 4.3, C*H*), 5.04 (2H, s, NCH_2), 7.09 – 7.12 (1H, m, ArC*H*), 7.20 – 7.23 (3*H*, m, ArC*H*), 7.27 – 7.37 (3*H*, m, ArC*H*), 7.43 – 7.46 (2*H*, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 19.3 (CH_3), 30.7 (*C*H), 39.3 (2 x *C*H_2), 43.0 (CH_2), 124.5 (Ar*C*H), 126.8 (Ar*C*H), 127.4 (Ar*C*H), 127.6 (Ar*C*H), 128.5 (2 × Ar*C*H), 129.1 (2 × Ar*C*H), 131.1 (Ar*C*H), 135.6 (Ar*C*), 137.1 (Ar*C*), 138.7 (Ar*C*), 171.9 (2 × *C*=O); *m*/*z* (TOF MS ES^+) 294.1485 (100%, MH^+ $C_{19}H_{20}NO_2$ requires 294.1494).

1-(Phenylmethyl)-4-(4-methylphenyl)piperidin-2,6-dione 212



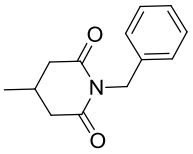
Using general procedure **D** starting with glutaric anhydride **204** (5.00 g, 24.5 mmol), benzylamine (2.67 cm^3, 24.5 mmol) and triethylamine (3.40 cm^3, 24.5 mmol), the title compound was obtained as white powder by recrystallisation from EtOAc : petrol (40 – 60) (5.10 g, 71%). Mpt 106 – 108 ^oC; υ_{max} (ATR)/cm^{-1} 2955, 2910, 1727, 1669, 1516; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.36 (3H, s, C*H*$_3$), 2.82 (2H, dd, *J* 17.1, 11.8, 2 × CH*H*), 3.03 (2H, dd, *J* 17.1, 4.2, 2 × CH*H*), 3.34 (1H, tt, *J* 11.8, 4.2, C*H*), 5.02 (2H, s, NC*H*$_2$), 7.09 (2H, d, *J* 8.0, ArC*H*), 7.18 (2*H*, d, *J* 8.0, ArC*H*), 7.26 – 7.35 (3H, m, ArC*H*), 7.39 – 7.52 (2*H*, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 21.0 (CH_3), 34.2 (*C*H), 40.1 (2 × *C*H$_2$), 42.9 (*C*H$_2$), 126.2 (2 × Ar*C*H), 127.5 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.9 (2 × Ar*C*H), 129.7 (2 × Ar*C*H), 137.1 (Ar*C*), 137.3 (Ar*C*), 138.6 (Ar*C*), 171.7 (2 × *C*=O); *m*/*z* (TOF MS ES$^+$) 294.1504 (100%, MH$^+$ $C_{19}H_{20}NO_2$ requires 294.1494).

1-(Phenylmethyl)-4-(1-naphthyl)piperidin-2,6-dione 213



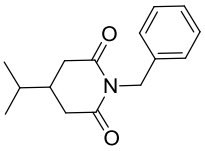
Using general procedure **D** starting with glutaric anhydride **205** (2.00 g, 8.33 mmol), benzylamine (0.90 cm^3, 8.33 mmol) and triethylamine (1.16 cm^3, 8.33 mmol), the title compound was obtained as white powder by recrystallisation from EtOAc : petrol (40 – 60) (1.42 g, 52%). Mpt 116 – 118 ^oC; υ_{max} (ATR)/cm^{-1} 3052, 2964, 1723, 1672, 1598, 1509; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.98 (2H, dd, *J* 16.9, 10.8, 2 × CH*H*), 3.21 (2H, dd, *J* 16.9, 3.8, 2 × CH*H*), 4.15 – 4.22 (1H, m, C*H*), 5.08 (2H, s, NC*H*$_2$), 7.23 – 7.38 (4H, m, ArC*H*), 7.40 – 7.48 (3H, m, ArC*H*), 7.53 – 7.61 (2H, m, ArC*H*), 7.82 (1H, d, *J* 8.2, ArC*H*), 7.92 (1H, d, *J* 7.6, ArC*H*), 8.0 (1H, d, *J* 8.2, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 30.0 (*C*H), 39.5 (2 × *C*H$_2$), 43.1 (*C*H$_2$), 122.2 (Ar*C*H), 122.3 (Ar*C*H), 125.5 (Ar*C*H), 126.1 (Ar*C*H), 126.8 (Ar*C*H), 127.6 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (2 × Ar*C*H), 129.1 (2 × Ar*C*H), 129.3 (Ar*C*H), 130.8 (Ar*C*), 134.1 (Ar*C*), 136.3 (Ar*C*), 137.1 (Ar*C*), 171.8 (2 × *C*=O); *m*/*z* (TOF MS ES$^+$) 330.1504 (100%, MH$^+$ $C_{22}H_{20}NO_2$ requires 330.1494).

1-(Phenylmethyl)-4-methylpiperidin-2,6-dione 214



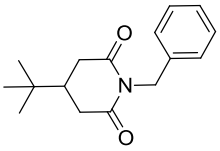
Using general procedure **D** starting with glutaric anhydride **206** (3.50 g, 27.3 mmol), benzylamine (2.93 g, 27.3 mmol) and triethylamine (3.82 cm^3, 27.3 mmol), the title compound was obtained as white powder by recrystallisation from 50% EtOAc : hexane (4.13 g, 70%). Mpt 68 – 70 ^oC; (Found: C, 71.74; H, 6.87; N, 6.46. $C_{13}H_{15}NO_2$ requires C, 71.87; H, 6.96; N, 6.45); υ_{max} (ATR)/cm^{-1} 2961, 1721, 1665; ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.08 (3H, d, *J* 6.4, C*H*$_3$), 2.17 – 2.29 (1H, m, C*H*), 2.31 – 2.37 (2H, m, 2 × CH*H*), 2.80 (2H, dd, *J* 16.7, 3.8, 2 × CH*H*), 4.97 (2H, s, NC*H*$_2$), 7.24 – 7.32 (3H, m, ArC*H*), 7.39 [2*H*, $(AX)_2$, ArC*H*]; ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 20.3 (*C*H$_3$), 24.5 (*C*H), 40.7 (2 × *C*H$_2$), 42.7 (*C*H$_2$), 127.4 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 137.3 (Ar*C*), 172.1 (2 × *C*=O); *m*/*z* (TOF MS ES^+) 218 (100%, MH^+ $C_{13}H_{16}NO_2$). Only ^1H NMR was cited in literature.[124]

1-(Phenylmethyl)-4-isopropylpiperidin-2,6-dione 215



Using general procedure **D** starting with glutaric anhydride **207** (2.00 g, 12.8 mmol), benzylamine (1.37 g, 12.8 mmol) and triethylamine (1.80 cm^3, 12.8 mmol), a yellowish liquid was obtained that turned to a yellowish solid upon standing. The solid was purified via flash column chromatography eluting with EtOAc : petroleum ether (40-60) (3:7) to afford the title compound as colourless liquid which turned to a white solid upon standing (2.10 g, 67%). Mpt 45 – 46 ^oC; (Found: C, 73.24; H, 7.75; N, 5.53. $C_{15}H_{19}NO_2$ requires C, 73.44; H, 7.81; N, 5.71); υ_{max} (ATR)/cm^{-1} 3031, 2960, 2900, 2874, 1724, 1668; ^1H NMR (400 MHz; $CDCl_3$) δ_H 0.95 (6H, d, *J* 6.7, 2 × C*H*$_3$), 1.57 (1H, octet, *J* 6.7, C*H*), 1.81 – 1.91 (1H, m, C*H*), 2.35 (2H, dd, *J* 17.1, 12.3, 2 × CH*H*), 2.82 (2H, dd, *J* 17.1, 4.0, 2 × CH*H*), 4.96 (2H, s, NC*H*$_2$), 7.23 – 7.32 (3H, m, ArC*H*), 7.39 [2H, $(AX)_2$, ArC*H*]; ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 19.2 (2 × *C*H$_3$), 31.4 (*C*H), 35.5 (*C*H), 36.9 (2 × *C*H$_2$), 42.8 (*C*H$_2$), 127.4 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 137.2 (Ar*C*), 172.6 (2 × *C*=O); *m*/*z* (TOF MS ES^+) 246.1504 (100%, MH^+ $C_{15}H_{19}NO_2$ requires 246.1494).

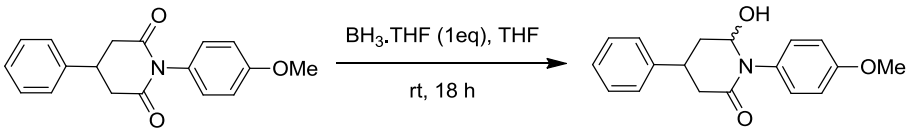
1-(Phenylmethyl)-4-*tert*-butylpiperidin-2,6-dione 216



Using general procedure **D** starting with glutaric anhydride **208** (1.30 g, 7.65 mmol), benzylamine (0.89 g, 7.65 mmol) and triethylamine (1.10 cm^3, 7.65 mmol), a yellowish solid was obtained. The solid was purified via flash column chromatography eluting with EtOAc : petroleum ether (40-60) (3:7) to afford the title compound as colourless liquid which turned to a white solid upon standing (1.12 g, 57%). Mpt 44 – 46 ^oC; υ_{max} (ATR)/cm^{-1} 2951, 2874, 1719, 1666; ^1H NMR (400 MHz; $CDCl_3$) δ_H 0.93 (9H, s, 3 × C*H*$_3$), 1.86 (1H, tt, *J* 13.5, 3.8, C*H*), 2.30 – 2.37 (2H, m, 2 × CH*H*), 2.83 (2H, dd, *J* 17.0, 3.8, 2 × CH*H*), 4.96 (2H, s, NC*H*$_2$), 7.24 – 7.33 (3H, m, ArC*H*), 7.39 [2H, $(AX)_2$, ArC*H*]; ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 26.5 (3 × *C*H_3), 31.8 (*C*), 35.0 (2 × *C*H_2), 39.2 (*C*H), 42.8 (*C*H_2), 127.5 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 137.2 (Ar*C*), 172.9 (2 × *C*=O); *m*/*z* (TOF MS ES^+) 260.1650 (100%, MH^+ $C_{16}H_{22}NO_2$ requires 260.1651).

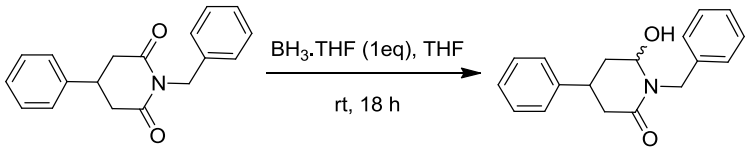
6.5 Experimental for the enantioselective desymmetrisation of glutarimides

Background reaction of *N*-(4-Methoxyphenyl)-4-phenylpiperidin-2,6-dione 173 with BH_3.THF



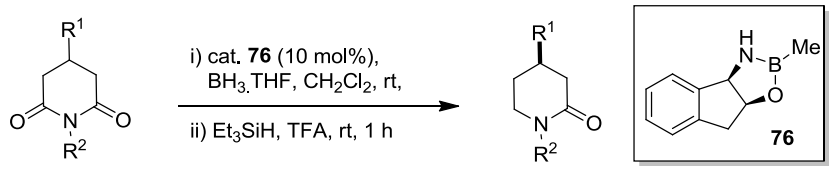
N-(4-Methoxyphenyl)-4-phenylpiperidin-2,6-dione **173** (0.15 g, 0.51 mmol) was dissolved in THF (4 cm^3) and treated with BH_3.THF (0.50 cm^3, 0.50 mmol). The mixture was allowed to stir at rt for 18 hrs. The reaction was quenched by addition of 1M HCl (1 cm^3) and H_2O (1 cm^3) and the product was extracted with CH_2Cl_2 (3 × 5 cm^3). The organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a white powder. ^1H NMR analysis showed no conversion to the corresponding hydroxy-lactam.

Background reaction of 1-(phenylmethyl)-4-phenylpiperidin-2,6-dione 174 with BH_3.THF



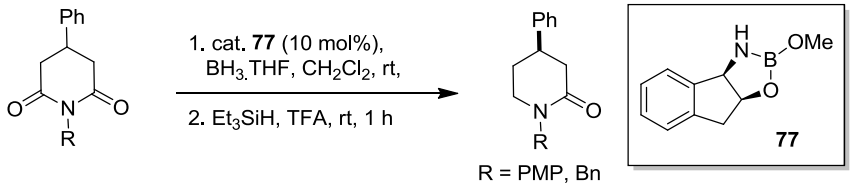
1-(Phenylmethyl)-4-phenylpiperidin-2,6-dione **174** (0.14 g, 0.50 mmol) was dissolved in THF (4 cm^3), treated with BH_3.THF (0.50 cm^3, 0.50 mmol) and allowed to stir at rt for 24 hrs. The reaction was quenched by addition of 1M HCl (1 cm^3) and H_2O (1 cm^3), the product was extracted with CH_2Cl_2 (3 × 5 cm^3) and the organic extracts dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a white powder. ^{1}H NMR analysis showed no conversion to the corresponding hydroxy-lactam.

General Procedure E for the asymmetric reduction of glutarimides using *B*-Me catalyst 76 followed by conversion to the corresponding lactam



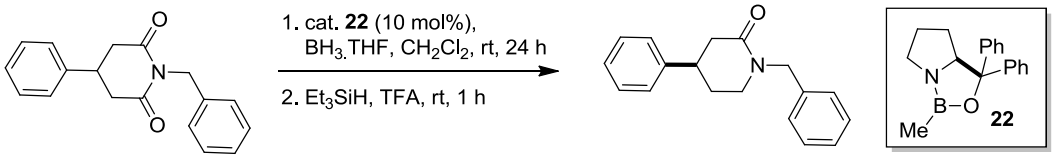
A suspension of (1*R*, 2*S*)-*cis*-amino-2-indanol (0.15 g, 1.00 mmol) in dry toluene (3 cm^3) was treated with trimethylboroxine (0.05 cm^3, 0.33 mmol) and allowed to stir under nitrogen for 30 mins. Dry toluene (5 cm^3) was added and the reaction distilled until approximately 2 cm^3 of solvent remained. This procedure was repeated twice after which the final volume of toluene was removed under pressure to give a yellow solid. Dry dichloromethane (5 cm^3) was added to give a stock solution of the *B*-Me catalyst **76**. The catalyst (0.5 cm^3, 10 mol %) was added to the solution of the glutarimide substrate (1.00 mmol) in dry dichloromethane (30 cm^3) followed by a drop-wise addition of BH_3.THF (1 cm^3, 1.00 mmol). The solution was then allowed to stir at room temperature for 3 hours (for *N*-PMP glutarimide) or 24 hours (for *N*-Bn glutarimides). The reaction was finally quenched by addition of MeOH (2 cm^3) and 1M HCl (2 cm^3), extracted with CH_2Cl_2 (3 × 15 cm^3), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give the crude hydroxy-lactam as a white powder which was immediately re-dissolved in CH_2Cl_2 (30 cm^3) and treated with TFA (1 cm^3) and triethylsilane (1 cm^3) in CH_2Cl_2 (5 cm^3). This mixture was allowed to stir at rt for 1 h, after which the solution was added to an ice-water mixture (15 cm^3) followed by extraction with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ (3 × 15 cm^3), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude white solid, which was purified via flash column chromatography eluting with EtOAc : petroleum ether (40-60) (7:3).

General Procedure F for the asymmetric reduction of 4-phenylglutarimides using *B*-OMe catalyst 77 followed by conversion to the corresponding lactam



A solution of (1*R*, 2*S*)-*cis*-1-aminoindan-2-ol (0.15 g, 1.00 mmol) in THF (3 cm^3) was treated with trimethylborate (0.10 cm^3, 1.00 mmol) and allowed to stir for 45 mins. The solution was then diluted to 5 cm^3 by further addition of THF, to give the catalyst **77** as a stock solution. The glutarimide (1.00 mmol) was dissolved in dry DCM (30 cm^3) under a nitrogen atmosphere and this solution was treated with the catalyst stock solution (0.50 cm^3, 10 mol%) then a drop-wise addition of BH_3.THF (1.00 cm^3, 1.00 mmol), and allowed to stir at rt for 3 hours (for *N*-PMP glutarimide) or 24 hours (for *N*-Bn glutarimide). The reaction was quenched by the addition of MeOH (5 cm^3) and 1M HCl (5 cm^3), and extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give the crude hydroxy-lactam as a white powder which was immediately re-dissolved in CH_2Cl_2 (25 cm^3) and treated with TFA (1 cm^3) and triethylsilane (1 cm^3) in CH_2Cl_2 (5 cm^3). This mixture was allowed to stir at rt for 1 h, after which the solution was added to an ice-water mixture (15 cm^3) followed by extraction with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ (15 cm^3), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a white solid, which was purified via flash column chromatography.

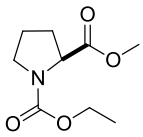
Procedure for the asymmetric reduction of *N*-(benzyl)-4-phenylpiperidin-2,6-dione 174 using CBS catalyst 22 followed by conversion to the corresponding lactam



A suspension of (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol **20** (0.25 g, 1.00 mmol) in dry toluene (3 cm^3) was treated with trimethylboroxine (0.05 cm^3, 0.33 mmol) and allowed to stir under nitrogen for 30 mins. Dry toluene (5 cm^3) was added and the reaction distilled until approximately 2 cm^3 of solvent remained. This procedure was repeated twice after which the final volume of toluene was removed under pressure to give a yellow solid. Dry dichloromethane (5 cm^3) was added to give a stock solution of the *B*-Me CBS catalyst. The

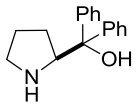
catalyst (0.50 cm^3, 10 mol %) was added to the solution of the glutarimide substrate **174** (0.28 g, 1.00 mmol) in dry dichloromethane (30 cm^3) followed by a drop-wise addition of BH_3.THF (1 cm^3, 1.00 mmol). The solution was then allowed to stir at room temperature for 24 hours. The reaction was finally quenched by addition of MeOH (2 cm^3) and 1M HCl (2 cm^3), extracted with CH_2Cl_2 (3 × 15 cm^3), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give the crude hydroxy-lactam as a white powder which was immediately re-dissolved in CH_2Cl_2 (30 cm^3) and treated with TFA (1 cm^3) and triethylsilane (1 cm^3) in CH_2Cl_2 (5 cm^3). This mixture was allowed to stir at rt for 1 h, after which the solution was added to an ice-water mixture (15 cm^3) followed by extraction with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ (15 cm^3), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude white solid, which was purified via flash column chromatography eluting with EtOAc : petroleum ether (40-60) (7:3) to afford the corresponding lactam as white solid (0.03 g, 13% over 2 steps). 14% ee. Chiral HPLC, Lux 3u Cellulose-2, 20% IPA in hexane, t_R (minor) 21.1 min and (major) 23.1 min. All data correspond to those reported for compound **180**.

(*S*)-(–)-*N*-Ethoxycarbonylproline methyl ester 260[141]



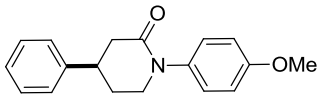
Potassium carbonate (6.80 g, 49.0 mmol) was added to a solution of L-proline (6.00 g, 52.0 mmol) in MeOH (100 cm^3). The solution was cooled to 0 °C and ethyl chloroformate (11.5 cm^3, 120 mmol) was added drop-wise. The mixture was allowed to warm to rt and was stirred overnight. MeOH was evaporated under reduced pressure and the residual oil was dissolved in water (15 cm^3). This solution was extracted with $CHCl_3$ (3 × 30 cm^3), the combined organic phases washed with brine (50 cm^3), dried over $MgSO_4$ and filtered. Subsequent concentration under reduced pressure and drying on Schlenk line yielded the product as thick, colourless oil (10.30 g, 98%). $[\alpha]_D^{20}$ -58.0 (*c* 1.05 $CHCl_3$), Lit.[141] - 60.3 (*c* 1.26 $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ_H 0.99 (2H, t, *J* 7.1 Hz, C*H*$_2$, rotamer A), 1.06 (2H, t, *J* 7.1 Hz, C*H*$_2$, rotamer B), 1.69 – 1.80 (4H, t, 2 × C*H*$_2$), 1.96 – 2.07 (1H, m, C*H*N), 3.23 – 3.39 (2H, m, C*H*$_2$N), 3.51 (1.5H, s, OC*H*$_3$, rotamer A), 3.52 (1.5H, s, OC*H*$_3$, rotamer B), 3.94 – 3.99 (2H, m, C*H*$_2$), 4.10 (0.5H, t, *J* 8.8, 4.0 Hz, C*H*N, rotamer A), 4.15 (0.5H, t, *J* 8.8, 4.0 Hz, C*H*N, rotamer B). All data are in accordance with the literature.

(*S*)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol 20[36]



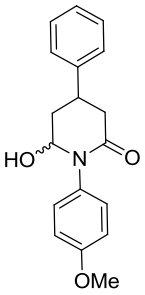
Magnesium turnings (9.66 g, 0.40 mol) and THF (100 cm^3) were introduced into a 250 cm^3 two-necked flask fitted with a dropping funnel. Bromobenzene (21.0 cm^3, 0.20 mol) and THF (75 cm^3) were introduced into the dropping funnel and added drop-wise over 1 h. The mixture was stirred for 1 h afterwards. (*S*)-*N*-Ethoxycarbonylproline methyl ester **260** (10.0 g, 0.05 mol) was introduced into a 500 cm^3 3-necked round bottomed flask fitted with a dropping funnel, followed by THF (100 cm^3). The mixture was cooled to 0 °C and the solution of phenylmagnesium bromide was transferred *via* a dropping funnel, then added drop-wise over 30 min. After addition was complete, the reaction mixture was warmed to rt and stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride solution (20 cm^3). The mixture was extracted with CH_2Cl_2 (2 × 200 cm^3), the combined organic phases washed with brine (100 cm^3) and concentrated under reduced pressure. The crude material was dissolved in MeOH (100 cm^3) into a round-bottom flask fitted with a condenser. Potassium hydroxide (28.0 g, 0.50 mol) was added and the mixture was heated at reflux for 24 h. After cooling to ambient temperature, methanol was removed under reduced pressure and the residue was treated with water (150 cm^3). This was extracted with dichloromethane (3 × 120 cm^3), the combined organic phases were washed with brine (100 cm^3), dried over magnesium sulfate and filtered. The crude product was recrystallised in hexane to yield (*S*)-α,α-diphenyl-2-pyrrolidinemethanol as pale brown crystals (7.85 g, 62%). Mpt 78 – 79 ºC (lit.[36] 79.0 – 79.5 ºC); $[\alpha]_D^{20}$ - 57.0 (*c* 0.21, MeOH) [lit.[36] - 57.2 (*c* 0.26, MeOH)]; (Found: C, 80.48; H, 7.59; N, 5.44; $C_{17}H_{19}NO$ requires C, 80.60; H, 7.56; N, 5.53); υ_{max} (ATR)/cm^{-1} 3086, 2972, 2944, 2834, 1598; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.58 – 1.79 (4H, m, 2 × C*H*$_2$), 2.98 (1H, dd, *J* 16.7, 7.3 Hz, C*H*HN), 3.03 – 3.08 (1H, m, C*H*HN), 4.29 (1H, t, *J* 7.5 Hz, C*H*N), 7.18 – 7.23 (2H, m, ArC*H*), 7.28 – 7.35 (4H, m, ArC*H*), 7.54 (2H, d, *J* 8.1, 7.3 Hz, ArC*H*), 7.61 (2H, d, *J* 8.1, 7.3 Hz, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 25.5 (*C*H$_2$), 26.3 (*C*H$_2$), 46.8 (*C*H$_2$N), 64.5 (*C*HN), 125.6 (2 × Ar*C*H), 125.9 (2 × Ar*C*H), 126.4 (Ar*C*H), 126.5 (Ar*C*H), 128.0 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 145.4 (Ar*C*), 148.2 (Ar*C*); *m*/*z* (TOF MS ES$^+$) 254.1550 (100%, MH$^+$ $C_{17}H_{20}NO$ requires 254.1545). All data are in accordance with the literature.

4(*R*)-1-(4-Methoxyphenyl)-4-phenylpiperidin-2-one 179



Using glutarimide **173** (0.30 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure **E** (0.07 g, 34% over 2 steps). Mpt 204 – 206 ^{o}C; $[\alpha]_D^{20}$ + 6.0 (*c* 1.3, $CHCl_3$; 95% ee); ν_{max} (ATR) / cm^{-1} 1640, 1506; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.11 – 2.21 (1H, m, CH*H*), 2.23 – 2.30 (1H, m, CH*H*), 2.73 (1H, dd, *J* 17.5, 10.8, CH*H*), 2.92 (1H, ddd, *J* 17.5, 5.3, 1.9, CH*H*), 3.29 (1H, tdd, *J* 10.8, 5.3, 3.4, C*H*Ph), 3.65 (1H, ddd, *J* 10.8, 5.3, 3.4, CH*H*), 3.74 – 3.81 (1H, m, CH*H*), 3.84 (3H, s, OCH_3), 6.96 [2H, $(AX)_2$, ArC*H*], 7.22 [2H, $(AX)_2$, ArC*H*], 7.28 – 7.32 (3H, m, ArC*H*), 7.38 – 7.42 (2H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 30.7 (CH_2), 38.8 (*C*H), 39.8 (CH_2), 51.0 (CH_2), 55.5 (CH_3), 114.6 (2 × Ar*C*H), 126.6 (2 × Ar*C*H), 126.9 (Ar*C*H), 127.4 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 135.9 (Ar*C*), 143.4 (Ar*C*), 158.3 (Ar*C*), 169.6 (*C*=O); *m*/*z* (TOF MS ES$^+$) 282.1493 (100%, MH^+ $C_{18}H_{20}NO_2$ requires 282.1494). Chiral HPLC, CELLULOSE-1, 20% IPA in hexane @ 1.0 mL min^{-1}, t_R (minor) 27.3 min and (major) 29.9 min. Optical rotation is comparable with literature for 4(*R*)-1-(4-methoxyphenyl)-4-(4-fluorophenyl)piperidin-2-one [+8.0 (*c* 1.3 $CHCl_3$).[99]

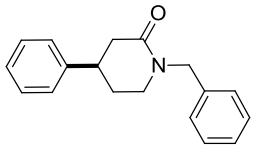
4(*R*)-5-Hydroxy-1-(4-methoxyphenyl)-4-phenylpiperidin-2-one 177



Using general procedure **E** with glutarimide **173** (0.30 g, 1.00 mmol) *but purifying the crude hydroxy-lactam before conversion to the N-PMP lactam* gave the title compound as a white powder in a 2:1 diastereomeric ratio (0.06 g, 20%). Mpt 156 – 158 ^{o}C; $[\alpha]_D^{20}$ + 18.2 (*c* 1.7, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3188, 3030, 2936, 2836, 2543, 2160, 2035, 1979, 1644, 1620, 1602, 1507; ^{1}H NMR (400 MHz; $CDCl_3$) **major diastereomer** δ_H 2.60 – 2.74 (2H, m, 2 × CH*H*), 2.86 – 2.96 (2H, m, 2 × CH*H*), 3.21 – 3.31 (2H, m, 2 × C*H*), 3.84 (3H, s, OCH_3), 5.30 – 5.34 (1H, m, O*H*), 6.96 – 6.98 (3H, m, ArC*H*), 7.28 – 7.30 (6H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) **major diastereomer** δ_C 30.7 (CH_2), 33.1 (*C*H), 51.0 (CH_2), 55.5 (CH_3), 81.9 (*C*H), 114.8 (2 × Ar*C*H), 126.7 (2 × Ar*C*H), 127.4 (Ar*C*H), 128.8 (2 × Ar*C*H), 129.2 (2 ×

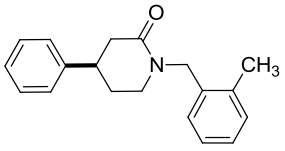
Ar*C*H), 133.4 (Ar*C*), 143.1 (Ar*C*), 158.9 (Ar*C*), 170.0 (*C*=O); *m*/*z* (TOF MS ES$^+$) 298.1446 (100%, MH$^+$ $C_{18}H_{20}NO_2$ requires 298.1443).

4(*R*)-1-(Phenylmethyl)-4-phenylpiperidin-2-one 180



Using glutarimide **174** (0.30 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure **E** (0.16 g, 60% over 2 steps) Mpt 80 – 82 ^{o}C (lit.[115] 88 – 90 ^{o}C); $[\alpha]_D^{20}$ + 33.0 (*c* 1.1, $CHCl_3$; 90% ee), lit.[100] $[\alpha]_D^{20}$ + 35.0 (*c* 1.1, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 1619, 1494; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.97 (1H, dtd, *J* 13.2, 10.8, 6.0, CH*H*), 2.07 – 2.14 (1H, m, CH*H*), 2.63 (1H, dd, *J* 17.5, 11.0, CH*H*), 2.83 (1H, ddd, *J* 17.5, 5.2, 2.0, CH*H*), 3.13 (1H, tdd, *J* 11.0, 5.2, 3.1, C*H*Ph), 3.26 – 3.37 (2H, m, 2 × CH*H*), 4.59 (1H, d, *J* 14.5, NCH*H*), 4.77 (1H, d, *J* 14.5, NCH*H*), 7.21 – 7.39 (10H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 30.3 (*C*H$_2$), 38.7 (*C*H), 39.5 (*C*H$_2$), 46.4 (*C*H$_2$), 50.0 (*C*H$_2$), 126.5 (2 × Ar*C*H), 126.8 (Ar*C*H), 127.5 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 137.1 (Ar*C*), 143.4 (Ar*C*), 169.3 (*C*=O); *m*/*z* (EI$^+$) 265 (100%, M$^+$ $C_{18}H_{19}NO$), 174 (12), 131 (32), 104 (230), 131 (32), 91 (70). Chiral HPLC, Lux 3u CELLULOSE-2, 20% IPA in hexane @ 1.0 mL min^{-1}, t_R (major) 23.5 min and (minor) 26.1 min. All data are in accordance with literature.[115, 100, 142]

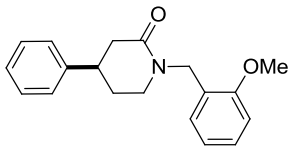
4(*R*)-1-(2-Methylbenzyl)-4-phenylpiperidin-2-one 182



Using glutarimide **175** (0.30 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure **E** (0.07 g, 25% over 2 steps) Mpt 72 – 74 ^{o}C; $[\alpha]_D^{20}$ + 26.58 (*c* 0.8, $CHCl_3$; 88% ee); (Found: C, 81.81; H, 7.82; N, 4.85. $C_{19}H_{21}NO$ requires C, 81.68; H, 7.58; N, 5.01); ν_{max} (ATR) / cm^{-1} 3024, 2915, 1737, 1627, 1605; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.93 – 2.03 (1H, m, CH*H*), 2.09 – 2.15 (1H, m, CH*H*), 2.34 (3H, s, C*H*$_3$), 2.64 (1H, dd, *J* 17.5, 11.1, CH*H*), 2.88 (1H, ddd, *J* 17.5, 5.2, 2.1, CH*H*), 3.15 (1H, tdd, *J* 11.1, 5.2, 3.1, C*H*Ph), 3.22 – 3.31 (2H, m, 2 × CH*H*), 4.63 (1H, d, *J* 15.1, NCH*H*), 4.81 (1H, d, *J* 15.1, NCH*H*), 7.17 – 7.29 (7H, m, ArC*H*), 7.35 – 7.39 (2H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 19.25 (*C*H$_3$), 30.3 (*C*H$_2$), 38.7 (*C*H), 39.5 (*C*H$_2$), 46.3 (*C*H$_2$), 47.7 (*C*H$_2$), 126.1 (Ar*C*H), 126.5 (2 × Ar*C*H), 126.8 (Ar*C*H), 127.5 (Ar*C*H), 128.1 (Ar*C*H), 128.8 (2 × Ar*C*H), 130.5

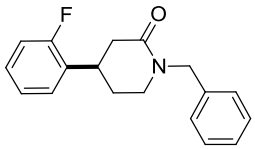
(Ar*C*H), 134.5 (Ar*C*), 136.6 (Ar*C*), 143.4 (Ar*C*), 169.2 (*C*=O); *m*/*z* (TOF MS ES$^+$) 280.1713 (100%, MH$^+$ $C_{22}H_{22}NO$ requires 280.1701). Chiral HPLC, Lux 3u CELLULOSE-2, 20% IPA in hexane @ 1.0 mL min^{-1}, t_R (major) 20.6 min and (minor) 22.3 min.

4(*R*)-1-(2-Methoxybenzyl)-4-phenylpiperidin-2-one 183



Using glutarimide **176** (0.30 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure **E** (0.06 g, 21% over 2 steps) Mpt. 80 – 82 ^oC; $[\alpha]_D^{20}$ + 21.72 (*c* 1.0, $CHCl_3$; 90% ee); ν_{max} (ATR) / cm^{-1} 2940, 2159, 1738, 1636; ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.95 – 2.03 (1H, m, CH*H*), 2.09 – 2.13 (1H, m, CH*H*), 2.62 (1H, dd, *J* 17.5, 11.1, CH*H*), 2.84 (1H, ddd, *J* 17.5, 5.3, 2.0, CH*H*), 3.15 (1H, tdd, *J* 11.1, 5.3, 3.2, C*H*), 3.31 – 3.37 (2H, m, CH_2), 3.86 (3H, s, CH_3), 4.65 (1H, d, *J* 15.1, NCH*H*), 4.77 (1H, d, *J* 15.1, NCH*H*), 6.90 (1H, d, *J* 8.0, ArC*H*), 6.97 (1H, td, *J* 7.5, 0.9, ArC*H*), 7.23 – 7.30 (5H, m, ArC*H*), 7.34 – 7.38 (2H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 30.4 (*C*H_2), 38.7 (*C*H), 39.5 (*C*H_2), 44.5 (*C*H_2), 46.8 (*C*H_2), 55.4 (*C*H_3), 110.3 (Ar*C*H), 120.7 (Ar*C*H), 125.1 (Ar*C*), 126.6 (2 × Ar*C*H), 126.8 (Ar*C*H), 128.5 (Ar*C*H), 128.7 (2 × Ar*C*H), 129.1 (Ar*C*H), 143.6 (Ar*C*), 157.6(Ar*C*), 169.4 (*C*=O); *m*/*z* (ES$^+$) 296.1563 (100%, M$^+$ $C_{19}H_{21}NO_2$ requires 295.1572), 264 (50), 176 (27), 149 (35), 121 (60), 91 (85). Chiral HPLC, Lux 3u CELLULOSE-2, 20% IPA in hexane @ 1.0 mL min^{-1}, t_R (major) 21.3 min and (minor) 23.6 min.

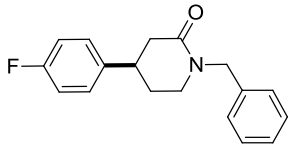
4(*R*)-1-(Phenylmethyl)-4-(2-fluorophenyl)piperidin-2-one 217



Using glutarimide **209** (0.30 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure **E** (0.14 g, 51% over 2 steps) Mpt 60 – 62 ^oC; $[\alpha]_D^{20}$ + 20.1 (*c* 2.1, $CHCl_3$; 82% ee); ν_{max} (ATR) / cm^{-1} 2925, 1616, 1587; ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.98 – 2.10 (2H, m, 2 × CH*H*), 2.64 (1H, dd, *J* 17.4, 10.8, CH*H*), 2.85 (1H, ddd, *J* 17.4, 5.3, 1.9, CH*H*), 3.25 – 3.38 (2H, m, 2 × CH*H*), 3.45 (1H, td, *J* 10.8, 5.3, 3.9, C*H*), 4.58 (1H, d, *J* 14.6, NCH*H*), 4.76 (1H, d, *J* 14.6, NCH*H*), 7.03 – 7.36 (9H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 28.9 (*C*H_2), 32.2 (d, *J* 1.5, *C*H), 38.0 (*C*H_2), 46.3 (*C*H_2), 50.1 (*C*H_2), 115.6 (d, $J_{C\text{-}F}$ 22.4, Ar*C*H), 124.4 (d, $J_{C\text{-}F}$ 3.5, Ar*C*H), 127.3 (d, $J_{C\text{-}F}$ 4.6, Ar*C*H), 127.5 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.3 (d, $J_{C\text{-}F}$ 8.4, Ar*C*H), 128.7 (2 × Ar*C*H), 130.1 (d, $J_{C\text{-}F}$ 14.2, Ar-F), 137.0

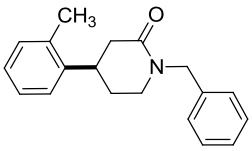
(Ar*C*), 160.6 (d, $J_{C\text{-}F}$ 245.8, Ar*C*), 169.1 (*C*=O); *m*/*z* (EI^+) 283.1382 (100%, M^+ $C_{18}H_{18}FNO$ requires 283.1372), 149 (50), 109 (25), 103 (58) 105 (93), 91 (95), 77 (98). Chiral HPLC, Lux 3u CELLULOSE-2, 20% IPA in hexane @ 1.0 mL min^{-1}, t_R (major) 16.4 min and (minor) 18.2 min.

4(*R*)-1-(Phenylmethyl)-4-(4-fluorophenyl)piperidin-2-one 218



Using glutarimide **210** (0.30 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure **E** (0.15 g, 54% over 2 steps) Mpt 114 – 116 ^oC; $[\alpha]_D^{20}$ + 30.0 (*c* 1.1, $CHCl_3$; 92% ee), lit.[100] $[\alpha]_D^{20}$ + 33.0 (*c* 1.07, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3071, 2927, 1625, 1601, 1510; ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.87 – 1.97 (1H, m, CH*H*), 2.07 – 2.10 (1H, m, CH*H*), 2.57 (1H, dd, *J* 17.4, 11.0, CH*H*), 2.83 (1H, dd, *J* 17.4, 3.4, CH*H*), 3.09 – 3.14 (1H, m, C*H*), 3.25 – 3.36 (2H, m, 2 × CH*H*), 4.57 (1H, d, *J* 14.5, NCH*H*), 4.77 (1H, d, *J* 14.5, NCH*H*), 7.03 [2H, $(AX)_2$, ArC*H*], 7.18 [2H, $(AX)_2$, ArC*H*], 7.28 – 7.38 (5H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 30.3 (CH_2), 38.0 (*C*H), 39.6 (CH_2), 46.2 (CH_2), 50.0 (CH_2), 115.5 (d, $J_{C\text{-}F}$ 21.2, 2 × Ar*C*H), 127.5 (Ar*C*H), 128.0 (d, $J_{C\text{-}F}$ 7.8, 2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.7 (2× Ar*C*H), 137.1 (Ar*C*), 139.1 (d, $J_{C\text{-}F}$ 3.0, Ar*C*), 161.7 (d, $J_{C\text{-}F}$ 245.0, Ar*C*), 169.1 (*C*=O); *m*/*z* (TOF MS ES^+) 284.1437 (100%, MH^+ $C_{18}H_{19}FNO$ requires 284.1451). Chiral HPLC, CHIRAL PAK IA, 7% IPA in hexane @ 1.0 mL min^{-1}, t_R (minor) 38.2 min and (major) 40.0 min. All data are in accordance with literature.[100, 131, 142]

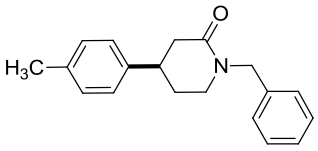
4(*R*)-1-(Phenylmethyl)-4-(2-methylphenyl)piperidin-2-one 219



Using glutarimide **211** (0.30 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure **E** (0.17 g, 61% over 2 steps) Mpt 68 – 70 ^oC; $[\alpha]_D^{20}$ + 39.4 (*c* 0.3, $CHCl_3$; 86% ee); ν_{max} (ATR) / cm^{-1} 2925, 1626, 1587; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.01 – 2.04 (2H, m, 2 × CH*H*), 2.37 (3H, s, CH_3), 2.56 (1H, dd, *J* 17.5, 11.0, CH*H*), 2.81 (1H, ddd, *J* 17.5, 5.2, 1.9, CH*H*), 3.28 – 3.37 (3H, m, 2 × C*H*H and C*H*), 4.55 (1H, d, *J* 14.5, NCH*H*), 4.85 (1H, d, *J* 14.5, NCH*H*), 7.16 – 7.22 (4H, m, ArC*H*), 7.33 – 7.40 (5H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 19.3 (CH_3), 29.3 (CH_2), 34.6 (*C*H), 39.0 (CH_2), 46.5 (CH_2), 50.1

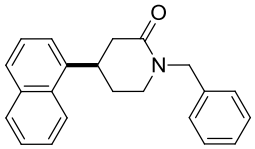
(*C*H$_2$), 125.0 (Ar*C*H), 126.5 (Ar*C*H), 126.6 (Ar*C*H), 127.5 (Ar*C*H), 128.3 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 130.7 (Ar*C*H), 135.3 (Ar*C*), 137.2 (Ar*C*), 141.5 (Ar*C*) 169.6 (*C*=O); *m*/*z* (TOF MS ES$^+$) 280.1710 (100%, MH$^+$ $C_{19}H_{22}NO$ requires 280.1701). Chiral HPLC, Lux 3u CELLULOSE-2, 20% IPA in hexane @ 1.0 mL min^{-1}, t_R (minor) 15.3 min and (major) 18.3 min.

4(*R*)-1-(Phenylmethyl)-4-(4-methylphenyl)piperidin-2-one 220



Using glutarimide **212** (0.30 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure **E** (0.14 g, 51% over 2 steps) Mpt 105 – 106 ^{o}C; $[\alpha]_D^{20}$ + 33.6 (*c* 1.1, $CHCl_3$; 88% ee); (Found: C, 81.58; H, 7.54; N, 4.90. $C_{19}H_{21}NO$ requires C, 81.68; H, 7.58; N, 5.01); ν_{max} (ATR) / cm^{-1} 2924, 1625, 1516; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.89 – 1.99 (1H, m, CH*H*), 2.05 – 2.12 (1H, m, CH*H*), 2.36 (3H, s, C*H*$_3$), 2.60 (1H, dd, *J* 17.5, 11.1, CH*H*), 2.83 (1H, ddd, *J* 17.5, 5.2, 2.0, CH*H*), 3.10 (1H, tdd, *J* 11.1, 5.2, 3.1, C*H*), 3.25 – 3.36 (2H, m, 2 × CH*H*), 4.59 (1H, d, *J* 14.6, NCH*H*), 4.76 (1H, d, *J* 14.6, NCH*H*), 7.13 [2H, $(AX)_2$, ArC*H*], 7.17 [2H, $(AX)_2$, ArC*H*], 7.28 – 7.39 (5H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 21.0 (*C*H$_3$), 30.4 (*C*H$_2$), 38.3 (*C*H), 39.6 (*C*H$_2$), 46.4 (*C*H$_2$), 50.0 (*C*H$_2$), 126.4 (2 × Ar*C*H), 127.4 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 129.4 (2 × Ar*C*H), 136.4 (Ar*C*), 137.2 (Ar*C*), 140.5 (Ar*C*) 169.4 (*C*=O); *m*/*z* (TOF MS ES$^+$) 280.1692 (100%, MH$^+$ $C_{19}H_{22}NO$ requires 280.1701). Chiral HPLC, CHIRAL PAK IA, 7% IPA in hexane @ 1.0 mL min^{-1}, t_R (minor) 31.3 min and (major) 32.9 min.

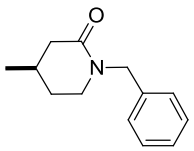
4(*R*)-1-(Phenylmethyl)-4-(1-naphthyl)piperidin-2-one 221



Using glutarimide **213** (0.33 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure **E** solid (0.06 g, 20% over 2 steps) Mpt 122 – 124 ^{o}C; $[\alpha]_D^{20}$ -13.3 (*c* 0.5, $CHCl_3$; 54% ee); ν_{max} (ATR) / cm^{-1} 3196, 2950, 1707, 1636, 1624; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.10 – 2.20 (1H, m, CH*H*), 2.25 – 2.28 (1H, m, CH*H*), 2.74 (1H, dd, *J* 17.5, 10.1, CH*H*), 3.05 (1H, dd, *J* 17.5, 3.6, CH*H*), 3.10 (1H, dt, *J* 10.1, 4.7, C*H*), 3.38 – 3.45 (1H, m, CH*H*), 3.95 – 3.99 (1H, m, CH*H*), 4.61 (1H, d, *J* 14.5, CH*H*), 4.84 (1H, d, *J* 14.5, CH*H*), 7.31 – 7.41 (6H, m, ArC*H*), 7.44 – 7.57 (3H, m, ArC*H*), 7.78 (1H, d, *J* 8.2, ArC*H*), 7.90 (1H,

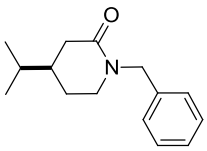
dd, *J* 7.7, 1.5, ArC*H*), 8.06 (1H, d, *J* 8.2, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 29.6 (*C*H_2), 33.8 (*C*H), 39.3 (*C*H_2), 46.2 (*C*H_2), 50.2 (*C*H_2), 122.4 (Ar*C*H), 122.7 (Ar*C*H), 125.6 (Ar*C*H), 125.7 (Ar*C*H), 126.3 (Ar*C*H), 127.4 (Ar*C*H), 127.5 (Ar*C*H), 128.3 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 129.1 (Ar*C*H), 131.0 (Ar*C*), 134.0 (Ar*C*), 137.1 (Ar*C*), 138.9 (Ar*C*), 169.5 (*C*=O); *m*/*z* (TOF MS ES$^+$) 316.1689 (100%, MH^+ $C_{22}H_{22}NO$ requires 316.1701). Chiral HPLC, CHIRAL PAK IA, 7% IPA in hexane @ 1.0 mL min^{-1}, t_R (major) 41.3 min and (minor) 44.9 min.

4(*R*)-1-(Phenylmethyl)-4-methylpiperidin-2-one 222



Using general procedure **E** and glutarimide **214** (0.22 g, 1.00 mmol) a crude oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : petroleum ether (40-60) : Et_3N (2:8:0.05) to afford the title compound as pale yellow oil (0.09 g, 46% over 2 steps) $[\alpha]_D^{20}$ + 46.6 (*c* 3.3, $CHCl_3$; 90% ee); ν_{max} (ATR) / cm^{-1} 3469, 2953, 2927, 2871, 2030, 1634, 1452; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.01 (3H, d, *J* 6.5, C*H*$_3$), 1.39 – 1.47 (1H, m, CH*H*), 1.78 – 1.85 (1H, m, CH*H*), 1.90 – 2.00 (1H, m, C*H*), 2.07 (1H, dd, *J* 17.2, 10.7, CH*H*), 2.58 (1H, ddd, *J* 17.2, 4.9, 2.1, CH*H*), 3.18 – 3.22 (2H, m, 2 × CH*H*), 4.48 (1H, d, *J* 14.7, NCH*H*), 4.72 (1H, d, *J* 14.7, NCH*H*), 7.24 – 7.34 (5H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 21.0 (*C*H_3), 28.0 (*C*H), 30.9 (*C*H_2), 40.5 (*C*H_2), 46.3 (*C*H_2), 50.0 (*C*H_2), 127.3 (Ar*C*H), 128.0 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 137.3 (Ar*C*), 169.7 (*C*=O); *m*/*z* (TOF MS ES$^+$) 217 (100), 204.1394 (70%, MH^+ $C_{13}H_{18}NO$ requires 204.1388),. Chiral HPLC, Lux 3u CELLULOSE-2, 20% IPA in hexane @ 1.0 mL min^{-1}, t_R (minor) 13.2 min and (major) 14.1 min.

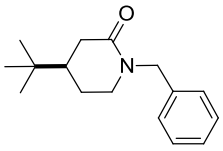
4(*R*)-1-(Phenylmethyl)-4-isopropylpiperidin-2-one 223



Using general procedure **E** and glutarimide **215** (0.22 g, 1.00 mmol) a crude oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : DCM : petroleum ether (40-60) (3:1:6) to afford the title compound as yellow oil (0.09 g, 41% over 2 steps) $[\alpha]_D^{20}$ + 44.3 (*c* 1.9, $CHCl_3$; 86% ee); ν_{max} (ATR) / cm^{-1} 3168, 2957, 2871, 2173, 1676, 1638; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.93 (6H, dd, *J* 6.6, 2.2, 2 × C*H*$_3$), 1.40 – 1.60 (3H, m,

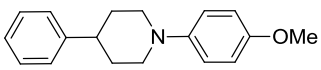
2 × CH*H* and C*H*), 1.85 – 1.90 (1H, m, C*H*), 2.17 (1H, dd, *J* 17.5, 11.6, CH*H*), 2.61 (1H, ddd, *J* 17.5, 4.9, 2.3, CH*H*), 3.15 – 3.27 (2H, m, 2 × CH*H*), 4.53 (1H, d, *J* 14.6, NCH*H*), 4.71 (1H, d, *J* 14.6, NCH*H*), 7.25 – 7.36 (5H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 19.3 (*C*H_3), 19.6 (*C*H_3), 26.6 (*C*H_2), 31.9 (*C*H), 36.3 (*C*H_2), 39.4 (*C*H), 46.8 (*C*H_2), 49.9 (*C*H_2), 127.3 (Ar*C*H), 128.0 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 137.2 (Ar*C*), 170.3 (*C*=O); *m*/*z* (TOF MS ES$^+$) 254 (30, M + Na^+), 232.1709 (100%, MH^+ $C_{15}H_{22}NO$ requires 232.1701). Chiral HPLC, Lux 3u CELLULOSE-2, 5% IPA in hexane @ 1.0 mL min^{-1}, t_R (minor) 47.1 min and (major) 49.0 min.

4(*R*)-1-(Phenylmethyl)-4-*tert*-butylpiperidin-2-one 224



Using general procedure **E** and glutarimide **216** (0.26 g, 1.00 mmol) a crude oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : DCM : petroleum ether (40-60) (3:1:6) to afford the title compound as yellow oil (0.11 g, 46% over 2 steps). $[\alpha]_D^{20}$ + 36.8 (*c* 1.4, $CHCl_3$; 87% ee); ν_{max} (ATR) / cm^{-1} 2957, 2867, 2173, 1636; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.90 (9H, s, 3 × C*H*$_3$), 1.40 (1H, qd, *J* 12.5, 5.5, CH*H*), 1.57 (1H, tdd, *J* 12.5, 4.8, 2.3, *t*-BuC*H*), 1.86 – 1.90 (1H, m, CH*H*), 2.21 (1H, dd, *J* 17.3, 12.5, COCH*H*), 2.59 (1H, ddd, *J* 17.3, 4.8, 2.3, COCH*H*), 3.17 (1H, td, *J* 12.6, 4.8, CH*H*N), 3.26 (1H, ddd, *J* 12.6, 5.5, 2.3, CH*H*N), 4.53 (1H, d, *J* 14.6, PhCH*H*N), 4.71 (1H, d, *J* 14.6, PhCH*H*N), 7.26 – 7.36 (5H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 24.6 (*C*H_2), 26.8 (3 × *C*H_3), 32.0 (*C*), 34.3 (*C*H_2), 43.2 (*C*H), 47.1 (*C*H_2), 49.9 (*C*H_2), 127.3 (Ar*C*H), 128.1 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 137.2 (Ar*C*), 170.5 (*C*=O); *m*/*z* (TOF MS ES$^+$) 246.1861 (100%, MH^+ $C_{16}H_{24}NO$ requires 246.1858). Chiral HPLC, Lux 3u CELLULOSE-1, 5% IPA in hexane @ 1.0 mL min^{-1}, t_R (minor) 11.3 min and (major) 12.4 min.

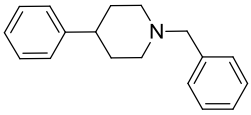
1-(4-Methoxyphenyl)-4-phenylpiperidine 178



Using general procedure **E** and glutarimide **173** (0.30 g, 1.00 mmol) the title compound was obtained as an undesired product as white crystals (0.08 g, 30% over 2 steps); Mpt 150 – 152 ^{o}C; (Found: C, 80.74; H, 7.91; N, 5.12. $C_{18}H_{22}NO$ requires C, 80.86; H, 7.92; N, 5.24); ν_{max} (ATR) / cm^{-1} 2953, 2938, 2917, 2840, 2810, 2744, 1508; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.95 – 1.96 (4H, m, 4 × CH*H*), 2.61 – 2.69 (1H, m, C*H*), 2.75 – 2.82 (2H, m, 2 × CH*H*), 3.65

– 3.69 (2H, m, 2 × CH*H*), 3.81 (2H, s, OCH_3), 6.90 [2H, $(AX)_2$, ArC*H*], 7.00 [2H, $(AX)_2$, ArC*H*], 7.24 – 7.38 (5H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 33.6 (2 × *C*H_2), 42.4 (*C*H), 52.2 (2 × *C*H_2), 55.6 (*C*H_3), 114.4 (2 × Ar*C*H), 118.9 (2 × Ar*C*H), 126.3 (Ar*C*H), 126.9 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 146.2 (Ar*C*), 146.4 (Ar*C*), 153.8 (Ar*C*); *m*/*z* (TOF MS ES$^+$) 268.1693 (100%, MH^+ $C_{18}H_{22}NO$ requires 268.1701). Only ^{1}H NMR and mass spectrometry were provided in the literature.[143]

1-(Phenylmethyl)-4-phenylpiperidine 181



Using general procedure **E** and glutarimide **174** (0.30 g, 1.00 mmol) the title compound was obtained as an undesired product as yellow oil (0.03 g, 12% over 2 steps ν_{max} (ATR) / cm^{-1} 3061, 3026, 2933, 2798, 2754, 1602; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.75 – 1.95 (4H, m, 4 × CH*H*), 2.05 – 2.21 (2H, m, 2 × CH*H*), 2.48 – 2.60 (1H, m, C*H*), 3.03 – 3.10 (2H, m, 2 × CH*H*), 3.60 (2H, s, NCH_2), 7.20 – 7.40 (10H, m, ArC*H*); ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 33.6 (2 × *C*H_2), 42.8 (*C*H), 54.3 (2 × *C*H_2), 63.5 (*C*H_2), 126.1 (Ar*C*H), 126.9 (2 × Ar*C*H), 127.0 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 138.6 (Ar*C*), 146.6 (Ar*C*); *m*/*z* (TOF MS ES$^+$) 252.1764 (100%, MH^+ $C_{18}H_{22}N$ requires 252.1752). All data are in accordance with literature.[144]

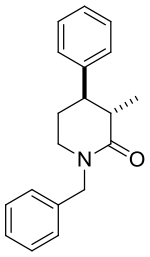
5.6 Experimental for the synthesis of α-substituted lactams

General Procedure G for the synthesis of 3-substituted *N*-Bn-4-phenylpiperidin-2-ones[145]

Diisopropylamine (1.10 cm^3, 7.50 mmol) was added to a flask containing dry THF (5.10 cm^3) under N_2 atmosphere at - 78 ^{o}C and stirred gently. *n*-BuLi (3.80 cm^3, 7.50 mmol, 2.0 M in hexane) was added drop-wise and the mixture stirred at - 78 ^{o}C for 10 mins to give the LDA stock solution (7.50 mmol / 10 cm^3 solution). The LDA (2.00 cm^3, 1.50 mmol) from the stock solution was added drop-wise to a solution of the *N*-benzyl substrate **180** (0.27 g, 1.00 mmol) in dry THF (5.00 cm^3) under N_2 atmosphere. The solution was allowed to stir at - 78 ^{o}C for 20 mins. Then the electrophile (1.00 equiv.) was slowly added and the mixture stirred at - 78 ^{o}C for 2 h, allowed to warm to room temperature slowly and further stirred for 18 h. The reaction was quenched by slow addition of saturated $NaHCO_3$ (10 cm^3), concentrated *in vacuo* and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a crude yellow

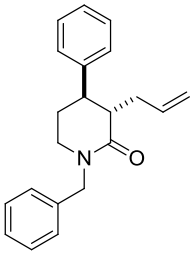
oily solid, which was purified via flash column chromatography eluting with EtOAc : petroleum ether (40-60) (3:7).

(3*S*, 4*R*)-1-(Phenylmethyl)-3-methyl-4-phenylpiperidin-2-one 245



Using general procedure **G** and methyl iodide (0.06 cm^3, 1.00 mmol) as the electrophile, the title compound was obtained as a yellow solid as a single diastereomer (0.17 g, 61%) Mpt 70 – 72 ^oC; (Found: C, 81.38; H, 7.85; N, 5.28. $C_{19}H_{21}NO$ requires C, 81.68; H, 7.58; N, 5.01); $[\alpha]_D^{20}$ + 26.1 (*c* 0.7, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3062, 3031, 2967, 2872, 2174, 1618; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.20 (3H, d, *J* 6.9, C*H*$_3$), 1.98 – 2.04 (2H, m, 2 × CH*H*), 2.64 (1H, dq, *J* 10.4, 6.9, C*H*), 2.70 – 2.76 (1H, m, C*H*), 3.26 – 3.40 (2H, m, 2 × CH*H*), 4.53 (1H, d, *J* 14.5, NCH*H*), 4.82 (1H, d, *J* 14.5, NCH*H*), 7.20 [2H, $(AX)_2$, ArC*H*], 7.25 – 7.40 (8H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 16.1 (*C*H_3), 30.6 (*C*H_2), 43.1 (*C*H), 46.5 (*C*H_2), 47.0 (*C*H), 50.5 (*C*H_2), 126.8 (Ar*C*H), 127.1 (2 × Ar*C*H), 127.4 (Ar*C*H), 128.1 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 137.4 (Ar*C*), 143.8 (Ar*C*), 172.7 (*C*=O); *m*/*z* (TOF MS ES^+) 280.1700 (100%, MH^+ $C_{19}H_{22}NO$ requires 280.1701).

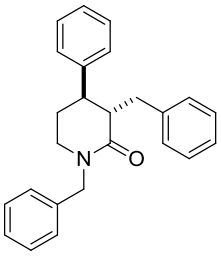
(3*S*, 4*R*)-1-(Phenylmethyl)-3-allyl-4-phenylpiperidin-2-one 246



Using general procedure **G** and allyl bromide (0.10 cm^3, 1.00 mmol) as the electrophile, the title compound was obtained as a yellow solid as a single diastereomer (0.19 g, 62%) Mpt 62 – 64 ^oC; $[\alpha]_D^{20}$ + 37.2 (*c* 1.2, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3029, 2977, 2920, 2959, 1633, 1585; ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.96 – 2.01 (2H, m, 2 × CH*H*), 2.13 (1H, ddd, *J* 13.6, 7.5, 3.9, C*H*), 2.76 – 2.88 (2H, m, 2 × CH*H*), 3.00 (1H, dt, *J* 9.9, 7.5, C*H*), 3.23 (1H, dt, *J* 12.1, 3.9, CH*H*), 3.33 (1H, ddd, *J* 12.1, 8.7, 7.5, CH*H*), 4.66 (1H, d, *J* 14.5, NCH*H*), 4.73 (1H, d, *J* 14.5, NCH*H*), 4.64 – 4.75 (2H, m, 2 × =CH*H*), 5.74 – 5.84 (1H, m, =C*H*), 7.20 [2H, $(AX)_2$, ArC*H*], 7.25 – 7.39 (8H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 30.4 (*C*H_2), 33.6 (*C*H_2),

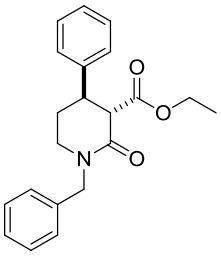
42.4 (*C*H), 46.4 (*C*H_2), 47.4 (*C*H), 50.6 (*C*H_2), 117.7 (=*C*H_2), 126.8 (Ar*C*H), 127.3 (2 × Ar*C*H), 127.4 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 135.4 (=*C*H), 137.3 (Ar*C*), 143.5 (Ar*C*), 171.3 (*C*=O); *m*/*z* (TOF MS ES^+) 328.1682 (80%, M + Na^+, $C_{21}H_{23}NONa$ requires 328.1677), 340 (100).

(3*S*, 4*R*)-1,3-di(Phenylmethyl)-4-phenylpiperidin-2-one 247



Using general procedure **G** and benzyl bromide (0.10 cm^3, 1.00 mmol) as the electrophile, a yellow oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : petroleum ether (40-60) (2:8) to afford the title compound as yellow solid as a single diastereomer (0.17 g, 57%) Mpt 66 – 68 ^oC; $[\alpha]_D^{20}$ - 4.6 (*c* 4.0, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3027, 2927, 2161, 1631, 1583; ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.88 – 1.94 (2H, m, 2 × CH*H*), 2.74 (1H, dd, *J* 13.7, 5.0, CH*H*), 2.84 (1H, td, *J* 9.7, 6.2, C*H*Ph), 3.07 – 3.15 (3H, m, 2 × CH*H* and C*H*), 3.48 (1H, dd, *J* 13.7, 5.0, CH*H*), 4.50 (1H, d, *J* 14.5, NCH*H*), 4.90 (1H, d, *J* 14.5, NCH*H*), 7.17 – 7.36 (15H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 30.8 (*C*H_2), 35.0 (*C*H_2), 41.9 (*C*H), 46.3 (*C*H_2), 48.5 (*C*H), 50.8 (*C*H_2), 126.2 (Ar*C*H), 126.8 (Ar*C*H), 127.4 (Ar*C*H), 127.4 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 130.1 (2 × Ar*C*H), 132.0 (Ar*C*), 139.2 (Ar*C*), 143.5 (Ar*C*), 171.4 (*C*=O); *m*/*z* (TOF MS ES^+) 356.2024 (100%, MH^+ $C_{25}H_{26}NO$ requires 356.2014). All data are in accordance with literature.[115]

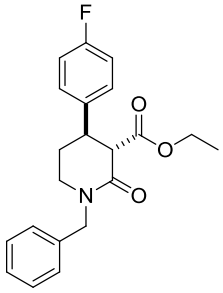
(3*S*, 4*R*)-1-Benzyl-2-oxo-4-phenylpiperidine-3-ethyl carboxylate 248



Using general procedure **G** and ethyl chloroformate (0.10 cm^3, 1.00 mmol) as the electrophile, a yellow oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : DCM : petroleum ether (2:1:7) to afford the title compound as yellow solid in 10:1 diastereomeric ratio (0.24 g, 71%) Mpt 140 – 142 ^oC; $[\alpha]_D^{20}$

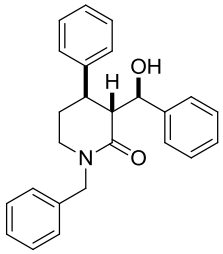
+ 3.0 (*c* 0.1, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3029, 2929, 2927, 1733, 1635; ^1H NMR (400 MHz; $CDCl_3$) **Major diastereomer** δ_H 1.12 (3H, t, *J* 7.1, C*H*$_3$), 2.00 – 2.11 (2H, m, 2 × CH*H*), 3.30 (1H, ddd, *J* 11.0, 5.3, 3.2, C*H*Ph), 3.39 – 3.50 (2H, m, 2 × CH*H*), 3.66 (1H, d, *J* 11.0, C*H*CO), 4.12 (2H, q, *J* 7.1, C*H*$_2$), 4.56 (1H, d, *J* 14.5, NCH*H*), 4.79 (1H, d, *J* 14.5, NCH*H*), 7.22 [2H, $(AX)_2$, ArC*H*], 7.29 – 7.39 (8H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.0 (*C*H$_3$), 29.3 (*C*H$_2$), 42.6 (*C*H), 46.2 (*C*H$_2$), 50.3 (*C*H$_2$), 56.5 (*C*H), 61.2 (*C*H$_2$), 126.9 (2 × Ar*C*H), 127.3 (Ar*C*H), 127.6 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 136.7 (Ar*C*), 141.4 (Ar*C*), 166.0 (O*C*=O), 170.1 (N*C*=O); *m*/*z* (TOF MS ES^+) 338.1758 (100%, MH^+ $C_{21}H_{24}NO_3$ requires 338.1756).

(3*S*, 4*R*)-1-Benzyl-2-oxo-4-(4-fluorophenyl)piperidine-3-ethyl carboxylate 257



Using general procedure **G**, starting with the 4-(*p*-fluorophenyl) lactam **218** (0.36 g, 1.00 mmol) and ethyl chloroformate (0.10 cm^3, 1.00 mmol) as the electrophile, a yellow oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : DCM : petroleum ether (40-60) (2:1:7) to afford the title compound as yellow solid in 10:1 diastereomeric ratio (0.22 g, 62%) Mpt 148 – 150 ^oC; $[\alpha]_D^{20}$ + 3.5 (*c* 0.1, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 2933, 1734, 1640, 1605; ^1H NMR (400 MHz; $CDCl_3$) **Major diastereomer** δ_H 1.14 (3H, t, *J* 7.1, C*H*$_3$), 1.98 – 2.09 (2H, m, 2 × CH*H*), 3.30 (1H, ddd, *J* 11.0, 5.4, 2.9, C*H*Ph), 3.39 – 3.49 (2H, m, 2 × CH*H*), 3.59 (1H, d, *J* 11.0, C*H*CO), 4.13 (2H, q, *J* 7.1, C*H*$_2$), 4.53 (1H, d, *J* 14.5, NCH*H*), 4.81 (1H, d, *J* 14.5, NCH*H*), 7.02 [2H, $(AX)_2$, ArC*H*], 7.18 [2H, $(AX)_2$, ArC*H*], 7.28 – 7.39 (5H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.0 (*C*H$_3$), 29.4 (*C*H$_2$), 41.9 (*C*H), 46.2 (*C*H$_2$), 50.3 (*C*H$_2$), 56.7 (*C*H), 61.3 (*C*H$_2$), 115.7 (d, $J_{C\text{-}F}$ 21.4, 2 × Ar*C*H), 127.6 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.4 (d, $J_{C\text{-}F}$ 8.0, 2 × Ar*C*H), 128.7 (2 × Ar*C*H), 136.6 (Ar*C*), 137.1 (Ar*C*), 161.9 (d, $J_{C\text{-}F}$ 245.5, Ar*C*), 165.8 (O*C*=O), 170.0 (N*C*=O); *m*/*z* (TOF MS ES^+) 356.1645 (100%, MH^+ $C_{21}H_{23}FNO_3$ requires 356.1662).

(3*S*, 4*R*)-1-Benzyl-3-[1(*R*)-hydroxyphenylmethyl]-4-phenylpiperidin-2-one 253



Using general procedure **G** and benzaldehyde (0.10 cm^3, 1.00 mmol) as the electrophile, a yellow oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : petroleum ether (40-60) : Et_3N (1:9:0.05) to afford the title compound as a yellow solid as a single diastereomer (0.23 g, 62%) Mpt 66 – 68 ^oC; $[\alpha]_D^{20}$ -13.4 (*c* 0.97, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3337 (broad), 3061, 3028, 2921, 1608, 1583; ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.80 – 1.98 (2H, m, 2 × CH*H*), 2.66 (1H, td, *J* 11.7, 4.4, C*H*Ph), 3.02 – 3.15 (2H, m, 2 × CH*H*), 3.44 (1H, dd, *J* 11.7. 4.4, C*H*), 4.61 (1H, d, *J* 4.4, OC*H*Ph), 4.75 (1H, d, *J* 14.7, NCH*H*), 4.96 (1H, d, *J* 14.7, NCH*H*), 6.77 (1H, bs, O*H*), 7.16 [2H, $(AX)_2$, ArC*H*], 7.27 – 7.34 (11H, m, ArC*H*), 7.41 [2H, $(AX)_2$, ArC*H*]; ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 31.7 (*C*H), 41.9 (*C*H_2), 46.8 (*C*H), 50.4 (*C*H), 52.0 (*C*H_2), 74.1 (*C*H_2), 127.3 (2 × Ar*C*H), 127.3 (Ar*C*H), 127.6 (Ar*C*H), 127.7 (Ar*C*H), 127.8 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 129.1 (2 × Ar*C*H), 136.1 (Ar*C*), 141.6 (Ar*C*), 142.4 (Ar*C*), 172.2 (*C*=O); *m*/*z* (TOF MS ES^+) 372.1967 (100%, MH^+ $C_{25}H_{26}NO_2$ requires 372.1964).

General Procedure H for the reduction of 3-substituted *N*-Bn-4-phenylpiperidin-2-ones to the corresponding piperidines using $LiAlH_4$.[121]

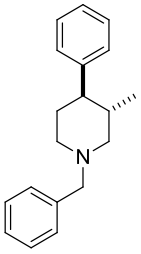
$LiAlH_4$ (3 equiv.) was added to a solution of the piperidin-2-one in dry THF. The mixture was heated at reflux for 24 h and cooled to room temperature. Saturated Na_2SO_4 (2 cm^3) was added and the resultant solution was filtered. The filtrate was concentrated *in vacuo* and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a yellow oil which was purified via flash column chromatography eluting with acetone : hexane : Et_3N (1:9:0.05).

General Procedure I for the reduction of 3-substituted *N*-Bn-4-phenylpiperidin-2-ones to the corresponding piperidines using BH_3.THF.[112]

BH_3.THF (3 equiv.) was added to a solution of the piperidin-2-one in dry THF. The mixture was heated at reflux for 5 h and cooled to room temperature. Distilled H_2O (2 cm^3) was slowly added and the resultant solution was extracted with CH_2Cl_2 (3 × 20 cm^3). The

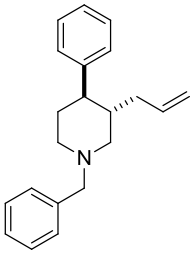
combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude material which was purified via flash column chromatography.

(3*S*, 4*R*)-1-(Phenylmethyl)-3-methyl-4-phenylpiperidine 249



Using general procedure **I** and compound **245** (0.08 g, 0.29 mmol) the title compound was obtained as a white solid in a 10:1 dr (0.05 g, 65%) Mpt 138 – 140 ^{o}C; $[\alpha]_D^{20}$ - 24.5 (*c* 1.8, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3026, 2957, 2927, 2870, 2333, 2275, 1652, 1600; ^{1}H NMR (400 MHz; $CDCl_3$) **Major diastereomer** δ_H 0.62 (3H, d, *J* 6.6, C*H*$_3$), 1.64 – 1.69 (1H, m, C*H*), 1.90 (1H, td, *J* 11.4, 3.8, CH*H*), 2.29 (1H, app t, *J* 11.4, PhC*H*), 2.68 (2H, d, *J* 9.8, 2 × CH*H*), 2.79 – 2.87 (1H, m, CH*H*), 3.00 (1H, ddd, *J* 11.4, 3.8, 2.3, CH*H*), 3.04 (1H, dt, *J* 7.3, 2.3, CH*H*), 4.14 (2H, s, NC*H*$_2$), 7.21 – 7.24 (4H, m, ArC*H*), 7.39 – 7.46 (6H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 17.5 (*C*H$_3$), 29.8 (*C*H$_2$), 31.8 (*C*H), 49.4 (*C*H), 56.5 (*C*H$_2$), 63.2 (*C*H$_2$), 70.4 (*C*H$_2$), 126.6 (Ar*C*H), 127.6 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 129.1 (Ar*C*H), 130.3 (Ar*C*), 133.2 (2 × Ar*C*H), 143.9 (Ar*C*); *m*/*z* (TOF MS ES$^+$) 266.1917 (100%, MH^+ $C_{19}H_{24}N$ requires 266.1909).

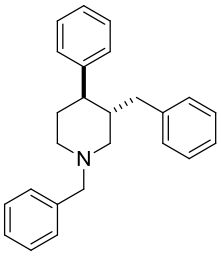
(3*S*, 4*R*)-1-(Phenylmethyl)-3-allyl-4-phenylpiperidine 250



Using general procedure **H** and compound **246** (0.10 g, 0.33 mmol) the title compound was obtained as a yellow oil (0.05 g, 52%) $[\alpha]_D^{20}$ - 15.0 (*c* 0.4, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3061, 3027, 2915, 2798, 2755, 1639, 1602; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.63 – 1.71 (1H, m, CH*H*), 1.76 – 1.84 (3H, m, 2 × CH*H* and C*H*), 1.94 – 2.03 (3H, m, 2 × CH*H* and C*H*), 2.20 (1H, td, *J* 11.0, 4.7, C*H*Ph), 2.97 (1H, dd, *J* 11.0, 8.1, C*H*H), 3.12 (1H, ddd, *J* 11.0, 3.3, 1.7, CH*H*), 3.49 (1H, d, *J* 13.1, CH*H*), 3.68 (1H, d, *J* 13.1, CH*H*), 4.85 – 4.92 (2H, m, 2 × =CH*H*), 5.59 – 5.69 (1H, m, =C*H*), 7.21 – 7.23 (3H, m, ArC*H*), 7.30 – 7.37 (7H, m, ArC*H*);

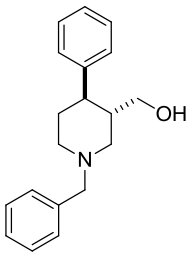
^{13}C NMR (100 MHz; $CDCl_3$) δ_C 34.9 (*C*H_2), 36.3 (*C*H_2), 40.8 (*C*H), 48.7 (*C*H), 53.9 (*C*H_2), 59.6 (*C*H_2), 63.5 (*C*H_2), 116.0 (=*C*H_2), 126.2 (Ar*C*H), 127.0 (Ar*C*H), 127.8 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 136.5 (=*C*H), 138.3 (Ar*C*), 145.0 (Ar*C*); *m*/*z* (TOF MS ES$^+$) 292.2061 (100%, MH^+ $C_{21}H_{26}N$ requires 292.2065).

(3*S*, 4*R*)-1-(Phenylmethyl)-3-benzyl-4-phenylpiperidine 251



Using general procedure **H** and compound **247** (0.17 g, 0.48 mmol) the title compound was obtained as a colourless oil (0.10 g, 61%) $[\alpha]_D^{20}$ - 16.6 (*c* 2.9, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3082, 3060, 3025, 2913, 2796, 2752, 1601; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.79 – 1.90 (3H, m, 2 × CH*H* and C*H*), 1.98 (1H, dd, *J* 14.9, 10.9, CH*H*), 2.11 (1H, dd, *J* 14.9, 10.9, C*H*H), 2.21 – 2.32 (2H, m, 2 × CH*H*), 2.63 (1H, app d, *J* 12.9, C*H*H), 2.92 – 3.02 (2H, m, CH*H* and C*H*), 3.34 (1H, d, *J* 13.1, CH*H*), 3.69 (1H, d, *J* 13.1, CH*H*), 7.04 (1H, d, *J* 7.1, ArC*H*), 7.15 – 7.36 (13H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 35.1 (*C*H_2), 38.4 (*C*H_2), 43.1 (*C*H), 49.4 (*C*H), 53.4 (*C*H_2), 59.8 (*C*H_2), 63.4 (*C*H_2), 125.7 (Ar*C*H), 126.3 (Ar*C*H), 126.9 (Ar*C*H), 127.8 (2 × Ar*C*H), 128.1 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 129.0 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 138.2 (Ar*C*), 140.5 (Ar*C*), 145.2 (Ar*C*); *m*/*z* (TOF MS ES$^+$) 342.2217 (100%, MH^+ $C_{25}H_{28}N$ requires 342.2222). All data are in accordance with literature.[115]

(3*S*, 4*R*)-1-(Phenylmethyl)-3-(hydroxymethyl)-4-phenylpiperidine 252



Using general procedure **I** and compound **248** (0.22 g, 0.65 mmol) the title compound was obtained as a white solid as a single diastereomer (0.10 g, 55%) Mpt 106 – 108 ^{o}C; $[\alpha]_D^{20}$ - 22.2 (*c* 2.0, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3063 (broad), 3030, 2926, 2867, 2353, 2277, 1646, 1602; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.68 – 1.73 (2H, m, 2 × CH*H*), 2.30 (1H, td, *J* 11.9, 4.3, PhC*H*), 2.62 – 2.80 (3H, m, 2 × CH*H* and C*H*), 2.39 – 2.98 (1H, m, CH*H*), 3.03 – 3.06

(1H, m, CH*H*), 3.17 – 3.24 (2H, m, 2 × CH*H*), 3.40 (1H, app dd, *J* 11.0, 3.0, O*H*), 4.17 (2H, s, NCH_2), 7.24 – 7.44 (10H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 29.4 (*C*H_2), 39.3 (*C*H), 43.2 (*C*H), 56.4 (*C*H_2), 59.3 (*C*H_2), 63.2 (*C*H_2), 70.6 (*C*H_2), 126.9 (Ar*C*H), 127.5 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 129.1 (Ar*C*H), 130.3 (Ar*C*), 133.2 (2 × Ar*C*H), 143.2 (Ar*C*); *m*/*z* (TOF MS ES$^+$) 282 (100%, MH^+ $C_{19}H_{24}NO$). All data are in accordance with literature.[115]

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