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**Studies on Asymmetric Approaches to (-)-Cytisine  
and Related Molecules.**

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**February 2013.**

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## **Acknowledgements.**

First of all, I should like to thank Martin, for your devotion and persistent help throughout this project. Thank you for teaching me to aim higher and reach further than I thought was possible. I should like to thank everyone from the Wills group for always being supportive during my time here: thanks to Zhijia (Amphy) Fang, Andy Rawlings, Charles Manville, Charlotte Zammit, Dave Morris, Eduardo Martins, Jon Hopewell, Katie Jolley, Mofta Darwish, Rina Soni, Tarn Johnson, Vicky Marlow and Vimal Parekh.

I should like to thank everyone at AstraZeneca for my time on placement in Alderley Park, and for financial support. In particular, I should like to thank Allan Dishington, Gail Wrigley and Teyrnon Jones for supervising me.

Thanks to everyone who contributed towards this project. In particular, thanks to Akira Shiibashi, for your work during the preliminary study; Jasmine Desmond, for your work during your MChem project; Guy Clarkson, for X-ray crystallography; Per Ryberg, for carrying out the asymmetric hydrogenation screens; and the EPSRC, for crystallography.

Thanks to all the support staff at Warwick and AstraZeneca. In particular, thanks to Ivan Prokes and Edward Tunnah in NMR; Phil Aston and Lijiang Song in MS; and Rob Jenkins for technical support.

I should like to thank my Mum and Dad, my family and all my friends for your support during this time. And lastly, I should like to thank God, for always encouraging me to carry on no matter what.

### **Declaration and Inclusion of Published Work.**

This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and has not been submitted in any previous application for any degree, apart from the asymmetric transfer hydrogenation (ATH) of enamide **1** in Section 2.2.1, which was previously submitted as part of Jasmine Desmond's final year MChem research project. The work presented (including data generated and data analysis) was carried out by the author except in the cases outlined below:

Section 2.1.1: During a preliminary study, the synthetic route and AH of enamides **1** and **227** was initially developed by Akira Shiibashi, a visiting PhD researcher who also obtained the X-ray crystal structures of these compounds (Figure 2.1.2). Subsequent work during this PhD project further developed and optimised the synthesis and hydrogenation of **1**. Section 2.2.1: Jasmine Desmond contributed towards the ATH of enamide **1** as part of her MChem project whilst under joint supervision with Martin Wills and the author. Sections 2.3 and 2.4: Per Ryberg undertook the AH screen of pyridone substrates **2** and **3**. The synthesis and characterisation of these compounds was carried out by the author. All X-ray structures in this thesis were determined by Guy Clarkson, except compound **269** which was determined by the EPSRC Crystallographic Service in liaison with Guy Clarkson.

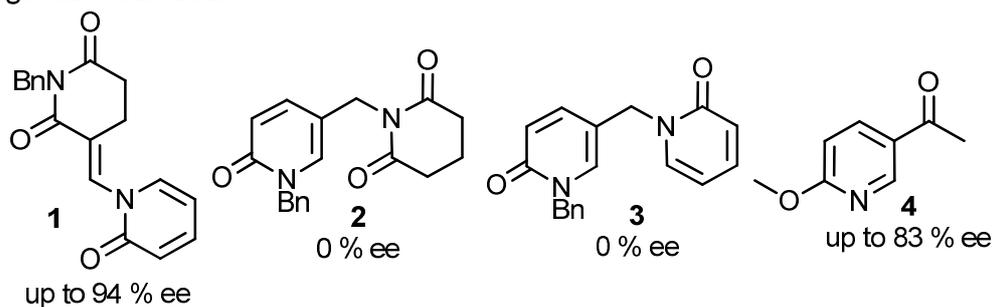
Parts of this thesis have been published by the author in the following publication:

Bisset, A. A.; Shiibashi, A.; Desmond, J. L.; Dishington, A.; Jones, T.; Clarkson, G. J.; Ikariya, T.; Wills, M. *Chem. Commun.*, **2012**, 48, 11978-11980.

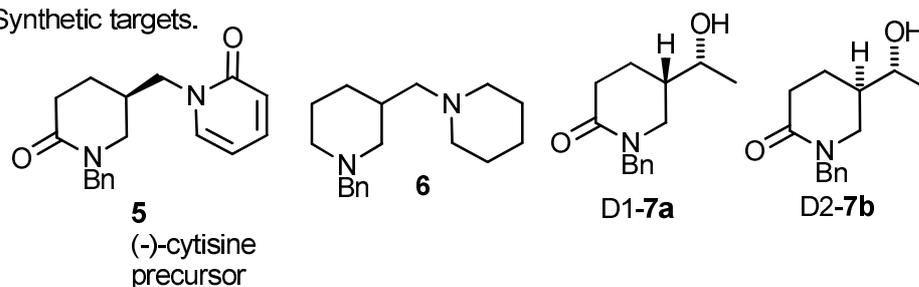
## Abstract.

In this project, the asymmetric pressure and transfer hydrogenation of a number of substrates was carried out in attempt to asymmetrically form 5-substituted 6-membered saturated heterocycles, directly applicable to the asymmetric synthesis of (-)-cytisine and other related compounds. The hydrogenation of *N*-acyl-aminoacrylate-like enamide **1** was successful, resulting in the formation of 5-substituted glutarimide **218** in up to 94 % ee. Unfortunately, subsequent reduction resulted in epimerisation and loss of ee, preventing an asymmetric synthesis of (-)-cytisine precursor **5**. The asymmetric reduction of pyridones **2** and **3** (featuring proximal coordinating groups) did not proceed with any enantioselectivity; however, the racemic reduction products were successfully utilised in novel syntheses of cytisine precursor **5** and bispiperidine **6** respectively. The ATH of pyridyl methyl ketone **4** with (*R,R*)-RutethTsDPEN, (*R,R*)-**248** resulted in the formation of pyridyl alcohol **303** in 78-83 % ee. This compound was converted to diastereomers (D1)-**7a** and (D2)-**7b** which are derivates of a cytisine precursor and other therapeutic targets.

Hydrogenation substrates:



Synthetic targets.



## Abbreviations.

$[\alpha]_D$	specific rotation of a substance measured at the wavelength of the sodium D line.
Ac	acetyl.
AH	asymmetric hydrogenation.
Ar	aryl.
ATH	asymmetric transfer hydrogenation.
atm	atmosphere.
BINAP	2,2'-bis(diarylphosphino)-1,1'-binaphthyl.
Boc	tert-butyl carbonate.
Bn	benzyl.
Bu	butyl.
<i>c</i>	concentration, g / 100 cm <sup>3</sup>
°C	degrees Celsius
cm <sup>3</sup>	cubic centimetre.
cm <sup>-1</sup>	wavenumber per centimetres.
COD	cyclooctadiene.
conv.	conversion.
COSY	correlation spectroscopy.
d	doublet.
D	dextrorotatory.
DCM	dichloromethane.
$\delta_H$ or $\delta_C$	chemical shift.
DIAD	diisopropyl azodicarboxylate.
DIPEA	diisopropylethylamine.
de	diastereomeric excess.
dr	diastereomeric ratio.
DKR	dynamic kinetic resolution.
DMAP	4-dimethylaminopyridine.
DMF	dimethylformamide.
DMSO	dimethylsulfoxide.
DPPA	diphenylphosphoryl azide.
dppp	1,3-bis(diphenylphosphino)propane.

EDC.HCl	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide.
KR	kinetic resolution.
RCY	radio chemical yield.
EI	electron ionisation.
ee	enantiomeric excess.
ESI	electrospray ionisation.
FA/TEA	formic acid – triethylamine azeotrope.
Et	ethyl.
FTIR	fourier transform infra-red.
g	gram.
GC	gas chromatography.
Hz	hertz.
HMQC	heteronuclear multiple-quantum correlation.
NMR	nuclear magnetic resonance.
HPLC	high performance liquid chromatography.
IPA	isopropanol.
<sup>i</sup> Pr	isopropyl.
<i>J</i>	coupling constant.
L	levorotatory.
LDA	lithium diisopropylamine.
M	mol dm <sup>-3</sup> .
Me	methyl.
mg	milligram.
min	minute.
mol %	molar percentage.
MS	mass spectroscopy.
MW	microwave.
<i>m/z</i>	mass-to-charge ratio.
m	meter.
MHz	megahertz.
Mp	melting point.
μL	microlitre.
mmol	millimole.

N/A	not applicable.
N/O	not obtained.
nOe	nuclear Overhauser effect
ppm	parts per million.
Prep	preparatory.
q	quartet.
quin	quintet.
RT	room temperature.
s	second or singlet.
SAR	structure activity relationship.
t	triplet.
TFA	trifluoroacetic acid.
TLC	thin layer chromatography.
TMS	trimethylsilane.
TsCl	tosyl chloride.
$v_{\max}$	absorption.
w/r	with respect to.



it is found that when mirror images of a molecule are not superimposable, the molecule will be optically active.

When two chiral centres are present in a molecule, a different type of isomerism occurs, due to the multiple arrangements of adjacent stereocentres that are possible. These isomers are called diastereomers. An example are tetroses, the four carbon sugars (Figure 1.2). Due to the two asymmetric carbon atoms, there are four possible arrangements or isomers, as shown. Isomers a and b of erythrose are mirror images of each other (or enantiomers). Isomers c and d of threose are also enantiomers of each other. However, isomers a and c, (-)-erythrose and (-)-threose, are not mirror images of each other. The same is for isomers b and d. These are both called diastereomers. Diastereomers often have completely different chemical properties (such as the melting point), whereas enantiomers have identical chemical properties.

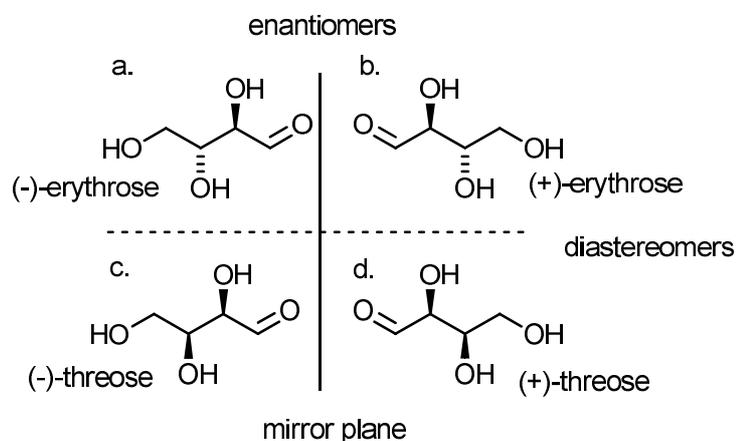


Figure 1.2: Enantiomers and diastereomers.

## **Section 1.2: Asymmetric Synthesis.**

Due to the prevalence of chirality in nature, a major theme of organic chemistry has been asymmetric synthesis. As a large proportion of biological molecules found in nature are chiral and present as a single enantiomer; consequently, enantiomers of drug molecules can have drastically different physiological and biochemical effects; for instance, the thalidomide tragedy.<sup>5</sup> Chirality is therefore a crucial consideration in the development and synthesis of drugs.<sup>6</sup>

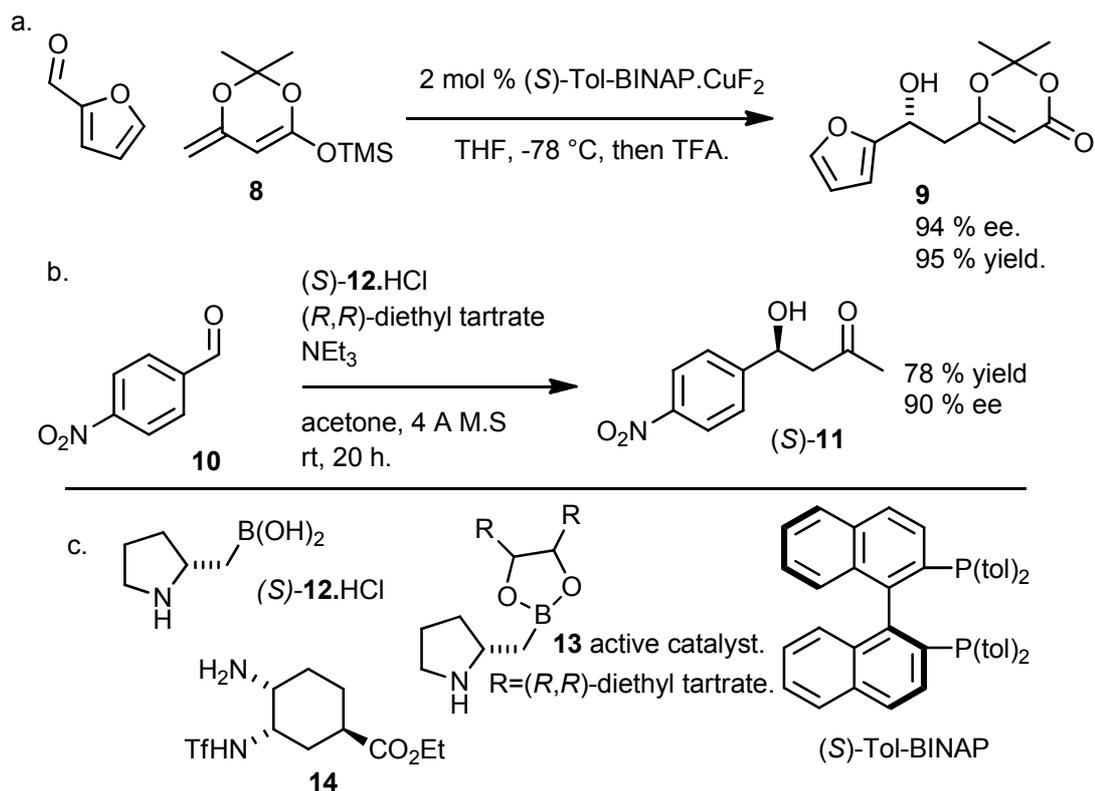
Single enantiomers of compounds have traditionally been obtained by the resolution of racemic mixtures by chemical or chromatographic means. The chiral pool of organic starting materials has also been an important contribution to synthetic chemistry. However, now, asymmetric options for many important synthetic transformations are available, enabling the selective formation of one enantiomer over another.<sup>7</sup> Asymmetric transition metal catalysts are commonly used, and asymmetric organo-catalysis is developing rapidly.

In this section, instead of reviewing well known asymmetric transformations, such as Sharpless' asymmetric dihydroxylation, a selection of recent asymmetric developments of important catalytic transformations will be briefly illustrated, to show the utility of these modern methods in the synthesis of therapeutically important compounds. The main topic of this theme, asymmetric alkene hydrogenation, will then be discussed in more detail.

### Section 1.2.1: Aldol Reactions.

Aldol reactions have been a powerful tool in C-C bond formations because two chiral centres may be formed in the transformation. The control of the diastereoselectivity of the reaction has been widely studied to enable the formation of *syn* or *anti* products, through the use of specific reagents. This is related to the geometry of the intermediate enolate, which may be influenced by the base and conditions used in the enolisation reaction. Early enantioselective modifications of this transformation were achieved by use of chiral auxiliary templates, but asymmetric transition metal catalyst-based methods were later developed. An example is a process developed by Carreira,<sup>8</sup> which catalyses the asymmetric aldol addition of dienolsilanes to aldehydes, utilising a chiral copper based Tol-BINAP-CuF<sub>2</sub> complex (Scheme 1.1a). The aldol addition of dienolate **8** to furfural proceeded to form the adduct **9** in 94 % ee and 95 % yield. In this case, adduct **9** was then used in the synthesis of the polyol subunit of the natural product, amphotericin.

More recently, asymmetric organocatalysis has risen to prominence. Following the first report of an asymmetric intermolecular aldol reaction by Barbas and List,<sup>9</sup> proline derived organocatalysts have become highly effective in this transformation.<sup>10</sup> An interesting example is the proline-based aminoboronic acid, homoboroproline (*S*)-**12**, developed by Whiting *et al* (Scheme 1.1b).<sup>11</sup> Bifunctional catalysts of this type enable formation of aldol products with a similar magnitude of enantioselectivity to that observed with L-proline. The system operates through combination of the catalytically active proline-derived unit, (*S*)-**12** with a chiral diol such as (*R,R*)-tartrate, resulting in the *in situ* formation of the active catalyst, **13**.

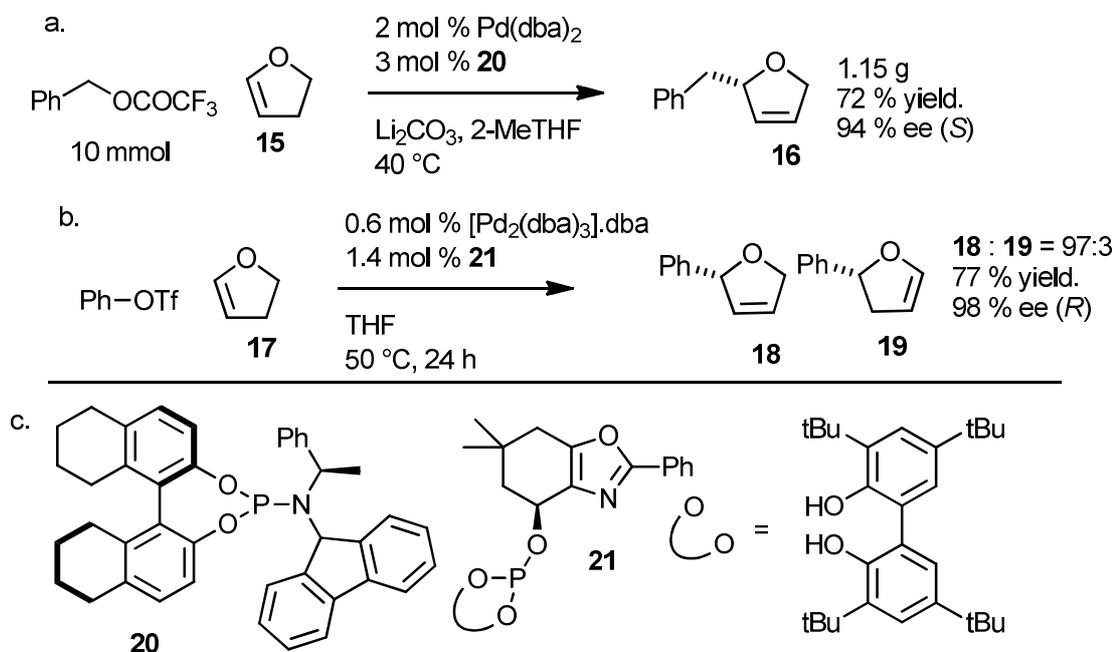


Scheme 1.1: Examples of asymmetric aldol reactions.

In the example shown (Scheme 1.1b), the reaction between *p*-nitrobenzaldehyde **10** and acetone was catalysed by 20 mol % of the precatalyst, (*S*)-**12** and (*R,R*)-diethyl tartrate, resulting in formation of the adduct (*S*)-**11** in 78 % yield and 90 % ee. The combined nucleophilic secondary amine and Lewis acidic boronic acid groups have been shown to be a necessary for activity. A bifunctional catalytic process involving the active catalyst, **13** and a six-membered transition state have been suggested to explain the observed configuration in comparison to L-proline.<sup>11a</sup> Other interesting recent work in this area includes the chiral *cis*-diamine-based Tf-amido organocatalyst, **14** by Moteki *et al*<sup>12</sup> which has been used in the aldol reaction between cyclohexanones and  $\alpha$ -keto esters in up to 94 % ee and 8 : 1 dr. Chiral animals have also been used in the organocatalysis of the  $\alpha$ -amination of aldehydes.<sup>13</sup>

### Section 1.2.2: Heck Couplings.

Asymmetric Heck couplings have enabled the formation of otherwise difficult chiral centres<sup>14</sup>; for instance, the synthesis of  $\alpha$ -arylated<sup>15</sup> or -benzylated furans<sup>16</sup>, **16** or **18**. An asymmetric Heck reaction with a benzylic electrophile was recently published by Zhou (Scheme 1.2a).<sup>17a</sup> Problems with isomerisation and slow olefin insertion encountered with benzylic electrophiles had previously prevented success in this area. The reaction between benzyl trifluoroacetate and 2,3-dihydrofuran **15** with phosphoramidite ligand **20** proceeded to form 2-benzyl-2,5-dihydrofuran **16** in 72 % yield and 94 % ee on a 10 mmol scale. The product **16** has direct use in the formation of analogues of adenophostin A, a potent IP<sub>3</sub> receptor agonist, useful in the investigation of IP<sub>3</sub>-mediated Ca<sup>2+</sup> signalling pathways.<sup>18</sup> In a second similar example, the asymmetric palladium catalysed phenylation of 2,3-dihydrofuran **17** with the novel phosphite-oxazole ligand **21** resulted in the formation of the arylated product **18** in high regioselectivity and 98 % ee (Scheme 1.2b).<sup>19</sup>

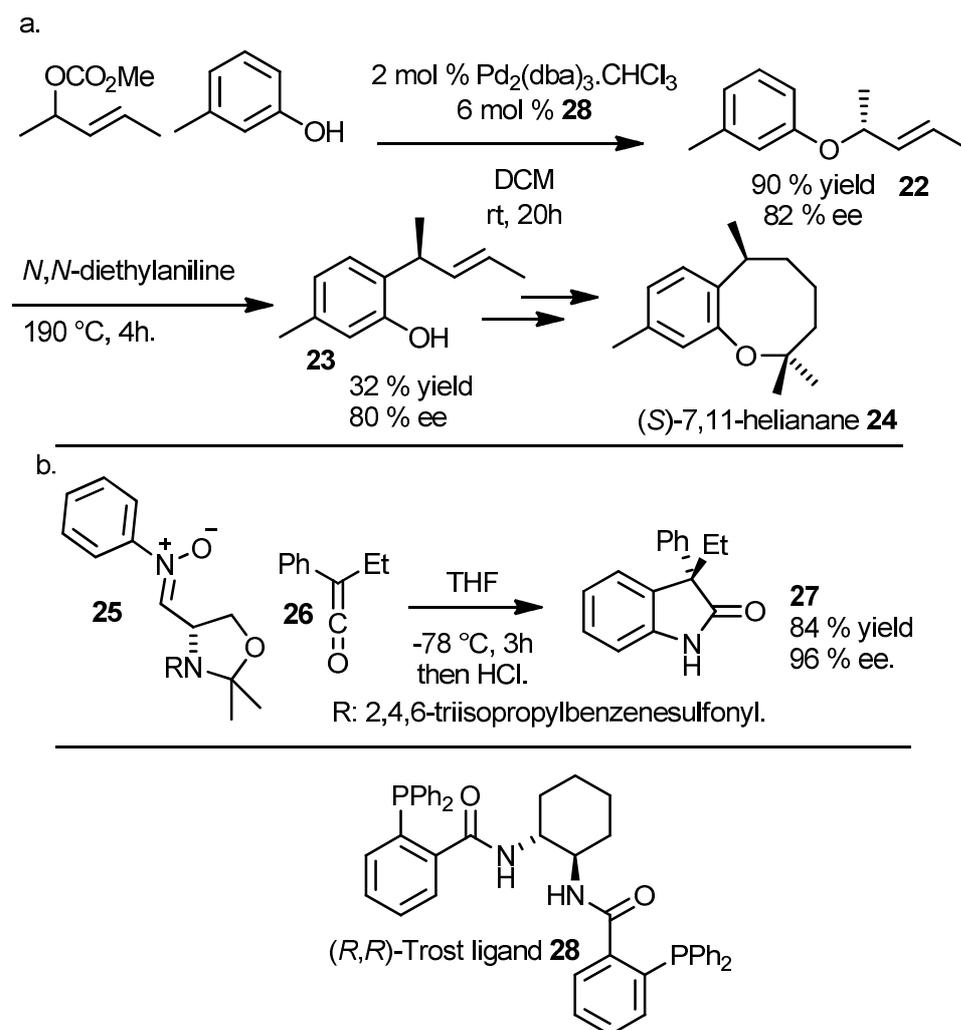


Scheme 1.2: Examples of asymmetric Heck reactions.

### *Section 1.2.3: Sigmatropic Rearrangements.*

In the following examples of sigmatropic rearrangements, these transformations proceed with retention of existing chirality. Asymmetric sigmatropic rearrangements have however been studied,<sup>20</sup> and recently the first example of an asymmetric Cope rearrangement of an achiral diene was published.<sup>21</sup>

In the first example, a thermal uncatalysed aromatic Claisen rearrangement was employed in the formation of a benzylic chiral centre, during the synthesis of the aromatic bisabolene sesquiterpene, (+)-7,11-helianane **24** (Scheme 1.3a). The starting material, ether **22**, was asymmetrically formed in 82 % ee with Trost's palladium catalysed allylic alkylation. A subsequent Claisen rearrangement resulted in the formation of the product **23** in up to 80 % ee.<sup>22</sup> An interesting synthesis of oxindoles was achieved through the reaction between an enantiomerically pure nitron (25) and an aryl-alkyl ketene **26** (Scheme 1.3b). The reaction proceeded through what was proposed to be a 1,3-dipolar cycloaddition and subsequent hetero-[3,3]-sigmatropic rearrangement to form oxindole **27** in 96 % ee and 84 % yield.<sup>23</sup> Other interesting examples include the asymmetric synthesis of allenes from tertiary propargylic alcohols and methyl aryl-diazoacetates via a rhodium-catalysed tandem oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement.<sup>24</sup>

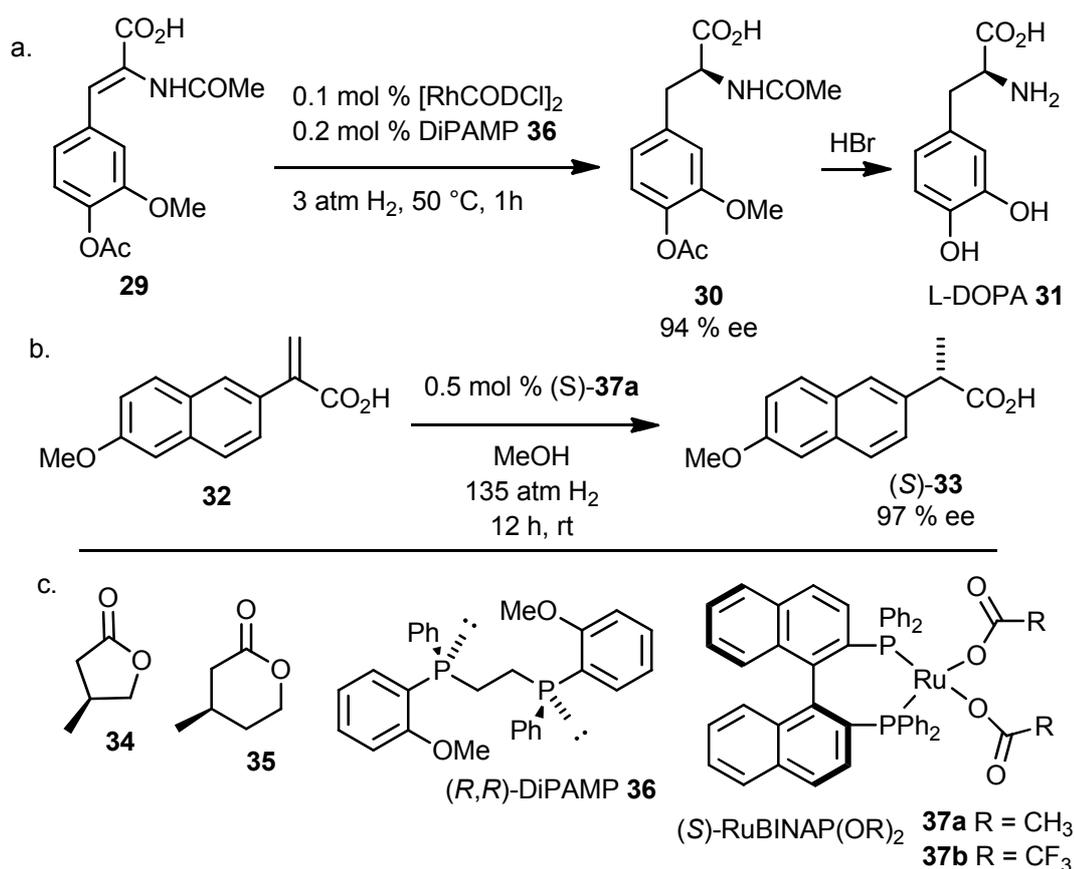


Scheme 1.3: Examples of asymmetric sigmatropic rearrangements.

#### Section 1.2.4: Asymmetric Alkene Hydrogenation.

Heterogeneous hydrogenations have been widely known for a long time,<sup>25a</sup> but it was only in 1965 that Wilkinson showed the first case of homogeneous transfer hydrogenation with the rhodium catalyst  $\text{RhCl}(\text{PPh}_3)_3$ .<sup>25b</sup> The iridium catalyst,  $[\text{Ir}(\text{PCy}_3)_3\text{py}(\text{COD})]\text{PF}_6$  (Crabtree's catalyst), was later developed by Crabtree in the 1970s. Later work by Knowles and Horner involving chiral phosphine analogues of Wilkinson's catalyst started the initial development of asymmetric alkene hydrogenation.<sup>26 27</sup> An important development was the asymmetric synthesis of L-DOPA **31**, a rare amino acid used in the treatment of Parkinson's disease, using a complex of the chiral diphosphine, DiPAMP **36** (Scheme 1.4a). Enamide **29** (a direct

precursor of L-DOPA) was reduced in up to 94 % ee.<sup>28</sup> This process was used in the industrial large scale synthesis of the amino acid. The use of enamides in the synthesis of  $\beta$ -amino acids sparked further research into this area, and enamides have subsequently become a ‘benchmark’ in the rating of catalytic activity. In the mid-80s, Noyori and Takaya achieved the highly successful asymmetric hydrogenation (AH) of  $\alpha,\beta$ -unsaturated carboxylic acids with ruthenium complexes of 2,2’-bis(diarylphosphino)-1,1’-binaphthyl (BINAP), such as (*S*)-RuBINAP(OAc)<sub>2</sub> **37a**.<sup>29-30</sup> An example is the asymmetric synthesis of (*S*)-naproxen (*S*)-**33** (an useful anti-inflammatory agent) via reduction of the  $\alpha$ -naphthyl unsaturated carboxylic acid, **32** (Scheme 1.4b).<sup>29</sup>



Scheme 1.4: a. Synthesis of L-DOPA; b. reduction of carboxylic acids with Ru(II)-BINAP.

Using 0.5 mol % (*S*)-**37a** with a high pressure of 135 atm H<sub>2</sub>, (*S*)-**33** was obtained in 97 % ee (Scheme 1.4b). Hydrogenation of oxygen-functionalised unsaturated

carboxylic acids has also enabled the asymmetric synthesis of otherwise difficult targets, such as the substituted lactones **34** and **35** (Scheme 1.4c).<sup>29</sup>

Following these two examples of initial advances, a plethora of asymmetric ligands were developed for the hydrogenation of a range of substrate types. The C<sub>2</sub>-symmetric bisphospholanes, DuPHOS **40** (Figure 1.3) and Me-BPE **53** (Scheme 1.5) developed by Burk have been two of the most successful ligands in the hydrogenation of (*E*)- and (*Z*)- amino acrylates. The Josiphos ferrocene-based biphosphenes **38** originally developed by Togni and Spindler were a unique class of ligands, due to potential modulation of the side chain through an alteration of the synthesis.<sup>31</sup> This enabled the fine-tuning of these ligands to acquire the properties necessary for optimum interaction with the substrate, enabling the ligand class to be used in multiple applications. From this class, the Mandyphos **39** and Taniaphos **41** types were later developed (Figure 1.3).<sup>32</sup>

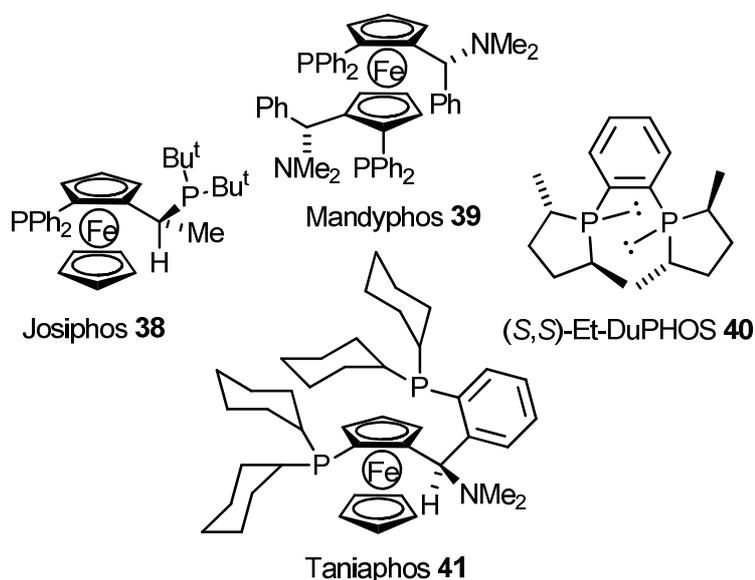


Figure 1.3: Ligands developed by Solvias.

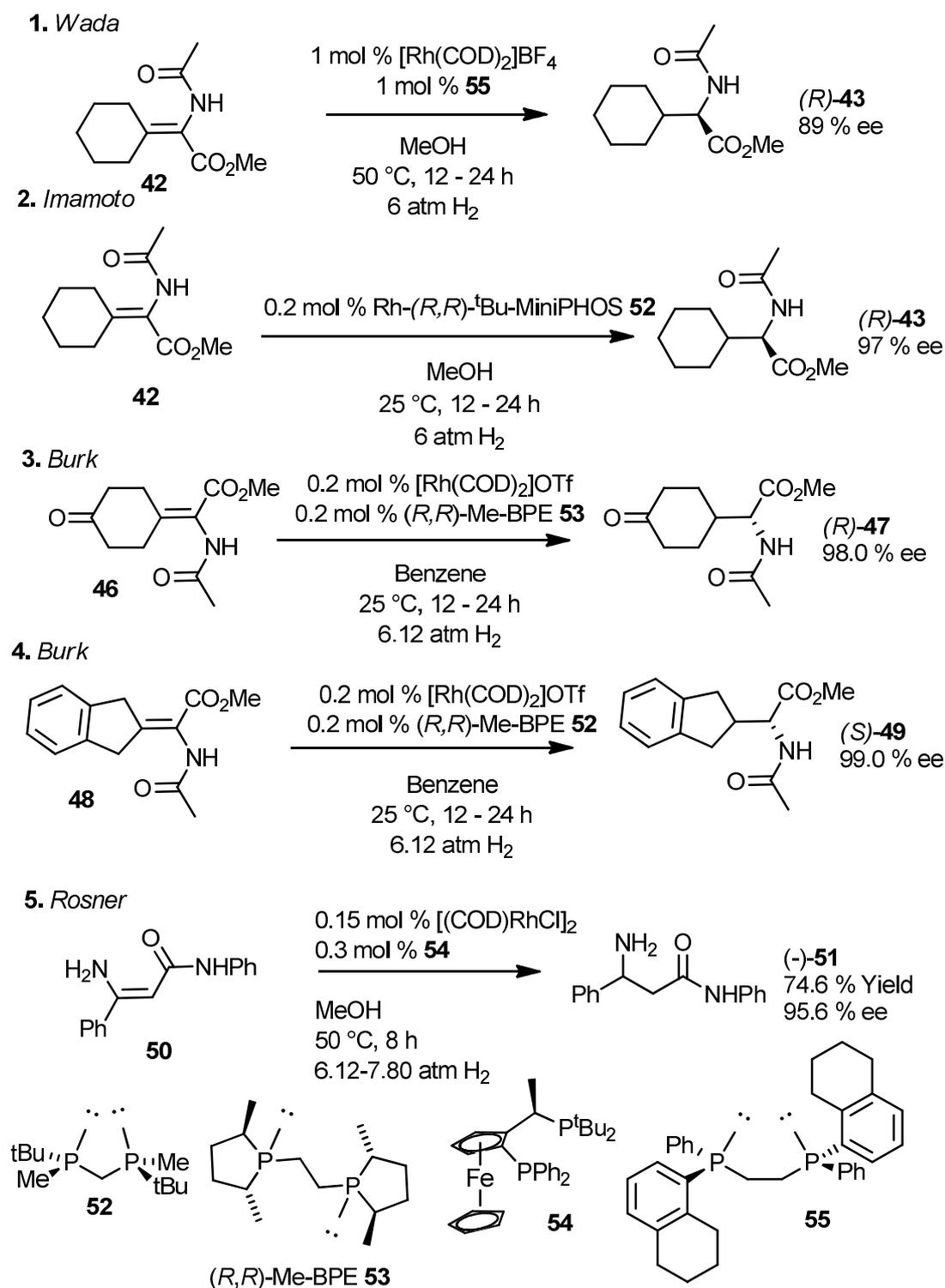
The term ‘privileged ligand’ was coined to ligand families which had high success in certain transformations. The further development of ligands has generally involved the further modulation of these privileged ligand families to generate a diverse range

of sub-types with steric and electronic diversity, with the intention that a suitable ligand may be available for any transformation.<sup>33-34</sup> The fine chemicals company, Solvias have taken this approach in preparing libraries of different derivatives of privileged ligands, including those based upon DuPHOS, BINAP, PAMP or JosiPHOS ligand backbones.

*AH of  $\beta,\beta$ -disubstituted acylamino acrylates.*

Despite there being many good examples of the AH of unsubstituted acylamino acrylates, there are relatively fewer examples featuring  $\beta,\beta$ -disubstituted substrates, since these have proven to be more challenging. Reactions 1-5 (Scheme 1.5) show five examples of the hydrogenation of  $\beta,\beta$ -disubstituted substrates. Wada<sup>35</sup> achieved the reduction of cyclohexene-fused  $\beta,\beta$ -disubstituted acylamino acrylate **42** to give **43** in 89 % ee, using the  $[\text{Rh}(\text{COD})_2]\text{BF}_4$  complex of chiral diphosphine **55** (reaction 1). However, with the chiral phosphine <sup>t</sup>Bu-MiniPHOS **52**, Imamoto<sup>36</sup> achieved the reduction of **42** in 97 % ee (reaction 2). Two excellent examples by Burk<sup>37</sup> feature hydrogenation of the similar ring fused  $\beta,\beta$ -disubstituted acylamino acrylates, **46** and **48** in 98 % and 99 % ee respectively with 0.2 mol % of the Rh-Me-BPE complex **53** (Scheme 1.5, reactions 3 and 4).

It has been shown that the mechanism of hydrogenation proceeds through the coordination of the alkene and acyl carbonyl groups to the rhodium atom (Figure 1.4). This co-ordination is very important in the mechanism and generally reductions without the acyl group have low enantioselectivities.<sup>38</sup>



Scheme 1.5: Reduction of  $\beta$ -disubstituted aminoacrylates.

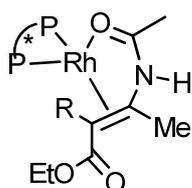
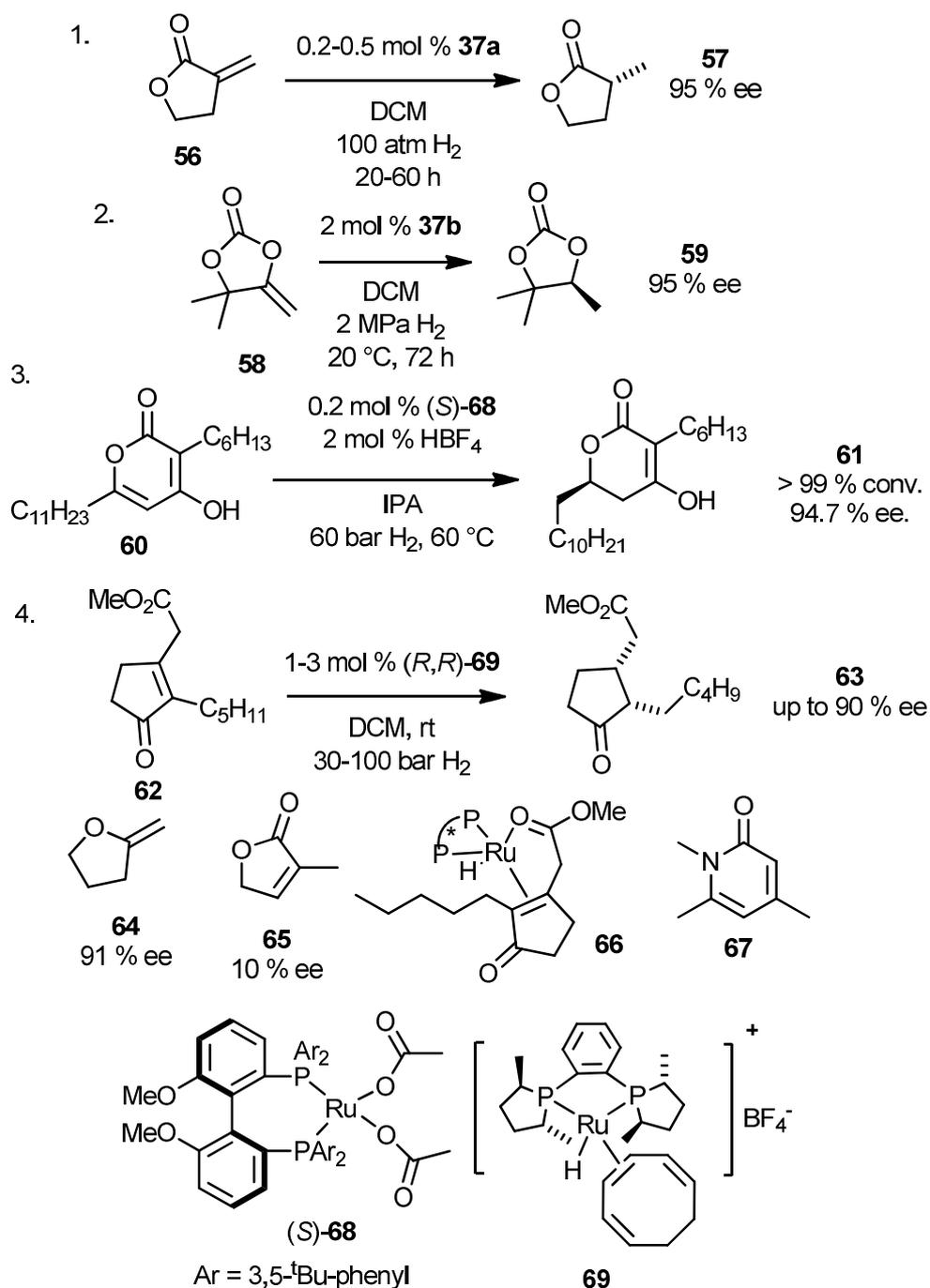


Figure 1.4: Coordination mode of acylamino acrylate reductions with Rh(II).

However, in some cases, enantioselectivity has been observed without the *N*-acyl coordinating group being present in the substrate. Collaboration between Rosner and Solvias achieved the reduction of  $\beta,\beta$ -disubstituted unprotected enamine, **50**. Using the Rh-ferrocenophosphine complex derived from  $[\text{Rh}(\text{COD})\text{Cl}]_2$  and ligand **54**, reduction in methanol at 50 °C, under 90-100 psi of hydrogen, resulted in the formation of amine **51** in over 95 % ee.<sup>39</sup> Limited evidence suggested that the mechanism proceeded through reduction of the imine tautomer, involving 1,5-chelation of the catalyst. The product of this reduction, i.e. **51**, is ideally suited to the synthesis of  $\beta$ -amino acids without the necessity of acyl removal.

In contrast to amino acrylates, there are a limited examples of enantioselective reductions of olefins with aprotic oxygen or nitrogen groups; for example,  $\alpha,\beta$ -unsaturated esters and lactones. Takaya achieved the enantioselective reduction of a number of cyclic  $\alpha,\beta$ -unsaturated ketones, alkylidene ketones and alkenyl ethers with Ru(II)-BINAP complexes (Scheme 1.6).<sup>40</sup> The enantioselectivity of such reductions has been shown to be dependent on the relative position of the alkene and oxygen functionalities. Substrates (such as **56** and **58**) with adjacent oxygen groups to the alkene are thought to enable intra-chelation to the Ru(II) centre, resulting in good enantioselectivity. However, endocyclic substrates such as **65** are reduced almost racemically and it is thought that the corresponding co-ordination mode is not formed. An example is 2-methylene- $\gamma$ -butyrolactone **56**. Reduction with (*S*)-**37a** under 100 atm H<sub>2</sub> resulted in the formation of lactone (*R*)-**57** in 95 % ee (reaction 1). Similarly, hydrogenation of  $\alpha$ -methylene carbonate **58** was achieved in 95 % ee with trifluoroacetate-derived Ru(II)-BINAP catalyst (*S*)-**37b** (reaction 2). This method has been applied to the asymmetric synthesis of substituted diols.<sup>41</sup> In a third example,  $\alpha$ -pyrone **60** was reduced with MeO-Biphep catalyst, (*S*)-**68** in the presence of aqueous

HBF<sub>4</sub>, resulting in formation of 5,6-dihydropyrone **61** (a direct precursor to the anti-obesity drug, tetrahydropapastatin) in 94.7 % ee (reaction 3). Brief experimentation with the pyridone analogues, **67** resulted in low enantioselectivity; the tautomeric nature of the compounds was considered to be a contributing factor.<sup>42</sup>



Scheme 1.6: Reduction of aprotic functionalised olefins.

A final example is the asymmetric synthesis of paradisone **63** ((+)-*cis*-methyl dehydrojasmonate), a perfumery compound which is made on an industrial scale.  $\beta$ -Oxoester **62** was reduced with [Ru(-)-Me-DuPHOS(H)-( $\eta^6$ -cot)]BF<sub>4</sub>, (*R,R*)-**69** (a catalyst formed from (*R,R*)-MeDuPHOS, [Ru(1,2:5,6- $\eta$ -cod)( $\eta^3$ -methallyl)<sub>2</sub>] and HBF<sub>4</sub>) (reaction 4).<sup>43</sup> Paradisone **63** was formed in up to 90 % ee as the *cis* diastereomer only. The high enantioselectivity of this reduction in contrast to the poor selectivity observed for **63** has been proposed to arise via the coordination mode **66**, in which the ruthenium centre is chelated between the alkene and ester carbonyl groups.<sup>44</sup>

### Section 1.3: (-)-Cytisine.

#### Section 1.3.1: Introduction.

(-)-Cytisine, **70** is a naturally occurring lupin alkaloid, found in the seeds of the plant species *Laburnum anagyroides*, commonly known as 'Golden Rain'.<sup>45</sup> The alkaloid consists of a piperidine core framework of two fixed piperidine cycles, A and B, which are fused to a 2-pyridone ring (C) (Figure 1.5). Its absolute configuration was established by Okuda *et al.*<sup>46</sup>

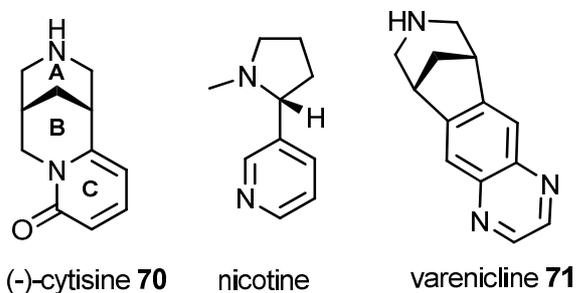


Figure 1.5.

Physiologically, the affects of (-)-cytisine are similar to (-)-nicotine; the alkaloid is highly toxic and active at nicotinic acetylcholine receptors. (-)-Cytisine is only a

partial agonist at these receptors, however it has a higher affinity than nicotine, with higher selectivity towards the  $\alpha_4\beta_2$  type receptor and sub-nanomolar affinity, yet exhibits comparable efficacy and potency in stimulating dopamine release, a key factor in the feeling of pleasure associated with tobacco use.<sup>47</sup> Consequently, it has been used as a smoking cessation drug; in therapeutic administration among smokers, cytisine is found to outbind nicotine and effect receptor stimulation sufficiently for the user to overcome cigarette cravings.<sup>48</sup> The drug varenicline **71**<sup>49a</sup> was developed by Pfizer through structure-activity relationship (SAR) studies with (-)-cytisine. The drug, 'Tabex', contains (-)-cytisine, for the same application.

There is also potential use for (-)-cytisine in the prevention of neurodegenerational diseases such as Parkinson's or Alzheimer's diseases, in which nicotinic receptors are altered in some way. Nicotinic acetylcholine receptors have been linked to many diseases. There are many different subtypes, which are all involved in different modes of action. However, their development as therapeutic targets has been limited by the inability to target selectively the individual subtypes. There is a lack of understanding of the SAR and specificity of active ligands to each subtype.<sup>50</sup> Consequently, research into this area has been driven by the need to determine these properties, and further discovery of highly selective subtype ligands.

(-)-Cytisine has been so widely studied because it has a uniquely high selectivity towards the  $\alpha_4\beta_2$  type receptor with sub-nanomolar affinity, whereas generally amongst the known ligands, selectivity is poor. It has a longer *in vivo* half life than (-)-nicotine and crosses the blood brain barrier making it particularly advantageous over other ligands. (-)-Cytisine has been routinely used as a benchmark in the study

of these receptors in the brain via positron emission tomography (PET).<sup>51</sup> [<sup>3</sup>H]Cytisine is commonly used. A synthesis of [<sup>18</sup>F]aryl cytisine has been developed and is shown in the next section.

These combined issues have driven a large amount of synthetic research into the alkaloid. There are now over ten total syntheses, although only three are asymmetric. There have been many direct derivatisations of cytisine and synthesis of modified related structures. In the following section, these synthetic strategies to (-)-cytisine will be reviewed in detail, followed by a summary of the progression of the pharmacological studies of derivatives.

### *Section 1.3.2: The Synthesis of Cytisine.*

The past retrosynthetic approaches to cytisine have been thoroughly reviewed by O'Brien<sup>45</sup>, who categorised them according to the retrosynthetic approach taken for the deconstruction of the bispidine core framework of the A, B or C rings. Although there are few asymmetric syntheses of the alkaloid, the racemic strategies still required careful diastereo-control to achieve the formation of the bispidine core skeleton. In this review, the syntheses will be listed chronologically in accordance with how the key diastereo- (and, if applicable, enantio-) selectivity was achieved. These generally fell into four categories.

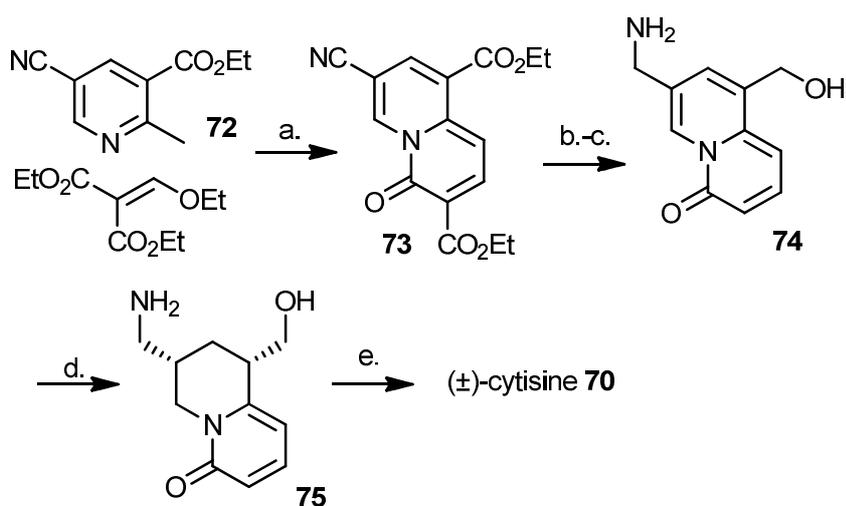
#### *Routes involving hydrogenation of a pyridine intermediate.*

The majority of past synthetic approaches to cytisine involved the hydrogenation of a substituted pyridine intermediate to achieve the required 3,5-*cis* geometry of the corresponding piperidine. During the hydrogenation, hydrogen addition to the same

pyridine face resulted in formation of a product containing the required *cis* geometry. All of the syntheses in this category were racemic. They also produced poor precedent for any future asymmetric modification - the AH of pyridines has generally resulted in poor enantioselectivity,<sup>52</sup> with the exception of a number of methods.<sup>53</sup>

*Govindachari.*

The first total synthesis of (±)-cytisine was achieved by Govindachari in 1957 (Scheme 1.7).<sup>54</sup> The first step involved the condensation of 3,5-substituted pyridine **72** and diethyl ethoxymethylenemalonate in alcoholic potassium ethoxide to give quinolizinone **73**. Following multiple reductions and decarboxylation, amino alcohol **74** was obtained in 24 % yield over three steps. Chemoselective reduction of the more reactive quinolizinone heterocycle with PtO<sub>2</sub>, under an atmosphere of hydrogen, resulted in the 3,5-*cis* piperidine **75** which was directly treated with phosphorous pentabromide and potassium carbonate, to give a crude material which upon sublimation and recrystallisation, yielded cytisine **70** in 4 % yield from **75**.

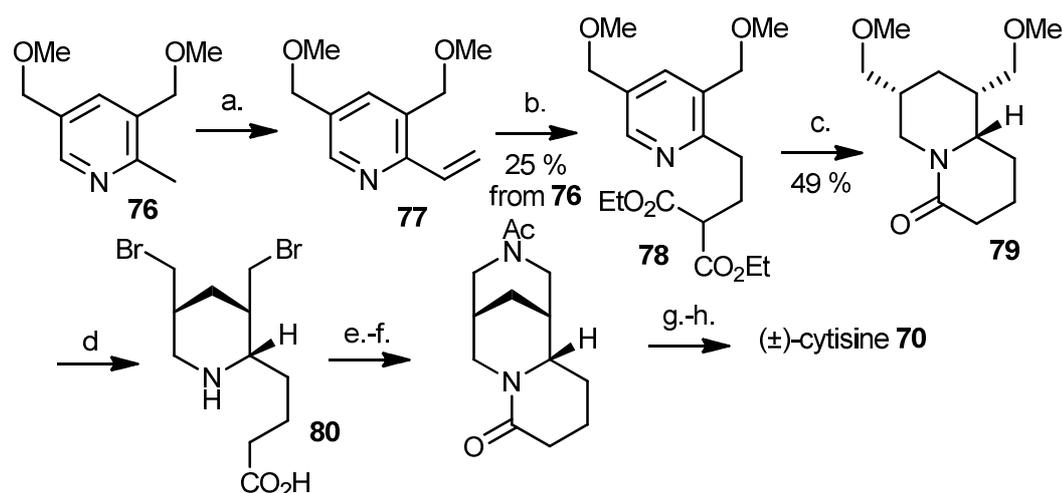


Reagents and conditions: (a) KOEt/EtOH, reflux, 4 h, 36 %; (b) i. PtO<sub>2</sub>, 1 atm H<sub>2</sub>, EtOH; ii. 6M HCl (aq), reflux, 1 h; iii. HCl, EtOH, 43%; (c) LiAlH<sub>4</sub>, Et<sub>2</sub>O, 24 %; (d) PtO<sub>2</sub>, 1 atm H<sub>2</sub>; (e) i. PBr<sub>3</sub>, benzene, 100°C, 4 h; ii. K<sub>2</sub>CO<sub>3</sub>, 18h, sealed tube, 100°C, 4 %.

Scheme 1.7: Govindachari's synthesis of cytisine.

*Bohlmann.*

At approximately the same time, Bohlmann also completed a synthesis of cytosine (Scheme 1.8). Homologation of 3,5-substituted pyridine **76** with formaldehyde resulted in formation of vinyl pyridine **77**, which subsequently underwent Michael addition with diethylmalonate. Hydrogenation with Raney nickel under 200 atmospheres of hydrogen at 185°C resulted in formation of the key 3,5-*cis* substituted piperidine, which spontaneously underwent cyclisation and decarboxylation to give quinolizinone **79**. Conversion of the ether groups to the corresponding bromide was achieved with HBr. However, under these conditions, ring opening also occurred, resulting in formation of carboxylic acid **80**. Assembly of the A ring was achieved by treatment with ammonia in ethanol at 0°C. Ring closure of the lactam was then achieved by heating the compound at 200 °C. Following protection of the basic nitrogen with acetic anhydride, oxidation of the lactam was achieved by dehydrogenation with palladium on carbon. Most of the yields were not reported.<sup>55-56</sup>

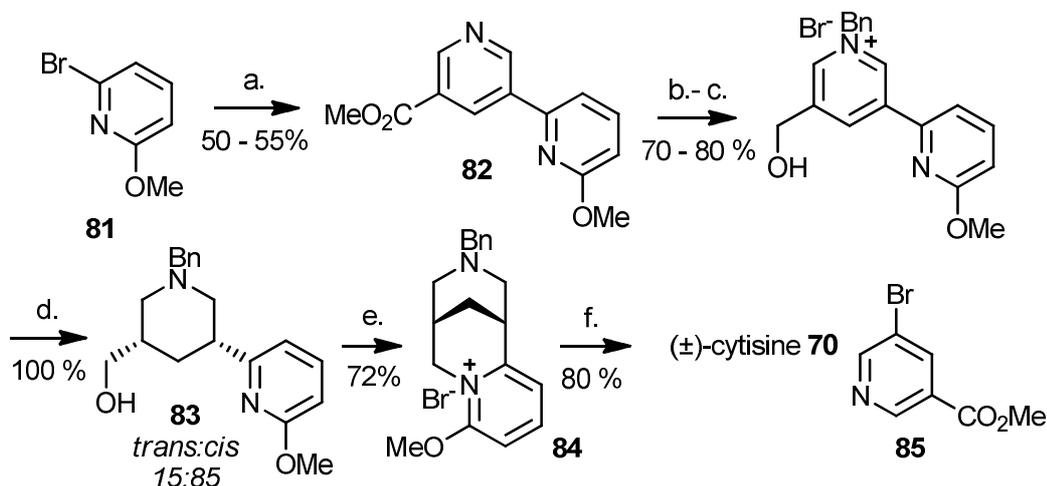


Conditions: (a) H<sub>2</sub>CO (aq), 140°C, 2 h; (b) NaOEt, 1 atm, H<sub>2</sub> H<sub>2</sub>C(CO<sub>2</sub>Et)<sub>2</sub>, EtOH, reflux, 1 h, 26 % from **76**; (c) Raney Ni, dioxane, 185 °C, 200 atm H<sub>2</sub>, 2 h, 49%; (d) HBr, 5 h, 120°C; (e) i. NH<sub>3</sub>, EtOH, 0°C; ii. 100°C, 10 h; iii. methylnaphthalene, 200°C, MeOH, 2 h; (f) Ac<sub>2</sub>O, rt, 16 h, 100°C, 30 min; (g) Pd/C, metal bath, 4.5 h; (h) HCl.

Scheme 1.8: Bohlmann's synthesis of cytosine.

O'Neill.

O'Neill's synthesis was published in 2000 (Scheme 1.9).<sup>57</sup> The first step was a Suzuki coupling of pyridines **81** and **85** to give bispyridine **82** – a transformation which was not available during the work to the previous two syntheses.



Conditions: (a) i. *n*BuLi, Et<sub>2</sub>O, -40°C; ii. B(OMe)<sub>3</sub>, Et<sub>2</sub>O; iii. pyridine **85**, Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq CsF, DME, 85°C, 12h; (b) LiAlH<sub>4</sub>, Et<sub>2</sub>O; (c) BnBr, MeCN; (d) PtO<sub>2</sub>, 1 atm H<sub>2</sub>, Et<sub>3</sub>N/MeOH; (e) i. MsCl, Et<sub>3</sub>N, DCM; ii. toluene, reflux; (f) Pd(OH)<sub>2</sub>, HCO<sub>2</sub>NH<sub>4</sub>, MeOH.

Scheme 1.9: O'Neill's synthesis of cytosine.

Lithium-halogen exchange of bromopyridine **81**, followed by trapping with B(OMe)<sub>3</sub>, formed the corresponding borane which was coupled to pyridine **85** with Pd(PPh<sub>3</sub>)<sub>4</sub> to form bispyridine **82** in 50-55 % yield.

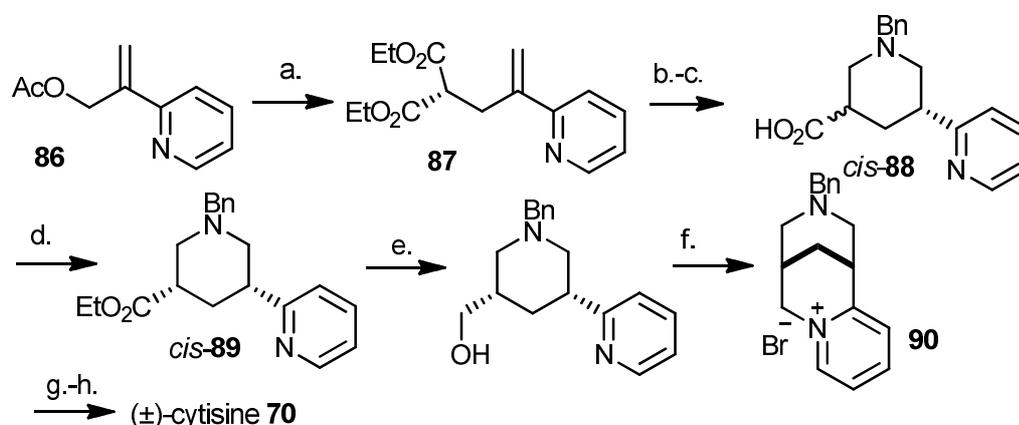
By reducing the ester group of **82**, it was found that regioselective *N*-protection of the less hindered pyridine was possible. The resulting pyridinium salt, formed in 70-80 % underwent mild reduction with PtO<sub>2</sub> to the desired piperidine alcohol *cis*-**83**, obtained as an 85:15 mixture of diastereomers. Attempted hydrogenation of the corresponding pyridinium salt of ester **82** resulted in poor diastereoselectivity. Mesylation of the alcohol **83** resulted in spontaneous cyclisation to **84**. Oxidation and debenzylation was achieved by transfer hydrogenolysis with Pd(OH)<sub>2</sub> and FA/TEA. Overall, (±)-cytosine was obtained in 25 % yield from **81**. A modification

by Plaquet afforded bispyridine **83** in 79 % yield, following a Negishi cross coupling with  $\text{Pd}(\text{PPh}_3)_4$  and  $\text{ZnCl}_2$ .<sup>58</sup>

*Routes involving assembly of a cis-piperidine intermediate.*

*van Tamelen.*

Van Tamelen's synthesis was completed alongside Govindachari and Bohlmann's initial routes (Scheme 1.10).<sup>59</sup> Substitution of acetate **86** with diethyl malonate resulted in formation of pyridine **87**. Hydrolysis to the carboxylic acid was followed by Mannich reaction with benzyl amine and formaldehyde to give the piperidine *cis*-**88**. A process involving an initial Mannich condensation to form the malonate enolate and concurrent decarboxylation, followed by intramolecular conjugate addition was proposed for this transformation. Carboxylic acid *cis*-**88** was directly converted to the ester *cis*-**89**, as an mixture of isomers (the ratio was not stated).



Reagents: (a) NaH, diethyl malonate, DMF/benzene, reflux, 52%; (b) 4M NaOH (aq), reflux; (c) HCl,  $\text{BnNH}_2$ ,  $\text{H}_2\text{CO}$  (aq), reflux, 16 h; (d) i. HCl, EtOH; ii. Na, EtOH, 55%; (e)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ , 99%; (f) i. HBr (aq); ii. benzene, reflux, 56%; (g) NaOH (aq),  $\text{K}_3\text{Fe}(\text{CN})_6$ , 100°C, 16 h, 22h; (h) HI, phenol,  $\text{NH}_4\text{I}$ , 5% auric chloride solution, 150°C, 0.5 h, 53%.

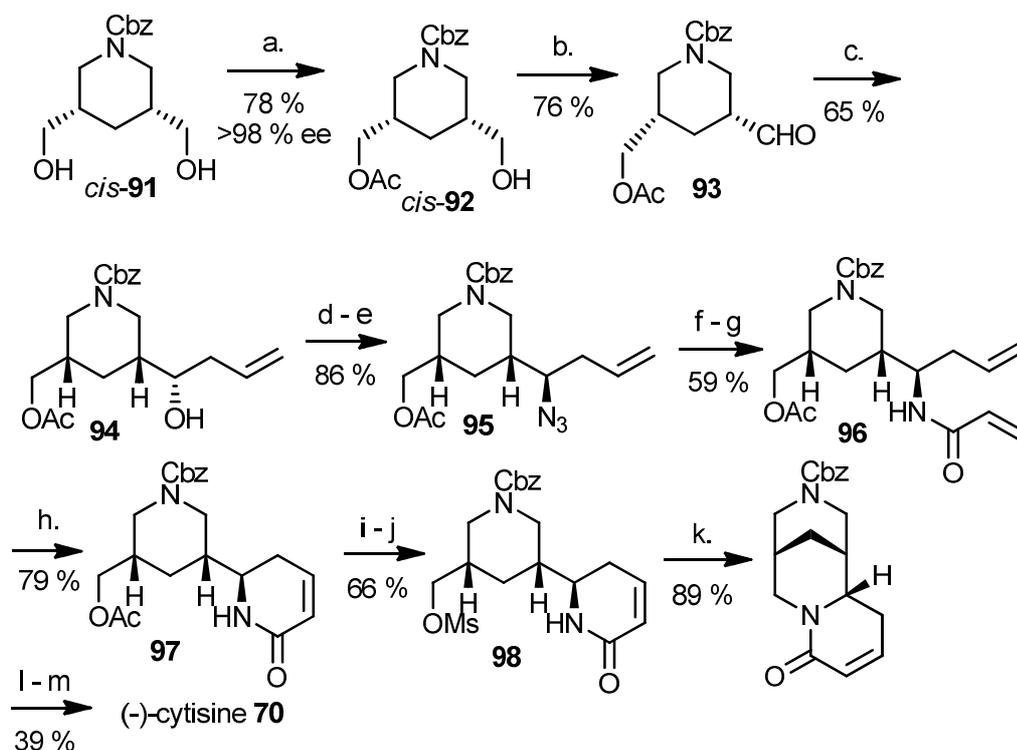
Scheme 1.10: van Tamelen's synthesis of cytosine.

An attempted epimerisation with an alcoholic base did not successfully convert the mixture to the desired *cis* isomer. Reduction to the alcohol was followed by treatment with HBr and subsequent cyclisation to the pyridinium intermediate, **90** which was then oxidised with alkaline ferricyanide. Debenzylation could not be

achieved catalytically and required the harsh boiling of the alkaloid in HI with auric chloride.

*Lesma.*

Lesma's group derived an asymmetric synthesis of (-)-cytisine conveniently starting with all required stereochemistry in place through the use of *cis*-piperidine-3,5-dimethanol monoacetate, *cis*-**92**. This compound was formed in > 98 % ee by the enzymatic resolution of alcohol *cis*-**91** with the lipase *Pseudomonas fluorescens* and vinyl acetate (Scheme 1.11).<sup>60 61</sup>



Conditions: (a) *Pseudomonas fluorescens* lipase, vinyl acetate, rt, 6h; (b) Swern oxidation; (c) (-)-*B*-methoxydiisopinocampheylborane, allylmagnesium bromide, Et<sub>2</sub>O, -78 °C, then NaOH, H<sub>2</sub>O<sub>2</sub>; (d) MsCl, NEt<sub>3</sub>, DCM, 99 %; (e) NaN<sub>3</sub>, DMF, 80°C, 87 %; (f) PPh<sub>3</sub>, THF, then H<sub>2</sub>O, 66 %; (g) acryloyl chloride, NEt<sub>3</sub>, DCM, 89 %; (h) Grubbs' catalyst, DCM, reflux; i. 0.5 M NaOH, THF, 98 %; (j) MsCl, NEt<sub>3</sub>, DCM, 67 %; (k) NaH, THF, rt; (l) DDQ, dioxane, 50 %; (m) HCl 6 N, 78 %.

Scheme 1.11: Lesma's asymmetric synthesis of (-)-cytisine.

Ester *cis*-**92** was oxidised under Swern conditions to give the configurationally stable aldehyde **93**, which was subsequently allylated with (-)-allyldiisopino-

camphenylborane, to give alkene **94** in 85 % yield as a 10:1 mixture of diastereomers.

Through use of the corresponding the (+)- borane reagent, access to the (*R*) configuration alcohol diastereomer was achieved in a similar yield and dr. Control of the chirality at this centre was not necessary for this synthesis and the allylation was equally successful with non-chiral reagents, however the step was studied for future asymmetric application to non-aromatic alkaloid derivatives. The alcohol **94** was mesylated and subsequently converted to the azide **95** in 87 % yield. Following reduction to the amine with PBr<sub>3</sub>, this amine was acylated with acryloyl chloride and NEt<sub>3</sub>, resulting in a 59 % yield of **96** over two steps. This alkene then underwent a ring closing metathesis reaction with Grubb's 1<sup>st</sup> generation catalyst, forming the lactam **97**. The remaining ester group was converted to mesylate **98**, which, following nitrogen deprotonation with NaH, cyclised to give the desired diazabicyclo[3.3.1]nonane framework. Dehydrogenation with DDQ gave *N*-benzoylcytisine in 50 % yield which then underwent deprotection with HCl, to give (-)-cytisine in 7 % overall yield after 13 steps.

#### *Honda.*

Honda's asymmetric synthesis was the first to derive a route to (+)-cytisine, the unnatural form of the alkaloid (Scheme 1.12).<sup>62</sup> The synthesis utilised an enantiomerically pure proline derivative and featured a samarium diiodide mediated pyrrolidine ring expansion to a key 5-substituted lactam intermediate which was later converted to the *cis* piperidine. A variation of the synthesis also provided a route to the alkaloids (-)-kuraramine, **99a**, (-)-isokuraramine, **99b**, and (-)-jussiaeiine A, **100** (Figure 1.6).

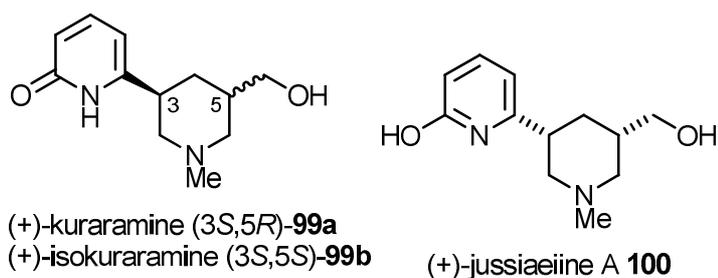
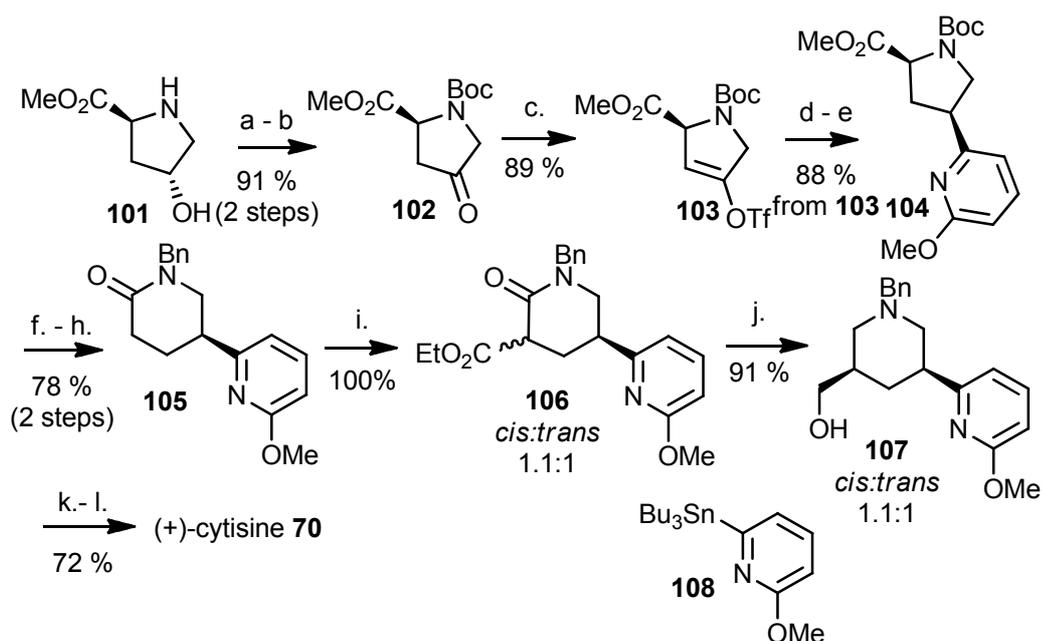


Figure 1.6.

To begin with, the starting material, 4*R*-hydroxy-*L*-proline **101** was converted to triflate **103**. Conversion to ketone **102** was achieved under Swern oxidation conditions, and the corresponding enolate was triflated, giving **103** in 81 % yield. Stille coupling with 2-tributylstannyl-6-methoxypyridine and Pd(PPh<sub>3</sub>)<sub>4</sub> was followed by alkene reduction with Pd / C, to give **104** in 88 % yield. Only the desired *cis* isomer was observed, presumably due to hydrogen addition to the least hindered face. Ring extension of **104** was achieved by a samarium diiodide-mediated reductive deamination and concurrent cyclisation of the resulting  $\delta$ -amino ester to give  $\delta$ -lactam **105** in 78 % yield. This compound was a common intermediate in the synthesis of the other featured alkaloids.

Following *N*-protection, ethoxycarbonylation was achieved with LDA and ethyl chlorocarbonate to give **106** in quantitative yield as a ca. 1:1 mixture of diastereomers. Isomerisation to the more stable 3,5-*cis* compound was not possible, resulting in only half of the piperidine being viable for the final cyclisation. Following ester reduction, alcohol **107** was obtained in 91 % yield as a separable mixture of diastereomers (1.1:1). Thermal cyclisation was achieved via the corresponding mesylate of *cis*-**107**, which was followed by hydrogenolysis of the benzyl group to give (+)-cytisine in 72 % yield over three steps. Overall the synthesis proceeded in 19 % yield over 11 steps.



Conditions: (a)  $(\text{Boc})_2\text{O}$ ,  $\text{NEt}_3$ ,  $\text{DCM}$ ,  $\text{rt}$ ,  $\text{quant.}$ ; (b)  $(\text{COCl})_2$ ,  $\text{DMSO}$ ,  $\text{NEt}_3$ ,  $\text{DCM}$ ,  $-40^\circ\text{C}$  to  $\text{rt}$ , 91 %; (c)  $\text{LiHMDS}$ , *N*-(5-chloro-2-pyridyl)triflimide,  $\text{THF}$ ,  $-78^\circ\text{C}$  to  $-20^\circ\text{C}$ , 89%; (d)  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{LiCl}$ ,  $\text{CuI}$ , 2-tributylstannyl-6-methoxypyridine **108**,  $\text{THF}$ ,  $65^\circ\text{C}$ , 88%; (e)  $\text{Pd/C}$ ,  $\text{H}_2$ ,  $\text{MeOH}$ ,  $\text{rt}$ ,  $\text{quant.}$ ; (f)  $\text{TFA}$ ,  $\text{DCM}$ ,  $0^\circ\text{C}$ ,  $\text{quant.}$ ; (g)  $\text{SmI}_2$ ,  $\text{THF-HMPA}$ ,  $\text{MeOH}$ ,  $0^\circ\text{C}$  to  $\text{rt}$ , 78%; (h)  $\text{NaH}$ ,  $\text{BnBr}$ ,  $\text{THF-HMPA}$ ,  $\text{THF}$ ,  $0^\circ\text{C}$  to  $\text{rt}$ ,  $\text{quant.}$ ; (i)  $\text{LDA}$ ,  $\text{ClCO}_2\text{Et}$ ,  $\text{THF}$ ,  $-78^\circ\text{C}$ ,  $\text{quant.}$ ; (j)  $\text{LiAlH}_4$ ,  $\text{THF}$ ,  $0^\circ\text{C}$  to  $\text{rt}$ , 91%; (k) i.  $\text{MsCl}$ ,  $\text{NEt}_3$ ,  $\text{DCM}$ ,  $0^\circ\text{C}$ ; ii.  $\text{toluene}$ ,  $\text{reflux}$ , 89%; (l)  $\text{Pd}(\text{OH})_2$ ,  $\text{HCO}_2\text{NH}_4$ ,  $\text{MeOH}$ ,  $\text{reflux}$ , 81%.

Scheme 1.12: Honda's asymmetric synthesis of (+)-cytisine.

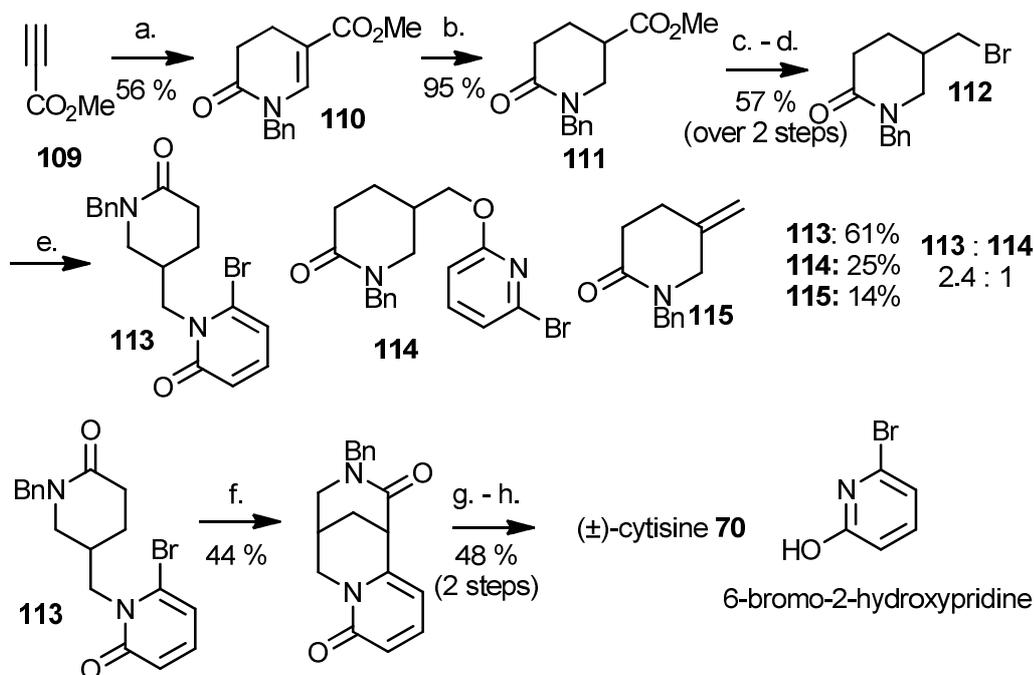
*Routes involving cyclisation of a 6-membered intermediate.*

*Gallagher.*

Gallagher's 1<sup>st</sup> generation approach to cytisine involved the synthesis and cyclisation of a 5-substituted  $\delta$ -lactam via a Buchwald-Hartwig coupling (Scheme 1.13). An asymmetric variant of this synthesis was later published.<sup>63</sup>

Enamide **109**, prepared via Stille's method<sup>64</sup> was used a starting material of this synthesis. The AH of enamide **110** with  $\text{Ru}(\text{R,R-Me-Duphos})[\text{COD}]\cdot\text{BF}_4$  proceeded with poor selectivity and lactam **111** was obtained in 24 % ee (Scheme 1.14a). Alternatively, reduction with palladium on charcoal gave the lactam in 95 % yield. Ester reduction and subsequent bromination with  $\text{PBr}_3$  gave bromide **112** in 57 %

overall yield. Alkylation with 6-bromo-2-hydroxypyridine initially resulted in poor yields of the desired *N*-alkylated product **113**, with the *O*-substituted isomer **114** in the majority alongside the elimination product **115**. Optimisation of conditions gave no further improvement; instead, a factorial experimental design method<sup>65</sup> investigating a number of parameters enabled conditions favouring the desired *N*-alkylation to be determined. This resulted in an overall 2.4:1 ratio of *N*- to *O*-products in 61 % yield with elimination product **115** isolated in 14 % yield. The key intramolecular Pd(OAc)<sub>2</sub> mediated  $\alpha$ -arylation of **113** with 2-bromopyridone resulted in formation of the arylated adduct in 44 % yield.<sup>66</sup>

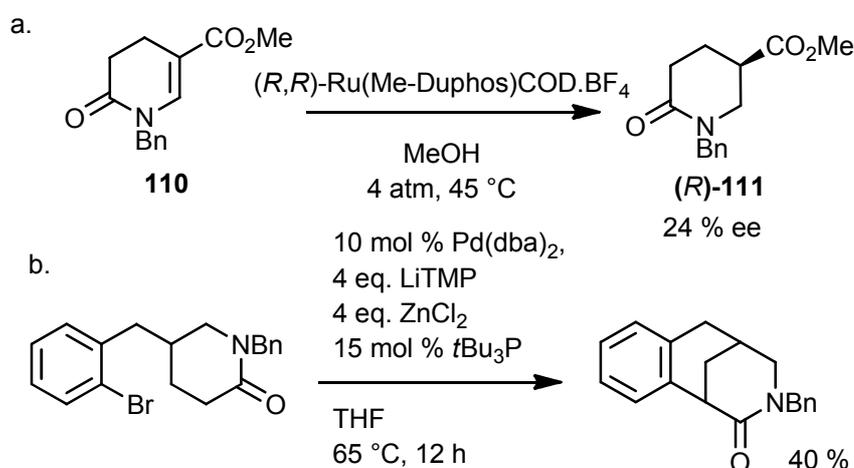


Conditions: (a) i. BnNH<sub>2</sub>, Et<sub>2</sub>O, rt then acryloyl chloride, THF, 70 °C, 56%; (b) 1 atm H<sub>2</sub>, Pd/C, Na<sub>2</sub>CO<sub>3</sub>, EtOH, 20 °C, 95%; (c) LiAlH<sub>4</sub>, THF, -10 °C; (d) PBr<sub>3</sub>, toluene, 110 °C, 57%; (e) 6-bromo-2-hydroxypyridine, NaH, LiBr, DME/DMF (24:1), concentration of **112** and **114** = 0.2M, 10 days, **113**: 61%; **114**: 25%; **115**: 14%; (f) 5 mol % Pd(OAc)<sub>2</sub>, 7.5 mol % (±)BINAP, KHMDS, THF, 70 °C, 44%; (g) BH<sub>3</sub>.THF, THF, 0 °C to rt, 55%; (h) HCl in MeOH, 1 atm H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, MeOH, 88%.

Scheme 1.13: Gallagher's first synthesis of cytosine.

Similarly, the Buchwald-Hartwig intramolecular arylation of 2-piperidinones has been developed by Maier<sup>67</sup> for application in the synthesis of related alkaloids (Scheme 1.14b).

Gallagher's synthesis was completed by selective lactam reduction with  $\text{BH}_3$ .THF and the product was subsequently deprotected with  $\text{Pd}(\text{OH})_2$  on charcoal, giving ( $\pm$ )-cytisine in 44 % yield; with an overall yield of 4 % from **109**.

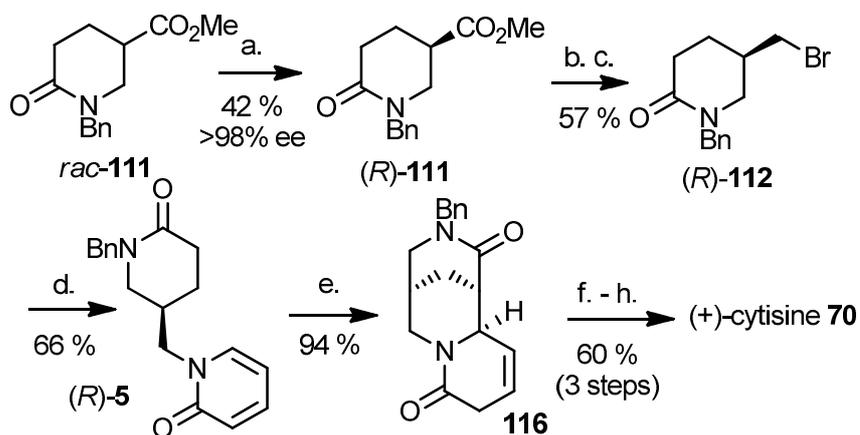


Scheme 1.14: a. AH of enamide **110**; b. Maier's Buchwald-Hartwig arylation of piperidinones.

#### Gallagher's 2<sup>nd</sup> generation asymmetric synthesis.

A modified asymmetric variant of this synthesis was later developed by the Gallagher and coworkers, who completed a route to (+)-cytisine and also the lupin alkaloids ( $\pm$ )-anagryne and ( $\pm$ )-thermopsine (Scheme 1.15). The desired chirality was achieved in the first step by the enzymatic resolution of ester **111** with  $\alpha$ -chymotrypsin.<sup>68</sup> The resolved ester was obtained in 42 % yield and > 98 % ee (*R*). The configuration was retrospectively assigned following competition of the synthesis. The unwanted carboxylic acid was obtained in 48 % yield and 64 % ee. Through the same method as previously, ester **111** was converted to the bromide **112**, then coupled with 2-hydroxypyridine to give the *N*-substituted product (*R*)-**5** in

66 % yield. In this synthesis, cyclisation was achieved by treatment with LHMDS or LDA via an internal 1,6-addition to the pyridone, forming the single diastereomer, **116**. This was the first intramolecular variant of this type and a later detailed study into the process was carried out. Oxidation by MnO<sub>2</sub>, followed by lactam reduction and debenzoylation, was achieved in 60 % yield over two steps. Overall, (+)-cytisine was obtained by 10 steps in 3.7 % overall yield. It was later shown that during the cyclisation of (*R*)-**5**, if the intermediate enolate was trapped with bis(trimethylsilyl)peroxide, the oxidised product pyridone product could be directly obtained in 60 % conversion.<sup>69</sup>



Conditions: (a)  $\alpha$ -chymotrypsin, 0.1 M phosphate buffer, acetone, pH 7.4; (b) LiAlH<sub>4</sub>, THF; (c) PBr<sub>3</sub>, toluene; (d) 2-pyridone, K<sub>2</sub>CO<sub>3</sub>, <sup>n</sup>Bu<sub>4</sub>NBr, H<sub>2</sub>O, toluene, reflux; (e) 2 eq. LHMDS, THF, 70 °C, sealed tube, 15 h, 94%; (f) MnO<sub>2</sub>, DCM, 79%; (g) BH<sub>3</sub>.THF, 0 °C to rt; (h) Pd(OAc)<sub>2</sub>, THF, HCl, MeOH, 1 atm H<sub>2</sub>.

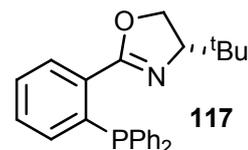
Scheme 1.15: Gallagher's asymmetric synthesis of (+)-cytisine.

*Coe.*

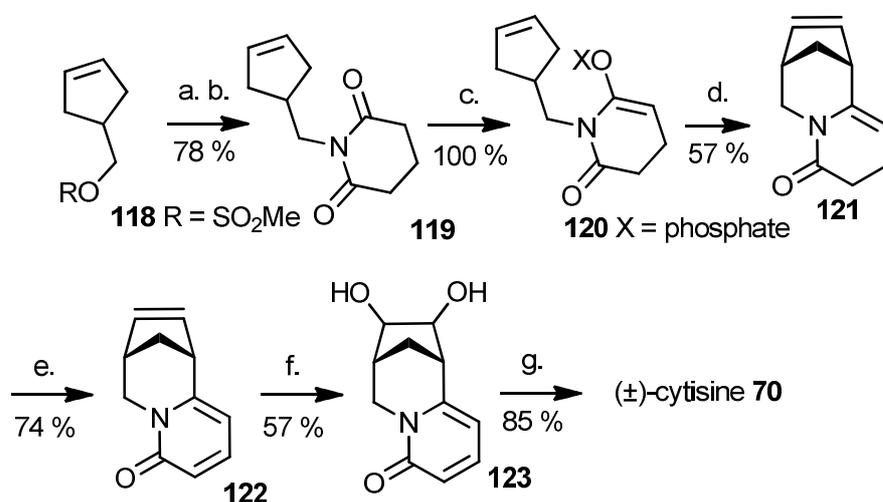
Coe derived a route to cytisine (Scheme 1.16).<sup>70</sup> The synthesis also provided a route to derivatives of cytisine **70** and varenicline **71**. The forward synthesis started with the *N*-substitution of cyclopentene **118** with glutarimide, giving *N*-substituted glutarimide **119** in 78 % yield. An intramolecular Heck coupling was used to achieve B ring closure. Conversion to the enol phosphate **120** was achieved with LiHMDS and diethylchlorophosphate in quantitative yield. A subsequent Heck coupling with

$\text{Pd}(\text{OAc})_2$  and  $\text{P}(\text{o-tol})_3$  enabled cyclisation to the key tricyclic dihydropyridine **121** in 57 % yield. An asymmetric variant of this coupling was carried out with the phosphinoxazoline ligand, **117** and  $\text{Pd}(\text{OAc})_2$  resulting in the formation of **121** in 22 % ee and 52 % yield.

Oxidation was achieved with  $\text{MnO}_2$  in refluxing benzene, giving **122** in 74 % yield. This was followed by



dihydroxylation with catalytic  $\text{OsO}_4$  and  $(\text{CH}_3)_3\text{NO}\cdot 2\text{H}_2\text{O}$ , resulting in an 85 % yield of **123**. Conversion of the diol to the amine substituent of cytosine was achieved via oxidative cleavage with  $\text{NaIO}_4$ , and subsequent reductive amination with  $\text{NH}_4\text{OH}$  and  $\text{Pd}(\text{OH})_2$ , under an atmosphere of hydrogen, giving cytosine in 57 % yield. Overall, ( $\pm$ )-cytosine was obtained in 16 % yield from intermediate **118**.

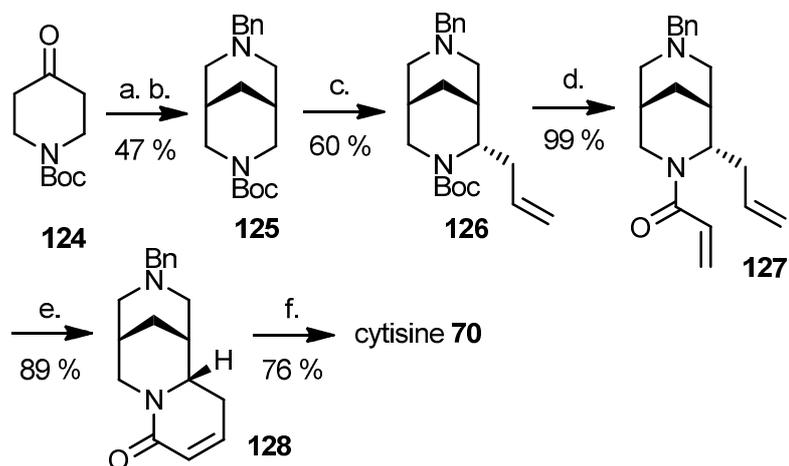


Conditions: (a) i. glutarimide,  $t\text{-BuOK}$ ,  $68^\circ\text{C}$ , THF, 1 h; ii. **118**, cat. DMF, cat.  $n\text{-Bu}_4\text{NI}$ ; (b) LHMDS, THF,  $0^\circ\text{C}$  to rt; (c) i. LHMDS, THF,  $0^\circ\text{C}$  to rt; ii.  $\text{CIP}(\text{O})(\text{OEt})_2$ ; (d) 2.5 mol %  $\text{Pd}(\text{OAc})_2$ , 5 mol %  $\text{P}(\text{o-tol})_3$ ,  $\text{NEt}_3$ , MeCN,  $83^\circ\text{C}$ , 24 h; (e)  $\text{MnO}_2$ , benzene,  $80^\circ\text{C}$ , 3h; (f)  $(\text{CH}_3)_3\text{NO}\cdot 2\text{H}_2\text{O}$ , cat.  $\text{OsO}_4$ , DCM; (g)  $\text{NaIO}_4$ , EtOH,  $\text{H}_2\text{O}$ , 30 m then  $\text{NH}_4\text{OH}$ ,  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$ , 48 - 72 h.

Scheme 1.16: Coe's synthesis of cytosine.

Section 1.2.4: Route involving the synthesis of bispidine.

O'Brien's synthesis was the first to start with a completed bispidine core, which negated the need for diastereoselective control (Scheme 1.17).<sup>47</sup> Although asymmetric Mannich reactions are known, no reference to any attempt was mentioned.<sup>71</sup> Construction of the bispidine core was achieved via a double Mannich reaction of *N*-Boc-piperidone **124** with benzylamine and formaldehyde followed NaBH<sub>4</sub> reduction of the corresponding tosyl hydrazone intermediate to give **125** in 47 % yield. Allylation of **125** was optimally achieved through a lithiation – transmetallation sequence. Lithiation of bispidine **125** was achieved with *s*-BuLi and TMEDA at – 78 °C in Et<sub>2</sub>O following a reaction time of 7 h. Transmetallation was then achieved via addition of 1 eq. CuCN.2LiCl in THF which then underwent allylation with allyl diphenylphosphate to give allylated bispidine **126** in 60 % yield as a single diastereomer. Boc deprotection followed further reaction with acryloyl chloride, to give the diene **127** in 99 % yield.



Conditions: (a) BnNH<sub>2</sub>, AcOH, (CHO)<sub>n</sub>, MeOH, reflux, 5 h; (b) i. TsNHNH<sub>2</sub>, EtOH, reflux, 2 h; ii. NaBH<sub>4</sub>, 4:1 THF / water, rt, 16 h then reflux, 3 h, 47 % from **124**; (c) i. 1.6 eq *s*-BuLi / TMEDA, Et<sub>2</sub>O, - 78 °C, 7 h; ii. 1.0 eq. CuCN.2LiCl, THF; iii. 2.2 eq. allyldiphenyl phosphate, 60 %; (d) i. 1:1 TFA/DCM, 0 °C, 2 h; ii. 10 % NaOH, acryloyl chloride, DCM, rt, 1 h, 99 %; (e) Ru(=CHPh)(PCy<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, toluene, reflux, 15 m, 89 %; (f) 10 % Pd / C, 2:1 toluene / cyclohexane, 100 °C, 12 h, 76 %.

Scheme 1.17: O'Brien's synthesis of cytosine.

This underwent ring closing metathesis with Grubb's 1<sup>st</sup> generation catalyst, resulting in the formation of lactam **128** in 89 % yield. Simultaneous dehydrogenation and benzyl group hydrogenolysis was achieved with palladium on charcoal in a solution of toluene and cyclohexene, to give cytosine in 76 % yield. This 6 step synthesis gave (±)-cytosine in 19 % overall yield from **124**.

### *Section 1.3.3: Related syntheses.*

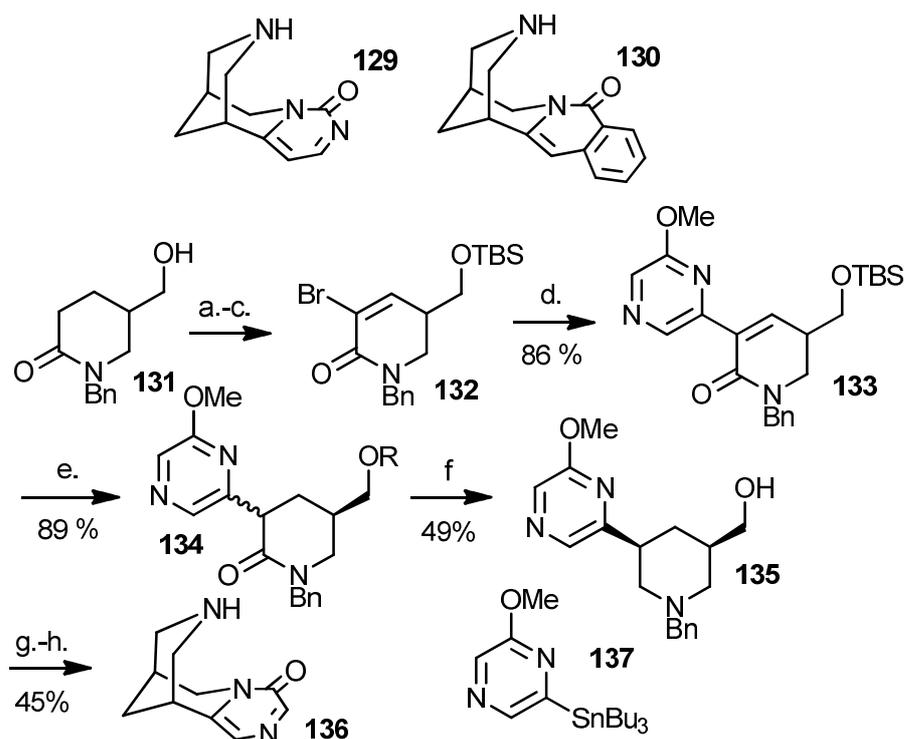
Due to the pharmacological interest in cytosine, there have been numerous syntheses of derivatives and structural variants of cytosine. These are listed in the following section.

#### *Gallagher's 3<sup>rd</sup> generation synthesis.*

The application of Gallagher's 1<sup>st</sup> and 2<sup>nd</sup> generation routes to the synthesis of pyridone core-modified derivatives **129** and **130** was not successful. These derivatives were found to decompose upon cyclisation to the bispidine adduct (corresponding to the transformation of (*R*)-**5** to **116**, Scheme 1.15). These compounds were of particular pharmacological interest for reasons to be outlined later in the next section. Instead, an alternative convergent synthesis was completed involving a late stage intermediate **132** which was used in the synthesis of the core-modified cytosine via coupling with the desired pyrazine or pyridine (Scheme 1.18).

The starting racemic lactam **131** was prepared through the method of Park *et al.*<sup>72</sup> An asymmetric synthesis of this lactam has also developed by Park and Gallagher (see Gallagher's 2<sup>nd</sup> generation synthesis of cytosine, in the last section). Following *O*-protection, introduction of the alkene bond was achieved through a selenide

oxidation-elimination sequence. Treatment of the resulting alkene with bromine, followed by  $\text{NEt}_3$ , furnished the common intermediate of the syntheses, bromide **132**, in 28 % overall yield. For the case of 4-azacytisine **136**, bromide **132** underwent Stille coupling with 6-methoxypyrazine tributylstannane **137** with  $\text{Pd}(\text{PPh}_3)_4$ , to give adduct **133** in 86 % yield. 6-Methoxypyrazine tributyl-stannane **137** was obtained from 2,4-dichloro-pyrazine via two consecutive substitutions with  $\text{NaOMe}$  and  $\text{Bu}_3\text{SnLi}$ . Reduction of adduct **133** was achieved with  $\text{LiAlH}_4$  to give lactam **134** as a 2.7:1 mixture of diastereomers in 89 % yield. Further lactam reduction with  $\text{LiAlH}_4$  and subsequent deprotection with TBAF achieved the diastereomerically pure product, *cis*-piperidine **135** in 49 % yield.



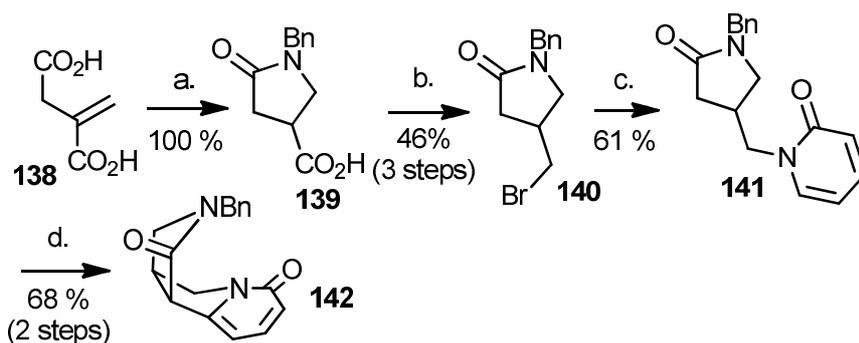
Conditions: (a) TBSCl,  $\text{NEt}_3$ , DCM, 37 h, 88%; (b) i.  $\text{BuLi}$ ,  $\text{PhSeCl}$ , THF,  $-78^\circ\text{C}$  to  $0^\circ\text{C}$ ; ii. THF/MeOH/ $\text{H}_2\text{O}$ ,  $\text{NaIO}_4$ , 14h, 50%; (c) i.  $\text{B}_2$ , DCM,  $45^\circ\text{C}$ , 3h; ii.  $\text{NEt}_3$ , DCM,  $45^\circ\text{C}$ , 17h, 63%; (d)  $[\text{Pd}(\text{PPh}_3)_4]$ ,  $\text{CuCl}$ ,  $\text{LiCl}$ , THF,  $70^\circ\text{C}$ , 15 h, 86 %; (e)  $\text{LiAlH}_4$ , THF,  $0^\circ\text{C}$ , 15 min, 89%, *cis/trans* 2.7:1.0; (f)  $\text{LiAlH}_4$ , THF, 15 h, then TBAF, THF/ $\text{H}_2\text{O}$  (9:1),  $50^\circ\text{C}$ , 16 h, 49%; (g) i.  $\text{MeSO}_2\text{Cl}$ ,  $\text{NEt}_3$ , DCM,  $0^\circ\text{C}$  to rt; ii.  $\text{NEt}_3$ , toluene/DMF (4:1),  $110^\circ\text{C}$ , 15 h, 73%; (h) i. 1-chloroethyl chloroformate, 1,2-dichloroethane,  $80^\circ\text{C}$ , 17 h; ii. MeOH,  $65^\circ\text{C}$ , 3 h, 61%.

Scheme 1.18: Gallagher's synthesis of core-modified cytisines.

Cyclisation of the corresponding mesylate of **135** was achieved with  $\text{NEt}_3$  through an *N*-alkylation - *O*-demethylation sequence to give *N*-benzyl-4-azacytisine in 73 % yield. Deprotection was then achieved via treatment with 1-chloroethyl chloroformate followed by subsequent methanolysis, to give 4-azacytisine **136** in 61 % yield.

### *Norbispidine.*

The novel 5-membered cytisinoid, bispidine **142**, was synthesised by Gallagher via the sequence shown in Scheme 1.19.<sup>69</sup> The initial pyrrolidinone **139** was formed via treatment of carboxylic acid **138** with benzylamine by conjugate addition and subsequent cyclisation, resulting in pyrrolidinone **139** in quantitative yield. Following reduction and bromination, bromide **140** underwent reaction with 2-hydroxypyridine to give *N*-pyridone **141** in 61 % yield. LiHMDS mediated cyclisation resulted in formation of the intermediate adduct in quantitative yield, which upon oxidation with  $\text{MnO}_2$ , gave norbispidine **142** in 68 % yield. Overall norbispidine was obtained in 19 % yield.

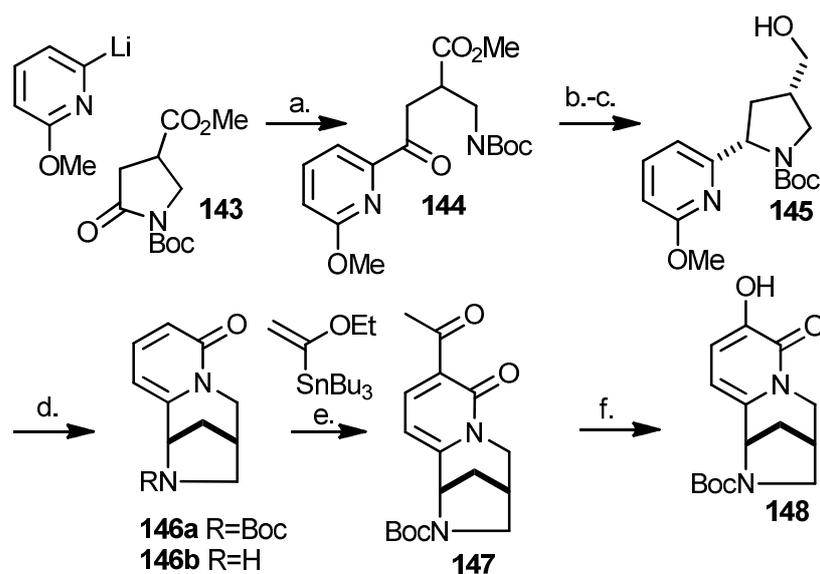


Conditions: (a)  $\text{BnNH}_2$ , 130 °C, quant.; (b) i.  $\text{MeOH}$ ,  $\text{H}_2\text{SO}_4$ ,  $\Delta$ ; ii.  $\text{NaBH}_4$ ,  $\text{MeOH}$ ,  $\text{H}_2\text{O}$ ; iii.  $\text{PBr}_3$ , toluene, 46%; (c) 2-hydroxypyridine,  $\text{K}_2\text{CO}_3$ , TBAB,  $\text{H}_2\text{O}$ , toluene,  $\Delta$ , 61%; (d) i. LiHMDS, THF, -78 °C, quant.; ii.  $\text{MnO}_2$ , dichloroethane,  $\Delta$ , 68%.

Scheme 1.19: Gallagher's synthesis of norbispidine.

*$\alpha$ -Hydroxypyridone.*

The natural product hydroxynorecytisine **148** was isolated from the legume family, *Laburnum anagyroides* by Hayman and Gray in 1989.<sup>73</sup> A total synthesis of the alkaloid was carried out by Caldwell to assess the selectivity profile at the  $\alpha_2\beta_4$  receptor (Scheme 1.20). The synthesis involved the isolation of the intermediate, ( $\pm$ )-norecytisine **146b** which was also pharmacologically interesting as it would enable direct comparison with (-)-cytisine.<sup>74</sup> Ring opening of *N*-Boc pyrrolidinone **143** with 6-lithio-2-methoxypyridine resulted in ketone **144** in 55 % yield. A reductive amination cyclisation with TFA and Pd/C, followed by re-protection with Boc<sub>2</sub>O gave pyrrolidine **145** as one diastereomer in 74 % overall yield. Following ester reduction, cyclisation was achieved via the mesylate, to give the key compound **146a** in 83 % yield. Deprotection then gave norecytisine ( $\pm$ )-**146b** in 41 % yield. Conversion to hydroxy-norecytisine **148** was achieved in 3 steps from **146a**. Bromination at the 3-position was achieved with NBS and CCl<sub>4</sub> in 54 % yield. Following Stille coupling with tributyl(1-ethoxyvinyl)stannane, acyl **147** was obtained in 70 % yield, which then underwent Bayer-Villiger oxidation with *m*-CPBA, followed by hydrolysis with KOH to give the target compound following deprotection.



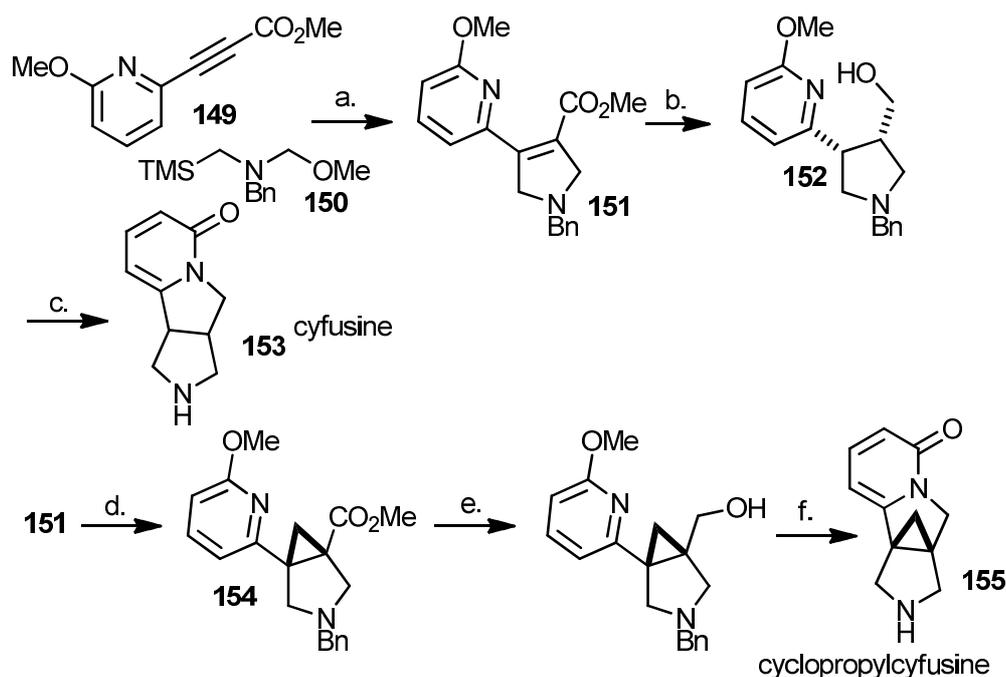
Conditions: (a) THF,  $-78^{\circ}\text{C}$ , 55 %; (b) i. TFA, DCM; ii.  $\text{H}_2$ , Pd/C, MeOH; iii.  $\text{Boc}_2\text{O}$ ,  $\text{NaHCO}_3$ , THF, 74 %; (c)  $\text{LiAlH}_4$ , THF, 90 %; (d) i.  $\text{MsCl}$ , DIEA, DCM; ii. toluene, reflux; (e) i. NBS,  $\text{CCl}_4$ , 54%; ii. ethoxyvinyl stannane,  $\text{Pd}(\text{PPh}_3)_4$ , toluene, reflux, 70 %; (f) i. *m*-CPBA,  $\text{CHCl}_3$ ; ii.  $\text{KOH}$ , MeOH, 40%; iii. TFA, DCM, 67%.

Scheme 1.20: Caldwell's synthesis of  $\alpha$ -Hydroxypyridone.

These compounds were determined to have an affinity to  $\alpha_2\beta_4$  nACh receptors that was 4 orders of magnitude less than (-)-cytisine.

#### *Cyfusine and cyclopropylcyfusine.*

The novel fused ring variants, ( $\pm$ )-cyfusine **153** and ( $\pm$ )-cyclopropylcyfusine **155** were synthesised by Yohannes *et al.* (Scheme 1.21).<sup>75</sup> These convergent routes involved the common intermediate **151**, simply constructed in 2 steps from **149**. Following treatment of alkyne **149** with the dipole precursor **150**, the [3+2] adduct **151** was obtained in 85 % yield. Multiple reductions gave alcohol **152** as a single diastereomer, which then underwent cyclisation with methanesulfonyl chloride to give cyfusine **153** in 16 % overall yield. The cyclopropyl variant **154** was prepared via cyclopropanation of intermediate **151** with dimethylsulfoxonium ylide, to give the product **154** in 61 % yield.



Conditions: (a) TFA,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt, 2 h, 85%; (b) i. 40 psi  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$ , MeOH, 2h, 41%; ii.  $\text{LiAlH}_4$ ,  $0^\circ\text{C}$  to rt, 1.5 h, 67%; (c) i.  $\text{MsCl}$ , DIPEA,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt, 67%; ii. 45 psi  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$ , MeOH; (d) dimethylsulfoxonium ylide, THF, rt, 1.5 h, 61%; (e)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$  to rt, 1.5 h, 95%; (f) i. 45 psi  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$ , MeOH,  $(\text{Boc})_2\text{O}$ , 94%; (ii)  $\text{MsCl}$ , DIPEA,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt, 16 h, 82%; (iii) 1N HCl, MeOH, EtOAc/hexanes, rt, 16 h, quantitative.

Scheme 1.21: Yohannes' synthesis of cyfusine and cyclopropylcyfusine.

Following reduction and cyclisation, **155** was formed in 38 % overall yield. The nAChR binding assays of these analogues were evaluated; interestingly, ( $\pm$ )-cyclopropylcyfusine **155** and cyfusine **153** showed similar selectivity to the  $\alpha_2\beta_4$  receptors to cytosine, but with much weaker binding.

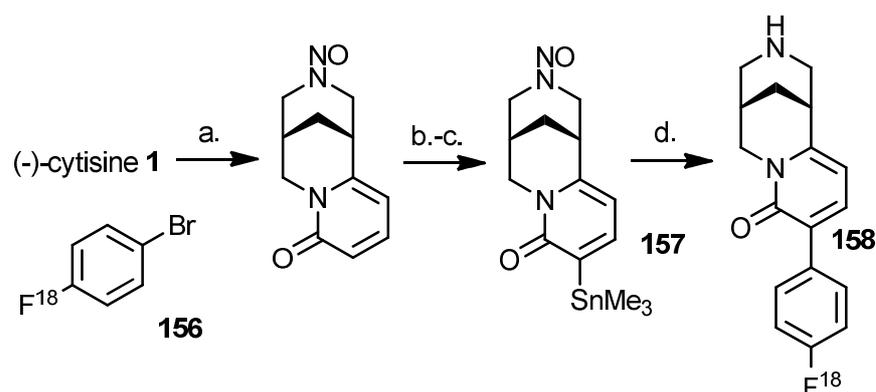
The total synthesis of the saturated derivative, tetrahydrocytosine has been also reported.<sup>76</sup>

#### Direct derivatisation of (-)-cytosine.

#### 9-(4'-[F<sup>18</sup>]fluorophenyl)cytosine.

A rapid synthesis of 9-(4'-[F<sup>18</sup>]fluorophenyl)cytosine was developed for application as a radioligand for PET studies of  $\alpha_4\beta_2$  nicotinic acetylcholine receptors (Scheme 1.22). Cytosine is particularly suited to use as a radioligand due to its high selectivity

to the  $\alpha_4\beta_2$  receptor subtype, and relatively higher *in vivo* half life in comparison to other radioligands.<sup>77</sup> During the synthesis, (-)-cytisine was directly *N*-protected with  $\text{NaNO}_2$ . Treatment with iodine in the presence of silver trifluoroacetate resulted in the formation of *N*-nitroso-9-iodocytisine, which was then converted to the corresponding stannane **157**, following treatment with hexamethylditin in dioxane in the presence of  $\text{Pd}(\text{PPh}_3)_4$ . The Stille coupling of **157** with readily synthesised 4-[ $\text{F}^{18}$ ]fluorobromobenzene **156**<sup>78</sup> and  $\text{PdCl}_2(\text{PPh}_3)_2$  followed in a short reaction time of 15 min at 110 °C. Subsequent denitrosation with 3M HCl at 110 °C for 2 min gave 9-(4'-[ $\text{F}^{18}$ ]fluorophenyl)cytisine **158** in 6-10 % radiochemical yield (RCY) overall (% yields were not stated).



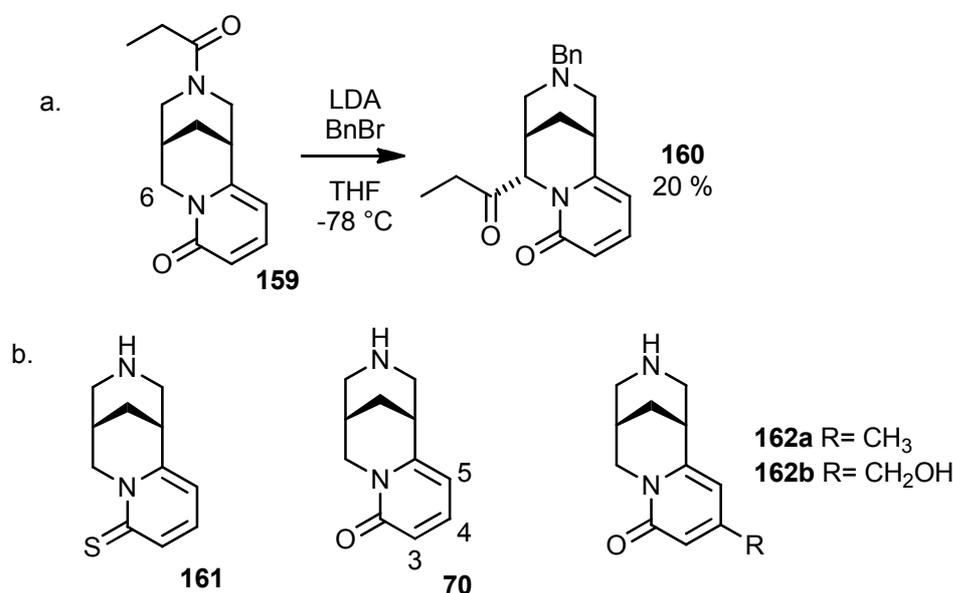
Conditions: (a)  $\text{NaNO}_2$ , HCl, rt, 12h, quant; (b) silver trifluoroacetate,  $\text{I}_2$ , 12h, rt, 50 %; (c) hexamethyldistannane,  $\text{Pd}(\text{PPh}_3)_4$ , dioxane, reflux, 3h, 70%; (d) i.  $\text{PdCl}_2(\text{PPh}_3)_2$ , [ $\text{F}^{18}$ ]-**156**, dioxane, 10 min, 110 °C, 56-74% RCY; ii. 3M HCl, 2 min, 110 °C, 75% RCY.

Scheme 1.22: Lasne's synthesis of 9-(4'-[ $\text{F}^{18}$ ]fluorophenyl)cytisine.

#### Other derivatives.

Following treatment with Lawesson's reagent, thiocytisine **161** was obtained and characterised by X-ray crystallography (Scheme 1.23b). Halogenated derivatives at the 3- and 5- positions of cytisine have been prepared via treatment with NCS, NBS or iodine mono chloride. The functional activity of these derivatives on cultured cells expressing three major types of nicotinic receptors was studied and suggested that halogenation at the 3-position imparts greater activity than (-)-cytisine.<sup>79</sup> Access to

derivatives at the 6-position were serendipitously discovered following the attempted benzylation of *N*-propionyl cytisine **159** with LDA (Scheme 1.23a). Instead of the expected benzylation, an unusual type of nitrogen to carbon acyl transfer occurred, forming 6-derivative, **160**. This transformation was then applied to the synthesis of a range of other 6-substituted derivatives.<sup>80</sup> Cytisine derivatives of flavonoids have recently been carried out.<sup>81</sup> The 4-substituted derivatives, **162a** and **162b** have been synthesised through an alteration of O'Neill's synthesis and were determined to be the most discriminating nicotinic ligands derived from cytisine.<sup>82</sup>



Scheme 1.23: a. LDA mediated carbon acyl transfer; b. derivatives of cytisine.

#### Section 1.3.4: Pharmacological Studies.

Following all the studies of the derivatives, the halogenated and methylated cytisines **162a** and **162b**; and cyfusine **153**, were the only ones to show any improvement or matching activity to (-)-cytisine. Derivatives in which the bispidine skeleton was altered in some way, such as norcytisine or  $\alpha$ -hydroxypyridones **148**, actually showed decreases in activity. A later *in silico* study by Abin-Carriquiry<sup>83</sup>, on the interaction between cytisine derivatives and  $\alpha_4\beta_2$  nAChRs, achieved the development of an accurate model, which could accurately predict the interaction of modified

cytisines within the binding site of the receptor. This was able to account for the limited effects that were observed for structural modifications to the cytosine bispidine scaffold. Significant bonding interactions exist between the charged bispidine nitrogen atom which is surrounded by what is described as an ‘aromatic box’ of tyrosine and tryptophan side chains. Any alteration to this bispidine region disrupts these important interactions. Derivatisation of the pyridone region was also considered most likely to result in improved interactions, and a key target for further study.<sup>83</sup> This rationale motivated Gallagher’s 3<sup>rd</sup> generation synthesis, which enabled the previously unreachable azacytisines **130** and **136** to be accessed. The available synthetic strategies to cytosine had not provided any means of accessing this type of derivatives.

#### **Section 1.4: (-)-Sparteine and Related Compounds.**

##### *Section 1.4.1: Introduction.*

The lupin alkaloid (-)-sparteine, (-)-**163a** is found in numerous species of plant, such as *Lupinus caudatus*, commonly known as Kellogg.<sup>84</sup> The alkaloid was first isolated by Stenhouse<sup>85</sup> in 1851, but it was not until 1931 that the structure was determined by Clemo.<sup>86</sup> Sparteine consists of a bispidine of equal chirality to (-)-cytosine, which is fixed to a further two piperidine rings. Due to isomerisation between these heterocycles, there are four naturally occurring stereoisomers; the enantiomers (-)-sparteine and (+)-sparteine, and the diastereomers  $\alpha$ -isosparteine **163b** and  $\beta$ -isosparteine **163c** (the latter of which was unusually discovered synthetically before its isolation from a plant) (Figure 1.7).<sup>87</sup> (-)-Sparteine is pharmaceutically active as a hypoglycemic agent and has been used in the treatment of diabetes, eczema, and as an anti-inflammatory agent.<sup>88</sup> Pharmacological study of derivatives is ongoing.<sup>88</sup> The

alkaloid has had large attraction in asymmetric synthesis as a chiral bidentate ligand.

<sup>89</sup> Other similar lupin alkaloids containing the piperidine core framework are known, such as (+)-anagyrine **215** (p 59) and aloperine **214**.

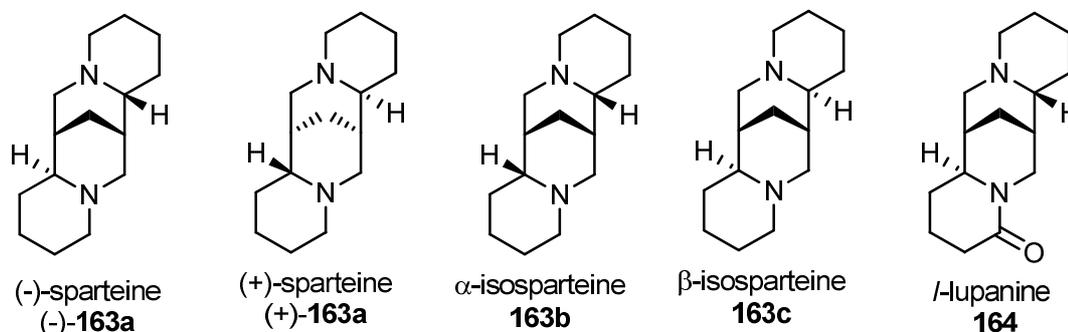


Figure 1.7: Isomers of sparteine.

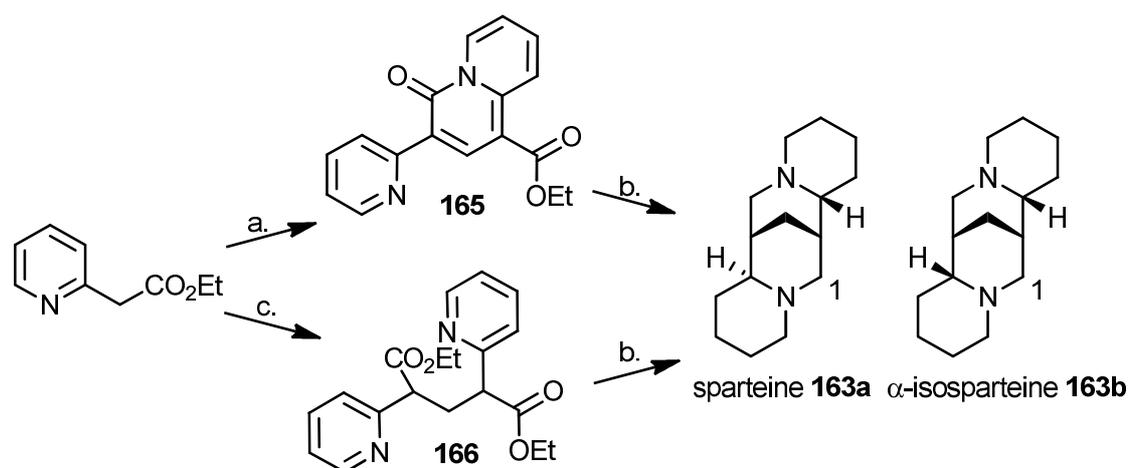
#### *Section 1.4.2: Synthetic Approaches to (-)-Sparteine and Related Compounds.*

The alkaloid ( $\pm$ )-sparteine, **163a** was first serendipitously synthesised by Clemo in 1928, who formed the alkaloid through reduction of *l*-lupanine, **164**. This established their close relation as lupin alkaloids and began many fully synthetic approaches to the alkaloid.<sup>86</sup> The relationship between (-)-sparteine and its naturally occurring stereoisomers was established through resolution with base, during early investigations. The diastereomers **163b** and **163c** were also observed as racemic side products in early synthetic attempts towards (-)-sparteine.<sup>90-92</sup> In this section the synthetic approaches to sparteine will be reviewed in detail, followed by syntheses of some related compounds.

#### *Leonard.*

In 1950, Leonard completed the synthesis of a mixture of sparteine ( $\pm$ )-**163a** and  $\alpha$ -isosparteine ( $\pm$ )-**163b** from two different precursors **165** and **166**, both derived from ethyl 2-pyridylacetate (Scheme 1.24). Hydrogenation of these precursors resulted in subsequent cyclisation to the alkaloid. Precursor **165** was formed by the combination

of ethyl 2-pyridylacetate with ethyl orthoformate and acetic anhydride. Alternatively, precursor **166** was formed by the condensation of ethyl 2-pyridylacetate with formaldehyde. Hydrogenation of both precursors with copper chromite formed a mixture of sparteine **163a** and  $\alpha$ -isosparteine **163b**.<sup>93</sup> In 1947, Sorm derived an almost identical synthesis to Leonard's glutarate **166** synthesis, except it was less efficient, forming lupanine, **164** as a side product.<sup>91</sup>

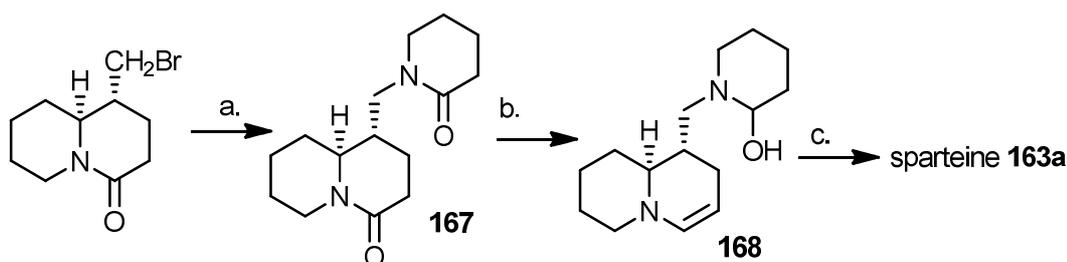


Conditions: (a) ethyl orthoformate, acetic anhydride; (b) copper chromite, dioxane, 250 °C, 300-350 atm H<sub>2</sub>; (c) formaldehyde.

Scheme 1.24: Leonard's synthesis of sparteine and  $\alpha$ -iso-sparteine.

### *Bohlmann.*

Bohlmann derived an early synthesis to sparteine **163a** from enamine **168**, involving a key ring closing reaction between the enamine and iminium intermediate (Scheme 1.25).<sup>94</sup> Reduction of amide **167** gave enamine **168**, which underwent dehydration and subsequent cyclisation and reduction with NaBH<sub>4</sub> to give ( $\pm$ )-sparteine.

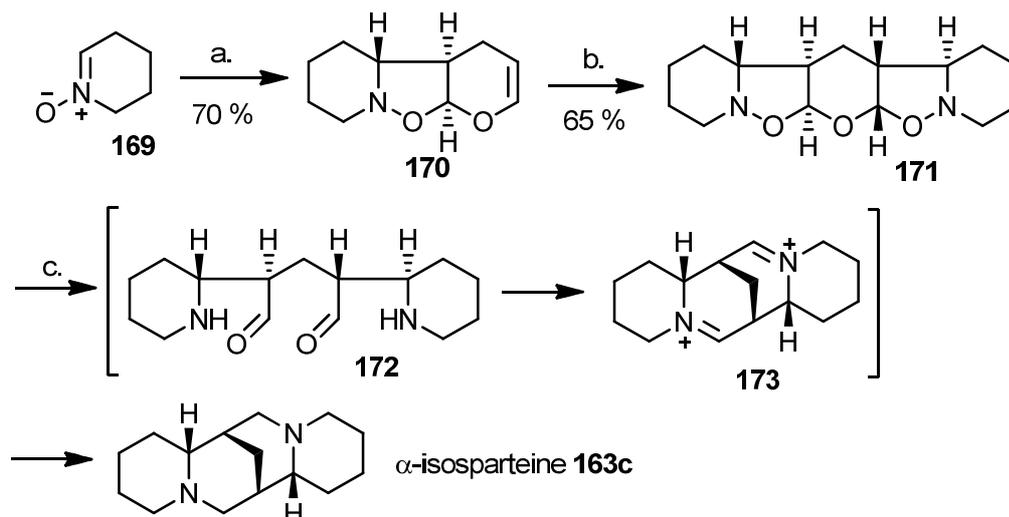


Conditions: (a) piperidinone; DIBAL-H; (c) NaBH<sub>4</sub> (limited information was available for this synthesis).

Scheme 1.25: Bohlmann's synthesis of sparteine.

### Oinuma.

Oinuma derived a diastereoselective, three-step synthesis of  $\alpha$ -isosparteine **163b** starting from the *N*-oxide, **169** (Scheme 1.26). Following a 1,3-dipolar cycloaddition dimerisation between **169** and 4*H*-pyran, the product, 4*H*-pyran **170** was obtained in 70 % yield, with high regio- and stereo-selectivity. Further reaction with *N*-oxide **169** was reported to form a 2:1 adduct containing what was characterised to contain the *exo,trans,exo*-addition product **171**, as determined by <sup>1</sup>H NMR. Hydrogenation with Pd(OH)<sub>2</sub> formed  $\alpha$ -isosparteine through the suspected intermediates **172** and **173** (some yields in this synthesis were not quoted).<sup>95</sup>



Conditions: (a) 4*H*-pyran, 140 °C, 70%; (b) **169**, 140 °C, 65%; (c) Pd(OH)<sub>2</sub>, MeOH.

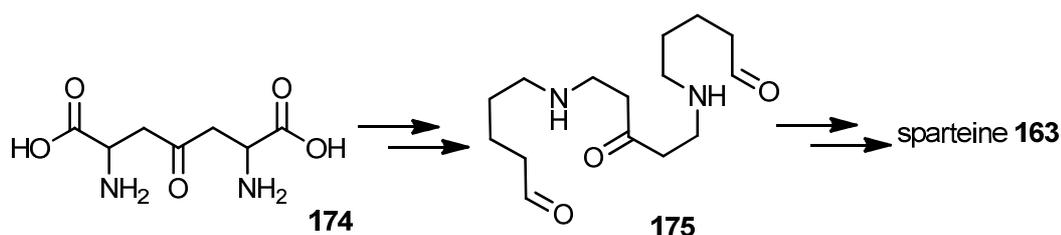
Scheme 1.26: Oinuma's synthesis of  $\alpha$ -isosparteine.

*Biogenic related syntheses.*

There has been much interest into the biosynthesis of the lupin alkaloids<sup>96 97</sup> resulting in a number of biogenic syntheses to sparteine **163a** and other related alkaloids. These alkaloids have been shown to originate from cadaverine **178**. Radio-labelling experiments have shown that cadaverine (itself derived from lysine) is the source of carbon and nitrogen atoms present in these alkaloids.

*Van Tamelen.*

Early study proposed sparteine to be derived from  $\gamma$ -keto- $\alpha$ - $\alpha'$ -diaminopimelic acid, **174** and lysine, through the intermediate **175** (Scheme 1.27). Based on this route, van Tamelen derived a biomimetic approach to sparteine **163a** via intermediate **175**.<sup>98</sup>

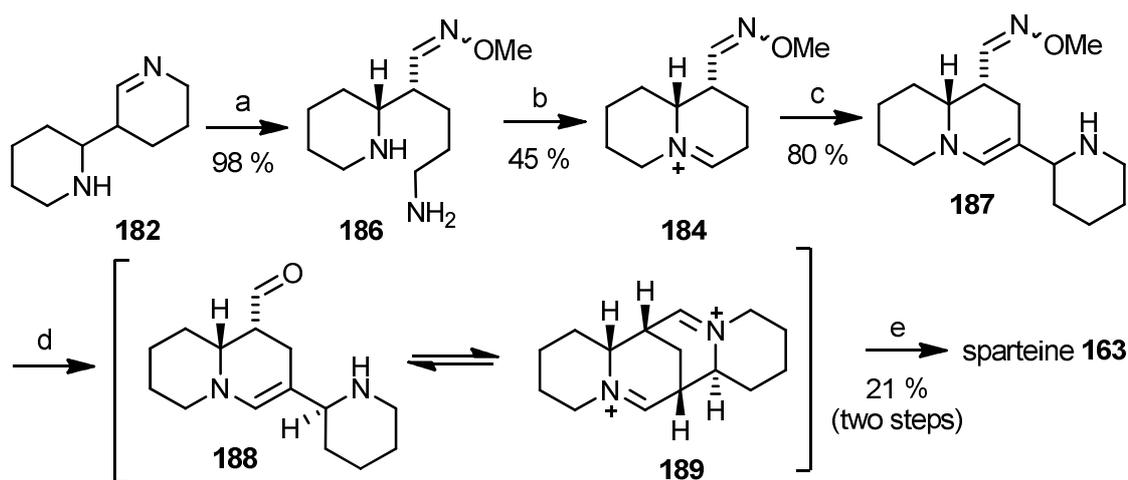


Scheme 1.27: Proposed biosynthesis of (-)-sparteine.

The synthesis formed **176** via condensation of acetone, formaldehyde and piperidine (Scheme 1.28). This was then dehydrogenated with mercuric acetate to form the proposed intermediate **177**, which underwent ring closure to keto-sparteine, **179**. Following carbonyl removal with hydrazine, a single diastereomer of sparteine was reportedly obtained in 57 % yield.



Koomen initiated the synthesis by the synthesis of tetrahydroanabasine **182**, via the procedure stated by Schöpf.<sup>99</sup> Treatment with  $\text{NH}_2\text{OMe}$  afforded oxime **186** in 98 % yield as a mixture of diastereomers. Deamination was achieved with o-quinone **185** to give the key intermediate, oxime **184**, in 54 % yield. For application to the synthesis of sparteine, the oxime **184** was subjected to further reaction with dehydropiperidine, **181** to form **187** in 80 % yield. Removal of the O-methyl oxime was achieved via treatment with  $\text{O}_3$  and  $\text{HCl}$  at  $-45^\circ\text{C}$  for 7 h. Hydrolysis of the resultant product formed **188**, which spontaneously undergoes cyclisation in  $\text{NaOAc}$  and  $\text{AcOH}$  to supposedly form intermediate iminium species **189**, which was reduced with  $\text{NaCNBH}_3$  to form sparteine as a single diastereomer in 21 % yield. Interestingly, if the oxime deprotection was carried out with  $\text{TiCl}_4$  and  $\text{HCl}$  at higher temperature, following the cyclisation and reduction procedure, the alkaloid was obtained as a 1.2:1 mixture of diastereomers  $\beta$ -isosparteine and sparteine. This has been attributed to the mildness of the ozonolysis process, which must proceed without epimerisation.



Conditions: (a)  $\text{NH}_2\text{OCH}_3$ ,  $\text{H}_2\text{O}$ ,  $\text{MeOH}$ , rt, 98%; (b) o-quinone **185**,  $\text{MeOH}$  0 C, 30 m, 45%; (c) **181**, sodium acetate,  $\text{MeOH}$ , 3 h, rt, 80%; (d)  $\text{HCl}$ ,  $\text{O}_3$ ,  $-50^\circ\text{C}$ ,  $\text{MeOH}$ , 7 h; (e)  $\text{NaCNBH}_3$ ,  $\text{MeOH}$ , rt, 14 h, 21%.

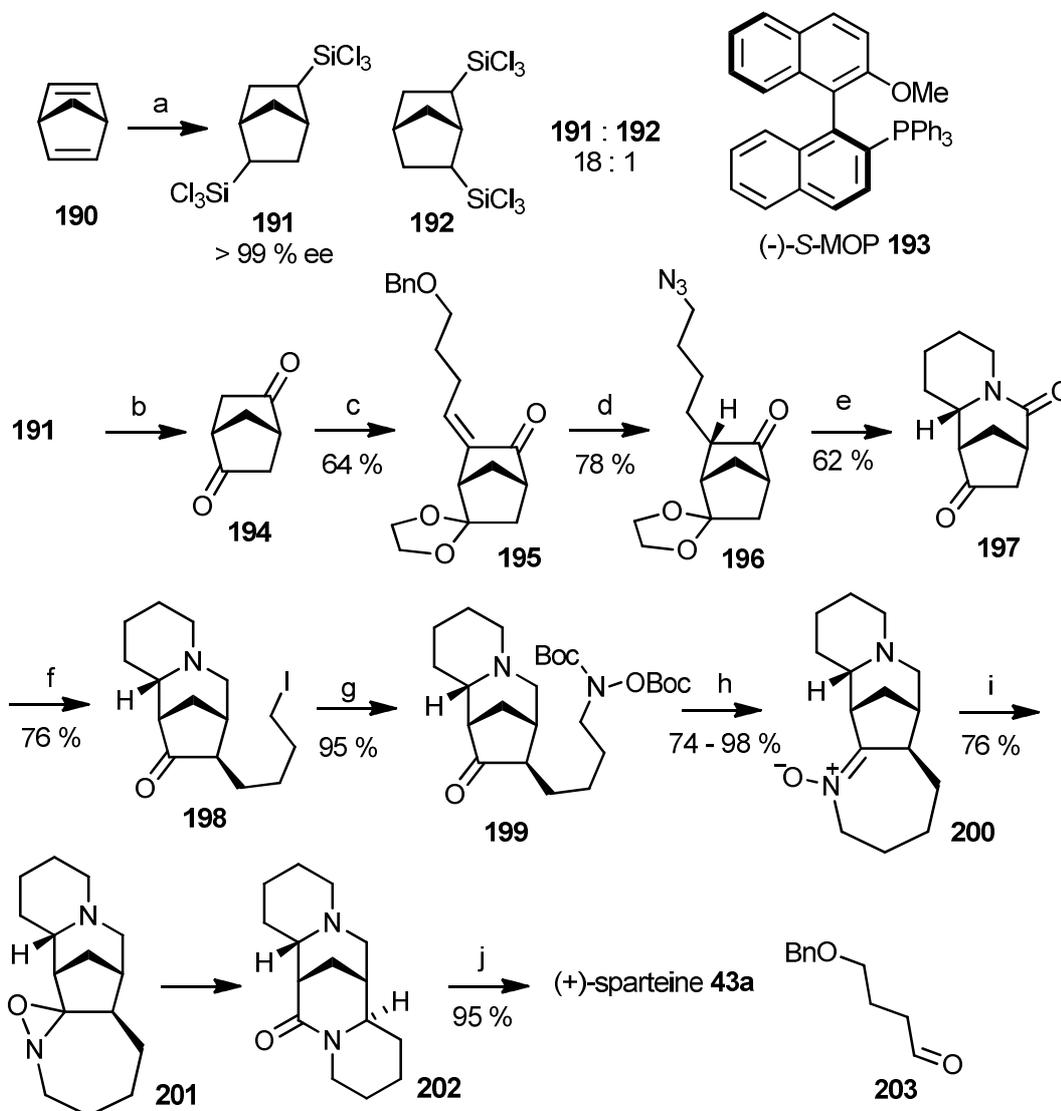
Scheme 1.30: Koomen's biomimetic synthesis of sparteine.

Configurationaly, the  $\beta$ -isosparteine isomer is more thermodynamically favoured and may be formed via epimerisation during the harsher conditions of the  $\text{TiCl}_4$  process.

*Wendt.*

The first asymmetric route to (-)-sparteine, (-)-**163a** was developed by Wendt<sup>100</sup> in 2002 utilising the chiral (bis)hydrosilation of norbornadiene **190**, developed by Hayashi (Scheme 1.31).<sup>101</sup> Norbornadiene underwent (bis)hydrosilation with  $[(\text{Allyl})\text{PdCl}]_2$  and  $\text{HSiCl}_3$  with (-)-*S*-MOP **193** to give disilylnorbornane **191** in > 99 % ee as a 18:1 mixture with the *meso* isomer **192**. Oxidation under Swern conditions gave (+)-**194**, which was used by Wendt as the starting material of the synthesis. Following monoketalisation, aldol reaction with aldehyde **203** gave enone **195** in 64 % yield. Alkene hydrogenation and benzyl deprotection was achieved with Pd/C, resulting in formation of the desired *endo* orientation, due to hydrogenation of the least hindered *exo* face. The resulting hydroxide group was converted to azide **196** by a modified Mitsunobu reaction with  $\text{Zn}(\text{N}_3)_2 \cdot 2\text{Py}$  in 78 % yield. Cyclisation of the C ring was achieved by an intramolecular Schmidt reaction with  $\text{TiCl}_4$ , which also deprotected the ketone, giving **197** in 62 % yield. Chemoselective removal of the amide carbonyl was achieved with Lawesson's reagent and Raney nickel. The resulting ketone was alkylated with LDA and  $\text{I}(\text{CH}_2)_4\text{Cl}$ , followed by iodination to give **198** as a single diastereomer in 76 % yield over 4 steps. Cyclisation of the D ring by a second Schmidt reaction was not possible, and so an alternative photo-Beckmann rearrangement was used. Reaction with BocNHOBoc then resulted in the formation of **199** in 95 % yield. Subsequent deprotection yielded the free hydroxylamine, which underwent intramolecular ketone condensation to give oxime **200** in 74-98 % yield. Photolysis initiated rearrangement to the lactam, **202** in 76 %

yield via proposed intermediate **201**. Finally, use of  $\text{LiAlH}_4$  achieved conversion to (+)-sparteine in 95 % yield; an overall yield of 15.7 % over 15 steps. In addition, Other racemic syntheses have been completed in the literature.<sup>102-105</sup>



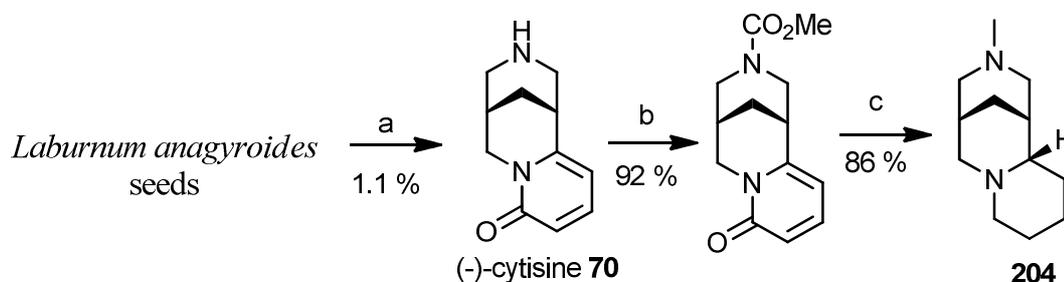
Conditions: (a) i.  $\text{HSiCl}_3$ ,  $[\text{Allyl}]\text{PdCl}_2$ , (-)-S-MOP **193**; (b) i.  $\text{H}_2\text{O}_2$ ; iii. Swern oxidation; (c) i. ethylene glycol,  $\text{TsOH}$ ; ii.  $\text{LDA}$ ,  $\text{BnO}(\text{CH}_2)_3\text{CHO}$ ; iii.  $\text{MsCl}$ ; iv.  $\text{DBU}$ ; (d) i.  $\text{H}_2$ ,  $\text{Pd/C}$ ,  $\text{Pd}(\text{OH})_2$ ; ii.  $\text{Zn}(\text{N}_3)_2 \cdot 2\text{Py}$ ,  $\text{DEAD}$ ,  $\text{PPh}_3$ ; (e)  $\text{TiCl}_4$ ; (f) i. Lawesson's reagent; ii.  $\text{Raney Ni}$ ; iii.  $\text{LDA}$ ,  $\text{I}(\text{CH}_2)_4\text{Cl}$ ; iv.  $\text{NaI}$ , acetone; (g)  $(\text{BocO})\text{NH}(\text{Boc})$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{DMF}$ ; (h) i.  $\text{TFA}$ ,  $4\text{ \AA MS}$ ; ii.  $\text{NaHCO}_3$ ; (i)  $\text{hn}$  (254 nm), benzene; (j)  $\text{LiAlH}_4$ ,  $\text{THF}$ , reflux.

Scheme 1.31: Wendt's synthesis of (+)-sparteine.

### Miscellaneous syntheses.

The low availability of the enantiomer, (+)-sparteine has been problematic to its further investigation as a chiral ligand.<sup>106</sup> To overcome this, (-)-cytisine has been used in the synthesis of a '(+)-sparteine surrogate' (**204**). This surrogate models the

D ring of the alkaloid with a *N*-methyl group and has been used experimentally as a readily available mimic (Scheme 1.32). Following extraction of (-)-cytisine from the seeds of *Laburnum anagyroides*, *N*-acylation was carried out. Multiple reductions gave the surrogate **204** in 86 % yield.<sup>107</sup>



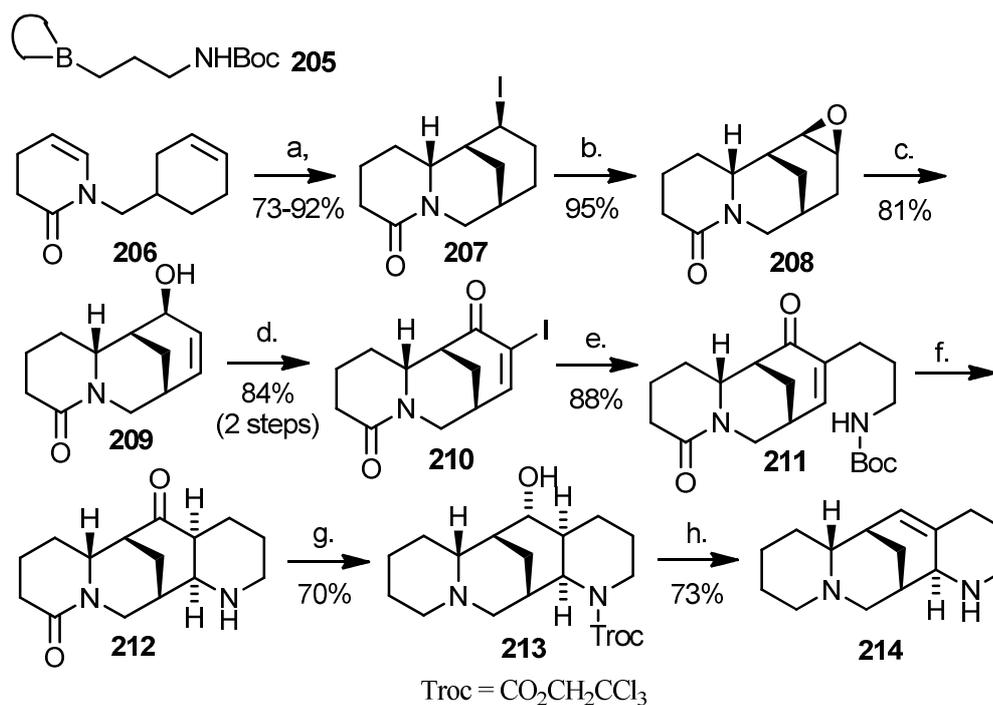
Conditions: (a)  $\text{NH}_4\text{OH}$  (aq), DCM, MeOH, rt, 3 d, 1.1%; (b)  $\text{NEt}_3$ ,  $\text{MeCO}_2\text{Cl}$ , DCM, rt, 3.5 h, 92 %; (c) i.  $\text{PtO}_2$ ,  $\text{H}_2$ , EtOH, rt, 5 h; ii.  $\text{LiAlH}_4$ , THF, reflux, 16 h, 86 %.

Scheme 1.32: O'Brien's synthesis of the '(+)-sparteine surrogate' from (-)-cytisine.

#### *Aloperine.*

A synthesis of aloperine **214**, a member of the Lupine alkaloids, was completed by Overman *et al* to enable further study of its cardiovascular, anti-inflammatory and anti-allergic activities (Scheme 1.33).<sup>108</sup> The starting material, **206** was obtained from ( $\pm$ )-3-cyclohexene-1-methanol. Treatment of **206** with TfOH and  $\text{Bu}_4\text{NI}$  at room temperature resulted in formation of tricyclic iodide **207** as a single diastereomer in 73-92 % yield. Elimination with DBU followed by epoxidation with *m*-CPBA achieved epoxide **208** as a single diastereomer in 95 % yield. Epoxide substitution with NaSePh, followed by selenide oxidation / elimination furnished the allylic alcohol **209** with  $\text{H}_2\text{O}_2$  in 81 % yield. Oxidation with TPAP-NMO followed by iodination with  $\text{I}_2$  and  $\text{CCl}_4$  achieved conversion to  $\alpha$ -iodo enone **210** in 84 % yield over two steps. Suzuki coupling with the 9-BBN derived borane **205** and  $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$  gave chain extended amine **211**. Subsequent intramolecular conjugate addition, followed by sequential treatment with TFA and NaOH resulted in formation of the *cis* fused product **212**, after a reaction time of 5 minutes.

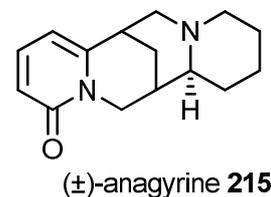
However, if the mixture was left for several days, the 1,2-addition imine product and *trans* fused products were obtained as a 4:1 mixture. Reduction and *N*-protection with 2,2,2-trichloroethyl chloroformate (Troc-Cl) afforded alcohol **213** which then underwent elimination with POCl<sub>3</sub> and deprotection with Cd-Pd and ammonium acetate to give aloperine in 73 % yield.



Conditions: (a) TfOH, nBu<sub>4</sub>NI, CHCl<sub>3</sub>, 73-92%; (b) i. DBU; ii. *m*-CPBA, 95%; (c) i. NaSePh, EtOH, 78°C; ii. H<sub>2</sub>O<sub>2</sub>, THF, rt to reflux, 81 %; (d) i. TPAP, NMO, 90%; ii. I<sub>2</sub>, CCl<sub>4</sub>, pyridine, 93%; (e) borane **205**, PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub>, NaOH, THF, H<sub>2</sub>O, rt, 88%; (f) i. TFA, rt; ii. NaOH, rt; (g) i. LiAlH<sub>4</sub>; ii. Troc-Cl, 70% over 2 steps; (h) i. POCl<sub>3</sub>, pyridine, 100°C; ii. 10% Cd-Pb, 1M NH<sub>4</sub>OAc, 73%.

Scheme 1.33: Overman's synthesis of Aloperine.

The alkaloid (-)-anagryne has been prepared via a number of racemic syntheses which share similarities with van Tamelen and Gallagher's routes to cytosine.<sup>109-111</sup>



### **Section 1.5: Asymmetric Syntheses of $\gamma$ - and $\delta$ - Lactams.**

Enantiomerically enriched  $\delta$ - and  $\gamma$ - lactams are key components in the synthesis and constituents of a number of natural products<sup>112 113</sup> and pharmaceuticals,<sup>114</sup> a key example being (-)-paroxetine, used in the treatment of depression.<sup>115</sup> Methods of synthesis have involved a number of transformations. Enantiomerically pure cyclic sulfamidates have been utilised in the synthesis of  $\delta$ - and  $\gamma$ - membered lactams and piperazines.<sup>116</sup> In one case, AH was utilised in the synthesis of a key sulfamidate which was used in the synthesis of the natural product (-)-aphanorphine.<sup>117</sup> There are a number of examples of transition metal catalysed asymmetric 1,4-conjugate arylations.<sup>118</sup> Ag-catalysed asymmetric Mannich reactions of enol ethers with various imines were employed in the asymmetric synthesis of various lactams and piperidines.<sup>119</sup> A number of organocatalytic methods have also been developed.<sup>120</sup>

### **Section 1.6: Conclusion.**

Although many derivatives and routes to cytosine have been achieved, there are still limitations to these syntheses. Few are versatile for derivatisation, and most are racemic. In a review<sup>45</sup> of the synthetic strategies to cytosine, O'Brien had concluded that, "there is a need to develop an approach to cytosine that delivers a late-stage intermediate that is equipped for analogue preparation." This statement has been quoted numerous times in syntheses and derivatisations. And so, through the new pharmacological insights into the SAR of these receptors, gained from the study by Abin-Carriquiry; and, these limitations in the majority of the available synthetic strategies, it is clear that further study into versatile syntheses of cytosine and its derivatives, is still key to the further development of this therapeutic area.

## Section 2: Results and Discussion.

### Section 2.1: 1<sup>st</sup> Generation Formal Synthesis of (-)-Cytisine: AH of Enamide 1.

#### *Section 2.1.1: Introduction.*

At the outset of this project, the main goal was to complete a divergent asymmetric synthesis of the lupin alkaloids: (-)-cytisine and (-)-sparteine, using transition metal catalysed asymmetric alkene hydrogenation as a means of inducing the desired chirality. More specifically, it was to complete the synthesis and hydrogenation of a common precursor to the alkaloids, which resembled  $\beta$ -disubstituted acylamino acrylates; a class of AH substrates which were reviewed in Section 1.2.4.

The topic of the AH of  $\beta$ -disubstituted acylamino acrylates is an established field with many good examples of substrates which may be reduced with high enantioselectivities. The mechanism of this process is well understood to proceed via the coordination of the chiral catalyst centre to the alkene bond and the carbonyl of the *N*-acyl group, which in the chiral environment of the catalyst may result in enantioselective reduction of the alkene (Figure 2.1.1a). This *N*-acyl group is required for activity; substrates without any coordinating group are reduced with little enantioselectivity. Within this context, the synthesis and hydrogenation of enamides **1** and **216** was investigated as a novel route to a number of potential alkaloid precursors.

Enamides **1** and **216** have the crucial *N*-carbonyl group (within the pyridone ring) adjacent to the alkene bond, and would be predicted to coordinate to the catalyst in a similar manner to  $\beta$ -disubstituted acylamino acrylates (Figure 2.1.1b). This class of

intermediate was to be key to the synthesis of the alkaloids, through the proposed retrosynthetic analysis shown in the next section.

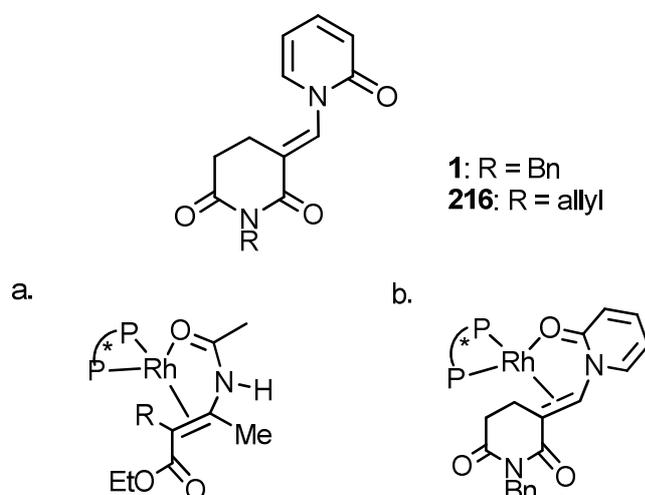
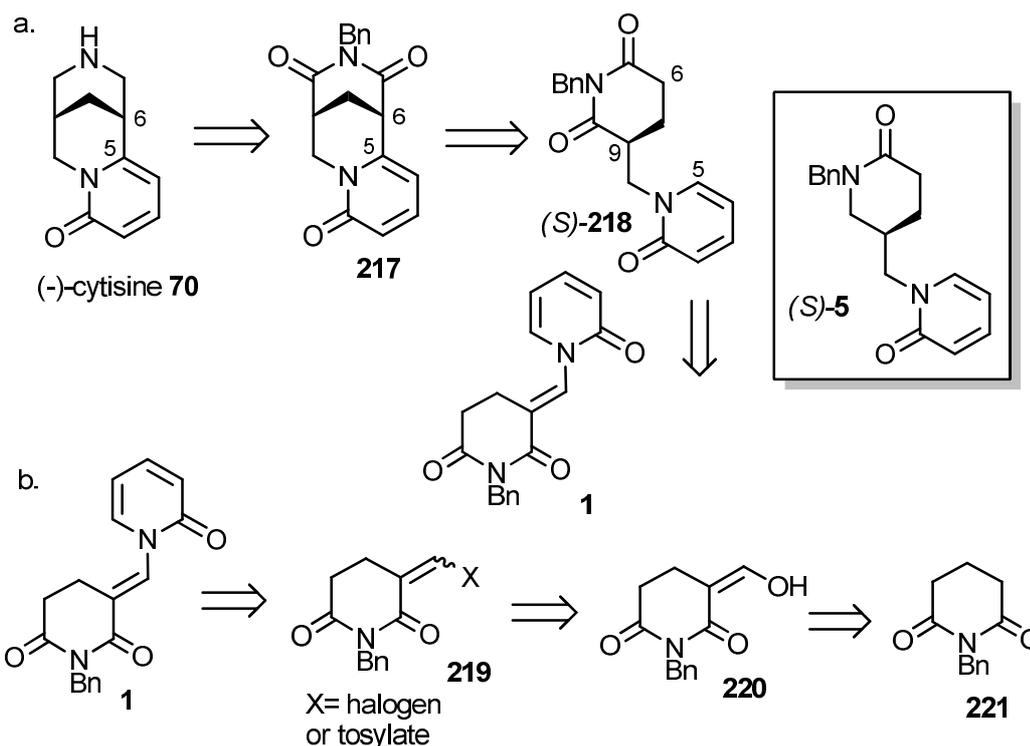


Figure 2.1.1: a. known coordination mode of acylamino acrylates to Rh(I) catalysts; b. proposed coordination mode by enamide **1**.

#### *Retrosynthesis of cytisine.*

The proposed retrosynthesis required disconnection the B ring at the C(5) – C(6) bond of cytisine precursor **217** (Scheme 2.1.1a) in a similar manner to the approaches carried out by Gallagher and Coe. This disconnection reveals glutarimide (*S*)-**218** as an intermediate, and may potentially be achieved through a nucleophilic ring closing substitution involving the formation of an enolate at C(6) in analogy to Gallagher’s method, which involved the corresponding lactam **5**. However, due to the potential for regioselectivity issues upon enolate formation at C(6), involving competing deprotonation at C(9), it may be necessary to carry out the cyclisation through lactam **5**, following the conversion of **218** to **5**. Enantiomerically enriched 5-substituted glutarimide **218** would be formed through AH of the aforementioned enamide **1**.



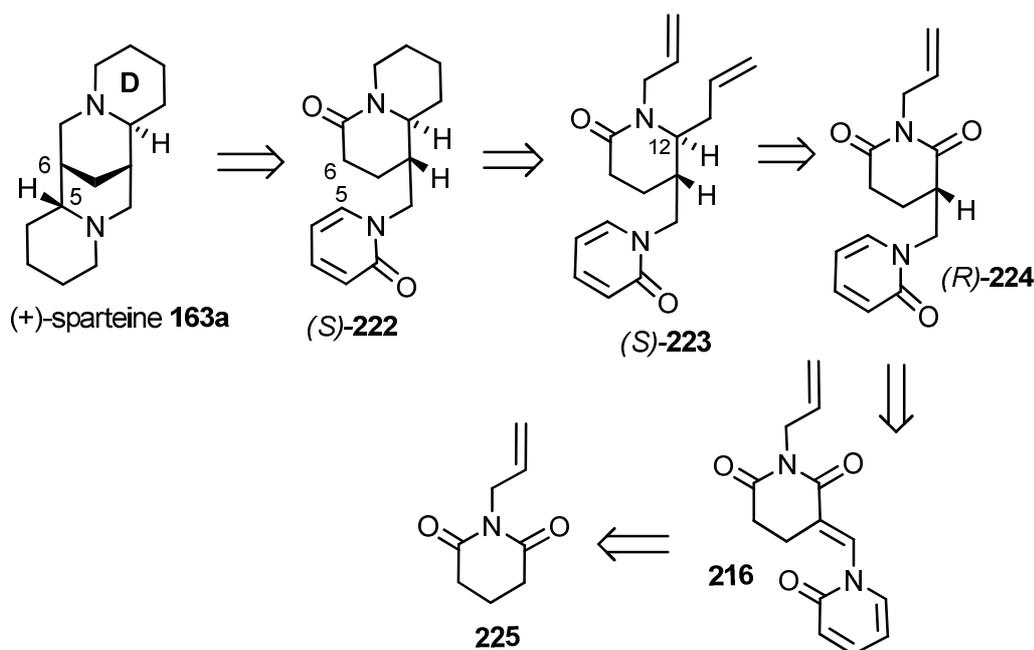
Scheme 2.1.1: proposed retrosynthesis of: a. cytisine **70** and b. enamide **1**.

It was envisaged that enamide **1** could be assembled via Michael addition of 2-hydroxypyridine to enamide derivative **219**, where X is a leaving group such as a halogen or tosylate group (Scheme 2.1.1b). This compound should be readily available from the corresponding precursor alcohol, **220**. Formyl addition was to be achieved from the reaction of *N*-benzyl glutarimide with an appropriate source of formate.<sup>121</sup>

#### *Retrosynthesis of sparteine.*

In a similar manner to the proposed (-)-cytisine synthesis, retrosynthetic analysis of sparteine (+)-**163a** gives compound **222**, through disconnection of the C(5) – C(6) bond (Scheme 2.1.2). The D ring may then be constructed from glutarimide **224** by a known literature method involving imide reduction and subsequent substitution of the *N*-acyliminium intermediate, forming **223**, which may then undergo subsequent ring closure by RCM.<sup>122</sup> (*R*)-**224** may be formed via AH of the aforementioned

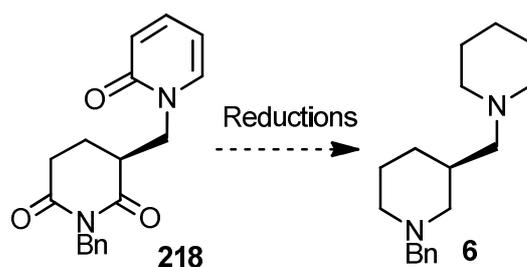
alkene **216**, formed from allyl glutarimide **225**. When multiple olefinic bonds are present in a molecule, catalysts such as Rh-Et-DuPHOS, **229** are known to have high regioselectivity towards enamides over other relatively less chelating alkene bonds. This gives some precedent for the selective reduction of enamide **216** to **223**, without unwanted overreduction of the allyl group.<sup>37</sup>



Scheme 2.1.2: approach to the total synthesis of (-)-sparteine and (-)-anagyrene.

*Underlying methodology – synthesis of 1-(piperidin-3-ylmethyl)piperidine **6**.*

An underlying theme of this project is the methodology of forming enantiomerically enriched 5-substituted glutarimides or lactams. This has been briefly reviewed in the introduction. An interesting extension of the asymmetric synthesis of glutarimide **218** may be the further reduction to 5-substituted piperidine, 1-(piperidin-3-ylmethyl)-piperidine **6** (bispiperidine) (Scheme 2.1.3).



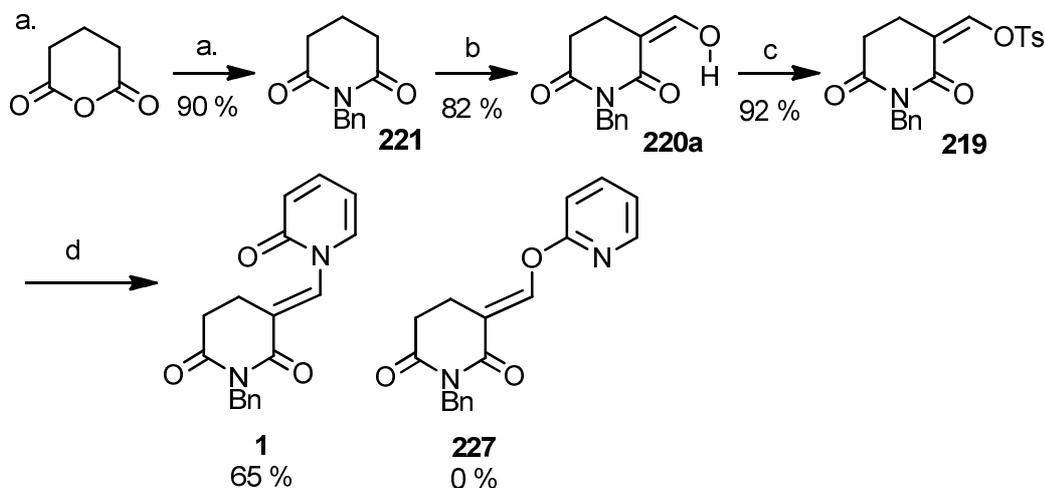
Scheme 2.1.3: formation of 5-substituted piperidine **6**.

### Section 2.1.2: Synthesis and Hydrogenation of Enamide **1**.

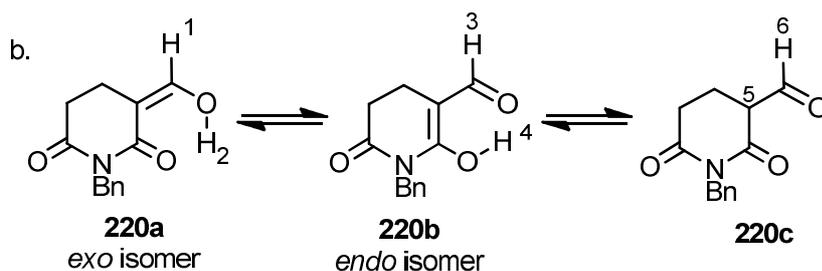
The work in this section began with the synthesis of the key enamide **1**.<sup>\*</sup> Synthesis of the starting material, *N*-benzyl glutarimide was carried out. Ring opening of glutaric anhydride with benzyl amine, in the presence of triethyl amine, formed the intermediate amide-acid,<sup>123</sup> which was subsequently heated in acetyl chloride to promote ring cyclisation, providing *N*-benzyl glutarimide **221** in 90 % (Scheme 2.1.4a). This method was preferred over others.<sup>124 125</sup> The alternative *N*-alkylation of glutarimide was avoided due to the higher price of glutarimide. A microwave and solvent free SiO<sub>2</sub>-TaCl<sub>5</sub> promoted synthesis with glutaric anhydride and benzyl amine was considered but the procedure required the meticulous drying of the reagents and was limited to smaller scale reactions (< 300 mg).<sup>126</sup> Treatment of the sodium ethoxide-generated enolate of glutarimide **221** with ethyl formate, resulted in the formation of enol-imide **220a**, observed (<sup>1</sup>H NMR, CDCl<sub>3</sub>) exclusively as the *exo* resonance form.<sup>127</sup> This assignment was made based upon the large *J* coupling observed between H(1) and H(2) (*J* = 12.3 Hz). Only a trace signal of what may have been the aldehyde proton (H(1) or H(3)) of the *endo* (**220b**) or aldehyde (**220c**) isomers were observed (<sup>1</sup>H NMR, CDCl<sub>3</sub>, δ 9.96, s); no other accurate assignments were possible (Scheme 2.1.4b). A similar transformation with triethylorthoformate was unsuccessful.<sup>128</sup> Tosylation with tosyl chloride and NEt<sub>3</sub> in DCM resulted in

<sup>\*</sup> The synthetic route to enamide **58** was initially developed by Akira Shiibashi, a visiting PhD researcher, during a preliminary study. Subsequent work during this PhD project further developed and optimised the synthetic route.

compound **219** as one isomer; presumably the *Z* alkene isomer based upon the assignment of **220a**, although this was not fully established.<sup>129</sup>



Conditions: (a) i.  $\text{NEt}_3$ ,  $\text{BnNH}_2$ , THF, reflux, 2 d; ii.  $\text{CH}_3(\text{CO})\text{Cl}$ , 2 d  
 (b)  $\text{HCO}_2\text{Et}$ , EtOH, NaH,  $\text{Et}_2\text{O}$ , 0 °C to rt, 18 h; (c)  $\text{NEt}_3$ , TsCl, 0°C to rt, 1h;  
 (d) 2-hydroxypyridine,  $\text{NEt}_3$ , toluene, 110 °C, 20 h.



Scheme 2.1.4: a. synthesis of hydrogenation substrate, **1**; b. isomers of **220**.

The formation of enamide **1** was achieved through a 1,4-addition-substitution of tosylate **219** with 2-hydroxypyridine and  $\text{NEt}_3$ .<sup>130</sup> Due to the binucleophilic nature of 2-hydroxypyridine, substitution at both oxygen and nitrogen sites was observed.<sup>131</sup> During initial reactions (toluene, 110 °C, 10 h) the isomers, *N*-addition product **1** and *O*-addition product **227** were formed as major and minor products respectively in varying yields (Table 2.1.1, entries 1 and 2). These compounds were separable by chromatography, however their  $^1\text{H}$  NMR spectra were ambiguous (these spectra can be seen in Appendix I). These isomers were assigned as the *N*-substituted and *O*-substituted products **1** and **227**, following X-ray diffraction of the two samples

respectively. These structures are shown in Figure 2.1.2. These structures were obtained by Akira Shiibashi.

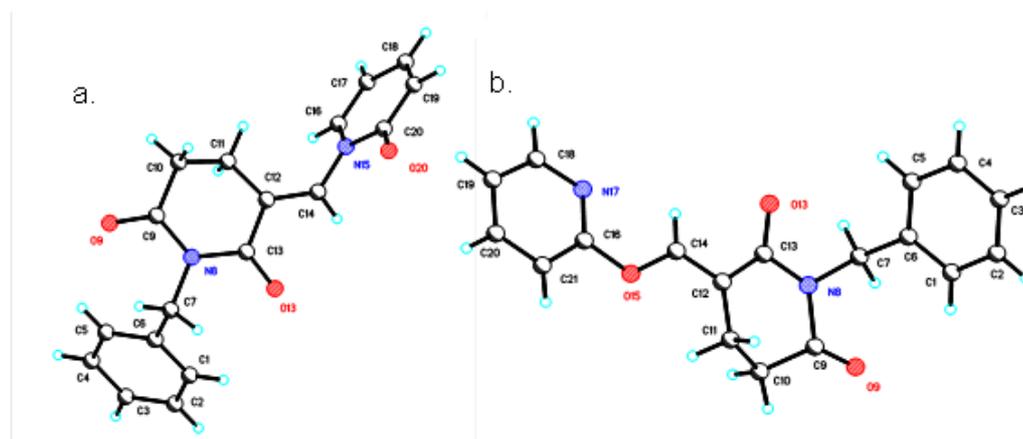


Figure 2.1.2: X-ray structures of: a. *N*-substituted product **1**; b. *O*-substituted product **227**.

Table 2.1.1: 1,4-addition-substitution of tosylate **219** with 2-hydroxypyridine and NEt<sub>3</sub>.

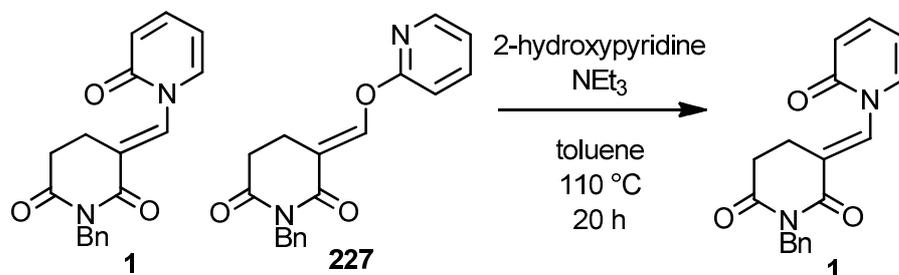
entry	scale / g	<b>1</b> / % <sup>a</sup>	<b>227</b> / % <sup>a</sup>	time (h)
1	0.45	32	12 <sup>a</sup>	10 <sup>a</sup>
2	0.28	75	0 <sup>b</sup>	20
3	1.32	65	0 <sup>b</sup>	20

a. isolated yield; b. determined by <sup>1</sup>H NMR of the crude reaction mixture.

Interestingly, lengthening the reaction time (20 h as opposed to 10 h) was found to result in an absence of *O*-addition product **227** (entries 3 and 4). It is possible that this is the result of a thermodynamic preference towards *N*-substituted product **1**, resulting from isomerisation between **1** and **227** during the reaction. *N*-substituted pyridones are known to be thermodynamically favoured over *O*-substituted isomers. Selectivity towards the formation of *N*-substituted pyridones is also known to occur when the formation of the pyridone is reversible, as is so in this reaction.<sup>167</sup>

To confirm this, an isomerisation experiment was carried out (Scheme 2.1.5): A mixture of **1** and **227** (1.5:1 ratio) and 2-hydroxypyridine, was stirred at 110 °C. After 20 h, the mixture was found only to contain only the *N*-substituted isomer **1** (as determined by <sup>1</sup>H NMR). This showed that during the reaction, isomerisation of **1** to **227** occurs with a preference for the formation of thermodynamic product **1**. During

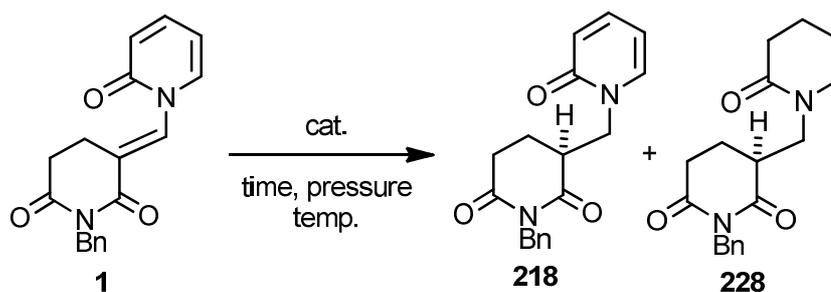
the reaction, the *O*-addition product **227** may be initially formed as a kinetic product which then isomerises to the thermodynamically favoured product **1**. Upon shorter reaction times there is not sufficient time for complete isomerisation to **1**, hence a mixture of the two isomers is observed (entry 1).



Scheme 2.1.5: isomerisation of *N*- and *O*-substituted products

#### *AH of enamide 1.*

With enamide **1** in hand, the AH was carried out (Scheme 2.1.6, Table 2.1.2). Enamide **1** underwent Pd/C mediated hydrogenation under 5 bar of hydrogen resulting in complete reduction of the alkene bond and pyridone ring to give the fully reduced imide **228** (entry 1). This overreduction of the pyridone ring was overcome by ceasing the reaction after 30 min under a balloon of hydrogen (entry 2). Due to the high polarity of the two products, some difficulty was experienced in the removal of palladium from the sample following silica gel chromatography (it was necessary to prepare metal-free samples to prevent high performance liquid chromatography (HPLC) column damage). These racemic hydrogenation products were later used as standards in the chiral HPLC analysis of AHs. Noting this potential overreduction, the AH was carried out with, [Rh((*R,R*)Et-DuPhos)COD]BF<sub>4</sub> ‘(*R,R*)-RhDuPHOS’, (*R,R*)-**229**.<sup>37</sup> The <sup>1</sup>H NMR spectra of the crude reaction mixtures obtained with this catalyst were clean, with only trace amounts of side products. The catalyst is easy to handle and air sensitivity is only an issue when the catalyst is in solution. It was, however, necessary to dry the substrate with MgSO<sub>4</sub> before use.



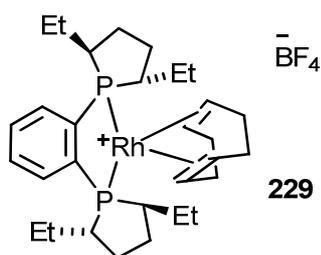
Scheme 2.1.6: hydrogenation of **1**.

Table 2.1.2: hydrogenation of **58**.

entry	scale (mg)	cat.	mol (%)	P (bar)	temp. (°C)	time	<b>218</b> (%)	<b>228</b> (%)	ee of <b>218</b> (%) <sup>c</sup>
1	50 <sup>d</sup>	Pd/C	5	5	RT	12 h	0	100	N/A
2	30 <sup>a</sup>	Pd/C	10	1	RT	30 min.	100	0	N/A
3	70 <sup>a</sup>	( <i>R,R</i> )- <b>229</b>	3	25	30	5 d	89	11	89 ( <i>S</i> )
4	110 <sup>a</sup>	( <i>R,R</i> )- <b>229</b>	3	25	30	5 d	60	40	93 ( <i>S</i> )
5	140 <sup>a</sup>	( <i>R,R</i> )- <b>229</b>	3	25	30	5 d	89	11	94 ( <i>S</i> )
6	800 <sup>a</sup>	( <i>R,R</i> )- <b>229</b>	3	25	RT	5 d	100	0	90 ( <i>S</i> )

a: [substrate] = 0.25 M; b: determined by <sup>1</sup>H NMR; c: indirectly determined by analysis of **228**;

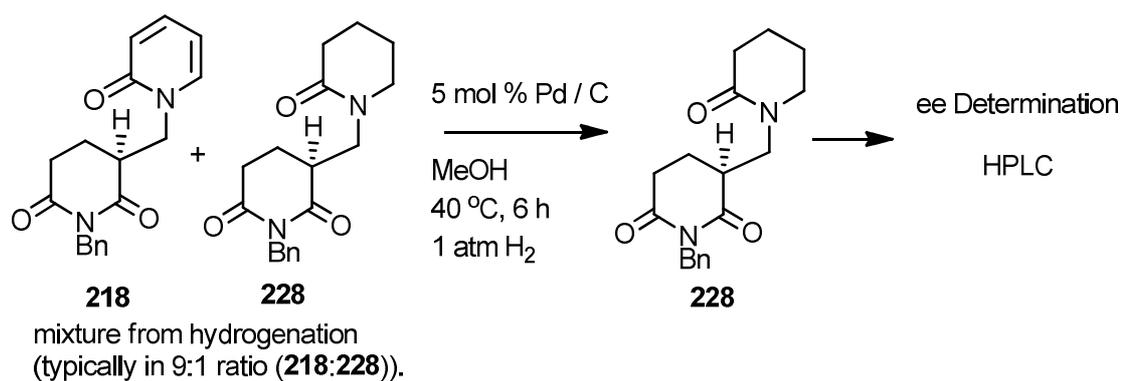
d: [substrate] = 0.06M.



The optimum reactions conditions to achieve complete conversion of the starting material and minimal overreduction are shown in entries 3-6; however fully reduced lactam **228** was generally always observed as a minor product in varying amounts. In the case of entry 6, only a trace of lactam **228** was observed.

During analysis by chiral HPLC it was found that the two compounds, **218** and **228** could not be resolved, preventing accurate determination of ee. To overcome this, steps were taken to indirectly determine the ee of **218** through a new procedure. The inseparable reaction mixture of **218** and **228** was hydrogenated with Pd/C, resulting in the full conversion of **218** to lactam **228** (Scheme 2.1.7). The ee of this new sample of **228** was then determined by HPLC, and taken as an indirect measurement

of the ee of compound **218**. This method assumed that **218** was a precursor of lactam **228** during the AH, and that the two products were formed in the same ee. This procedure was routinely used as the indirect method of ee determination of imide **218**. In each case the ee was consistently high, ranging from 89 – 94 % ee even at larger scales of 800 mg. This was very encouraging and showed that this class of enamides could be enantioselectively reduced in the way predicted.



Scheme 2.1.7: Method of indirect ee determination.

A sample of **218** (90 % ee) containing trace amounts of lactam **228** was obtained in high purity. Recrystallisation (DCM and hexane) provided crystals which were submitted for X-ray diffraction to confirm the structure (Figure 2.1.3). Interestingly, the crystal selected for analysis was actually racemic (determined by the diffraction pattern). This prevented the determination of absolute configuration. Presumably, racemic crystals from both enantiomers, are formed more readily than crystals formed from only one enantiomer.

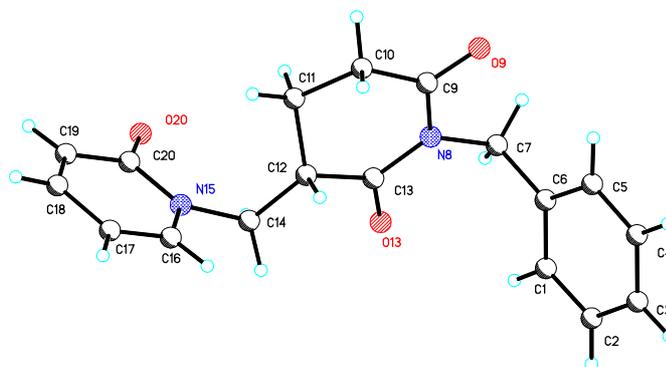
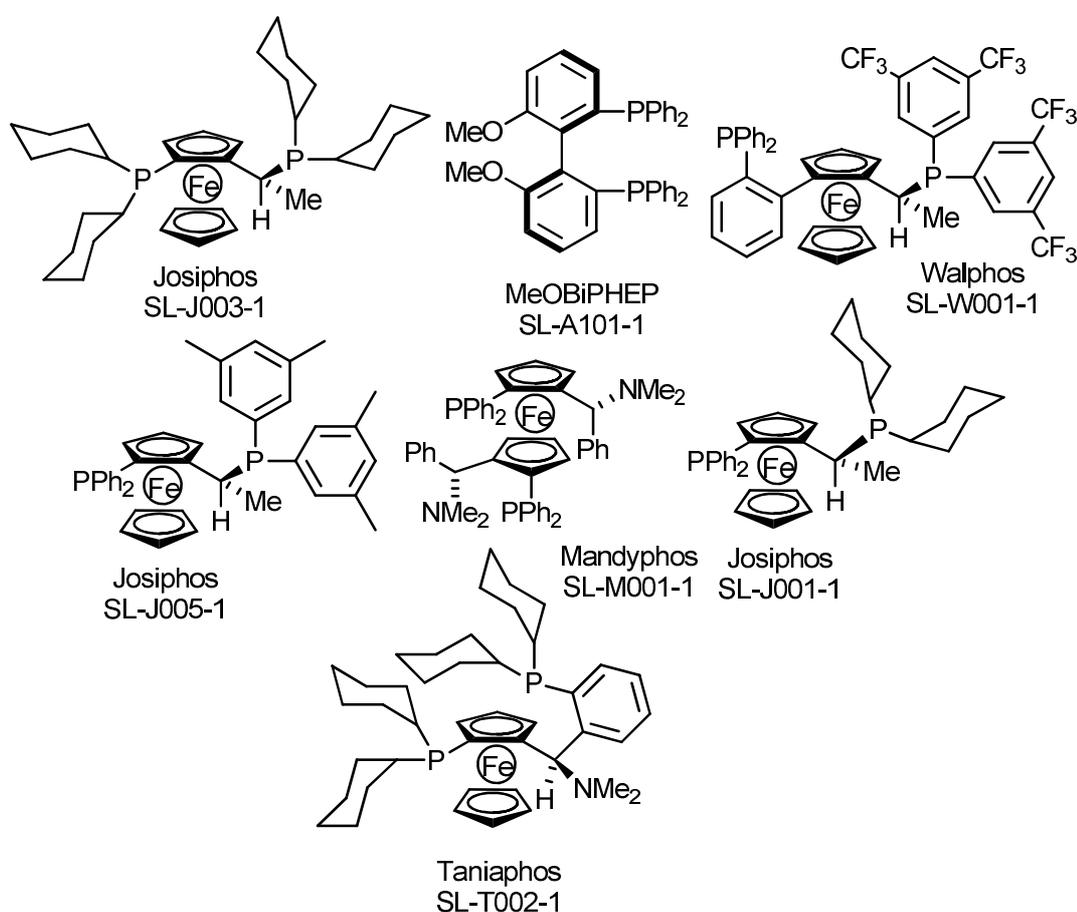


Figure 2.1.3: refined X-ray structure of **218**.

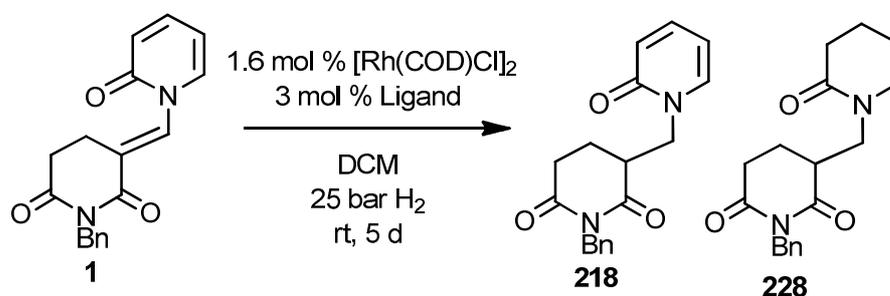
*AH catalyst screen.*

With these results in hand, further screening of the AH was carried out. A range of phosphine ligands were obtained for research purposes through a collaboration with the fine chemicals company *Solvias*. These included ligand derivatives of the following types: Taniaphos, Josiphos, Walphos, Mandyphos, and MeOBiPhep. Details on the background and use of these in asymmetric alkene hydrogenation were reviewed in the introduction.



To enable comparison to the earlier reductions with (*R,R*)-Rh-Et-DuPHOS (*R,R*)-**229**, reactions were carried out under equivalent conditions, except the temperature was reduced from 30 °C to ambient room temperature (20-22 °C) (in the past there were problems of maintaining a consistent temperature throughout the duration of the reaction). Experiments were performed on a 30 mg scale. The catalyst was

formed *in situ* by combination of the phosphine ligand with  $[\text{Rh}(\text{COD})\text{Cl}]_2$ , according to a literature procedure.<sup>132</sup> DCM was used as solvent due to insolubility of the alkene in methanol. Conversion was determined by  $^1\text{H}$  NMR. At this point, it was found that at a lower scale (30 mg), the hydrogenation products imide **218** and lactam **228** could be separated (silica gel chromatography, slow elution). This enabled the ee of the each product to be separately determined by direct HPLC analysis. The method used to determine the absolute configuration of compounds **218** and **228** will be discussed in a later section.



Scheme 2.1.8: Asymmetric ligand screen.

Table 2.1.3: Hydrogenation of **1** with various asymmetric ligands.

entry	ligand	ligand type	conv. <sup>a</sup> (%)	<b>218</b> (%) <sup>a</sup>	<b>218</b> ee (%) <sup>b</sup>	<b>228</b> (%) <sup>a</sup>	<b>228</b> ee (%) <sup>b</sup>
1	SL-T002-1	Taniaphos	100	trace	N/A	100	98 ( <i>R</i> ) <sup>d</sup>
2	( <i>R,R</i> ) Et-DuPhos <sup>c</sup>	DuPhos	82	82	91 ( <i>S</i> ) <sup>e</sup>	0	N/A
3	SL-J001-1	Josiphos	42	42	76 ( <i>R</i> ) <sup>e</sup>	0	N/A
4	SL-J003-1	Josiphos	56	56	87 ( <i>S</i> ) <sup>e</sup>	0	N/A
5	SL-W001-1	Walphos	47	27	N/O	20	13 ( <i>R</i> ) <sup>d</sup>
6	SL-M001-1	Mandyphos	100	40	N/O	60	17 ( <i>R</i> ) <sup>d</sup>
7	SL-J005-1	Josiphos	0	0	N/A	0	N/A
8	SL-A101-1	MeOBiPhep	9	9	N/O	0	N/A

a. determined by  $^1\text{H}$  NMR; b. determined by chiral HPLC; c.  $[\text{Rh}((R,R)\text{Et-DuPhos})\text{COD}]\text{BF}_4$  used as catalyst; d. direct analysis of **228** following isolation; e. direct analysis of **218**; N/O = not obtained; N/A = not applicable.

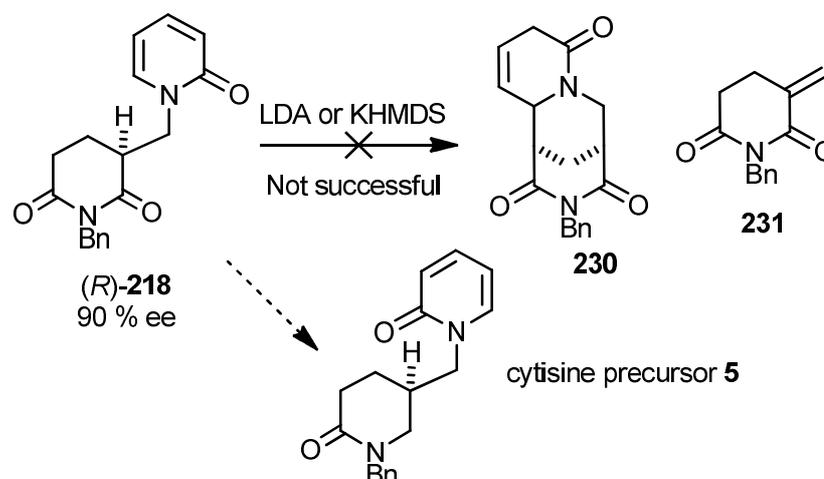
The results of the ligand screen are shown above in Table 2.1.3. Use of the Josiphos and Taniaphos ligands (entry 1, 3 and 4) resulted in high enantioselectivity (Scheme 2.1.8). Entry 1 shows major over-reduction to **228**. In relation to the synthesis of bispiperidine **6** (Scheme 2.1.3), this result was very encouraging. This is discussed further in Section 2.1.3. Inversely, despite the high selectivity obtained with the

Josiphos ligands (entry 3 and 4), these reactions show low consumption of the starting material. With the long reaction time (5 days), there is limited scope for further optimisation. The reduction with (*R,R*)-RhDuPhos on this low scale (30 mg) gave incomplete conversion of the starting material, whereas at larger scales (> 50 mg, see Table 2.1.2) under the same conditions conversion is closer to 100 %.

In conclusion, these results were very encouraging and showed that this class of enamide was effective as an AH substrate as predicted, and a novel method for the preparation of 5-substituted glutarimides with particular relevance to the synthesis of cytosine. This work was subsequently published.<sup>178</sup>

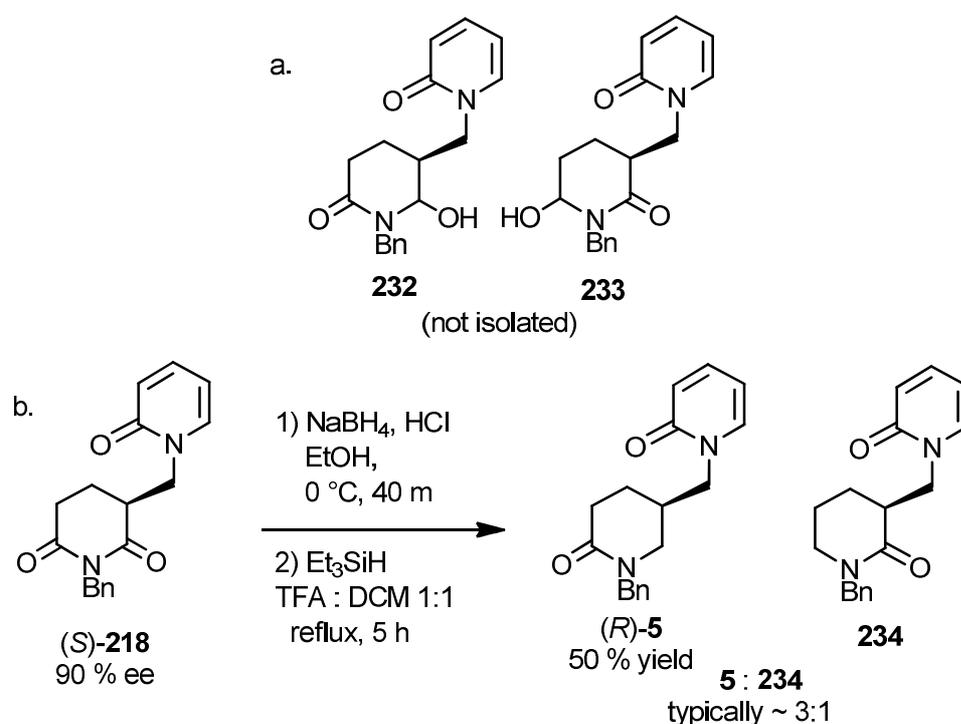
### Section 2.1.3: Completion of the Formal Synthesis of (-)-Cytosine.

The project then moved on to the utilisation of 5-substituted glutarimide **218** in an asymmetric synthesis of cytosine. The first approach involved attempted conversion to cytosine precursor **230** via base-induced cyclisation (Scheme 2.1.9). Pyridone **218** was treated with a series of bases, however only the elimination product **231** was obtained and there was no evidence for formation of the cyclised adduct **230**.



Scheme 2.1.9: attempted cyclisation and conversion to cytosine precursor **5**.

From this point, the most obvious route to completion was reduction of the imide to the cytosine precursor, lactam **5** (Scheme 2.1.10). This compound was used as a cyclisation precursor in Gallagher's 2<sup>nd</sup> generation synthesis (Section 1.3.2, Scheme 1.15). There is a large amount of related literature for similar carbonyl reductions.<sup>133</sup> This reduction was initially attempted with a number of reductants, notably NaBH<sub>4</sub> and HCl; and LiAlH<sub>4</sub>. According to the literature, regioselective reduction of imides may be carried out with NaBH<sub>4</sub> and HCl. HCl is thought to promote the reaction by either the *in situ* generation of BH<sub>3</sub>; or by activation via protonation of the imide carbonyl.<sup>133c,134</sup> Indeed, this affect was observed experimentally, when the imide was treated with NaBH<sub>4</sub> and HCl was added periodically to maintain a pH of approximately 7, resulting in the formation of the  $\alpha$ -hydroxylactam isomers **232** and **233**. The reaction was inconsistent, with conversions widely ranging from 30 to 69 % (determined by <sup>1</sup>H NMR). No attempt was made to isolate the  $\alpha$ -hydroxylactam isomers **232** and **233**.<sup>122</sup>



Scheme 2.1.10: Reduction of **218** to cytosine precursor **5**.

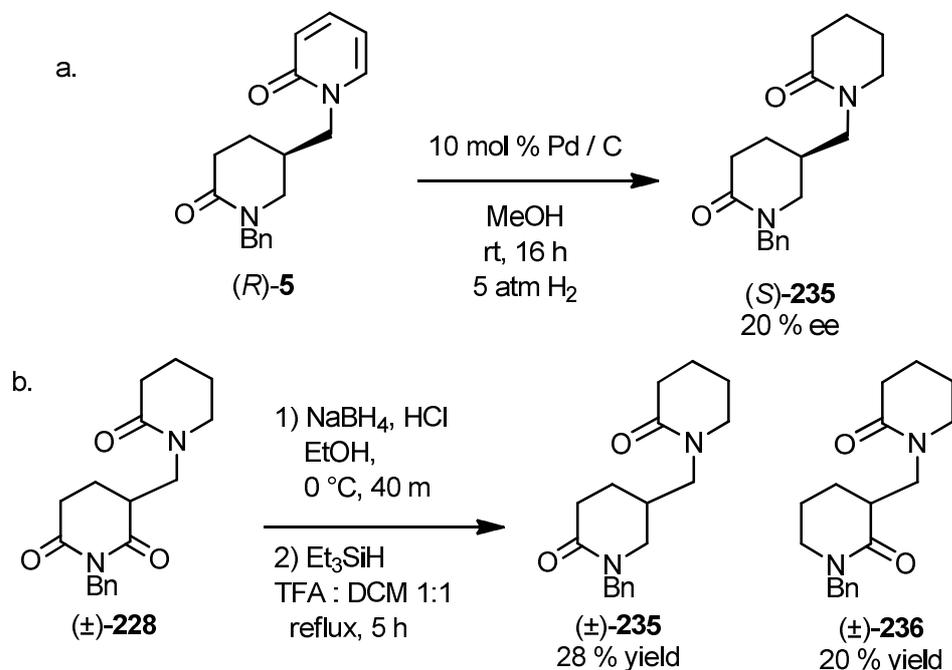
Instead, the crude reaction mixture was treated with TFA and triethylsilane to give a sample of lactam **5** and what is thought to be an inseparable mixture of the second regioisomer **234** and unreacted starting material, following purification (silica gel chromatography).<sup>135</sup> The formation of this inseparable mixture prevented full analysis of the supposed regioisomer **234**, although the <sup>1</sup>H NMR spectrum was in agreement with its identity.

At best, the obtained yield of the two step transformation of **218** to the known compound **5** in pure form was 50 %, although this has been inconsistent. Typically compound **5** was obtained in ~3:1 regioselectivity over the regioisomer **234**. Compound **5** is a precursor to (-)-cytisine following the synthesis completed by Gallagher and its synthesis secured the formal synthesis of cytisine. The optical rotation of a sample of compound **5** derived from the reduction with (*R,R*)-RhEt-DuPHOS), (*R,R*)-**229** was shown to be + 8.8 (*c*0.7 in CHCl<sub>3</sub>, 25 °C). Comparison with the literature value <sup>68</sup> ( $[\alpha]_{\text{D}}^{24} = + 31.3$ , *c*0.8 in CHCl<sub>3</sub>), 98 % ee) enabled the assignment of the absolute configuration of compound **5** as *R*. Retrospectively, the absolute configuration of the precursors of compound **218** have also been assigned.

#### *Determination of the ee of compound 5.*

Following the imide reduction of **218**, it was necessary to determine the ee of compound **5** to determine whether the compound had retained its high enantiopurity. This was carried out by the HPLC analysis of a hydrogenated (Pd/C) sample of **5** (derived from a sample of **218** from the reduction with (*R,R*)-Rh-Et-DuPHOS (*R,R*)-**229**; established to be of 90 % ee) using the racemic standard, **235** (Scheme 2.1.11a). At the time this work was carried out, this method was favoured over direct ee

determination of **5** because of the ease of accessing the racemic standard **235**. Racemic standard **235** and regioisomer **236** were formed by the NaBH<sub>4</sub> / Et<sub>3</sub>SiH reduction of compound (±)-**228** (Scheme 2.1.11b).

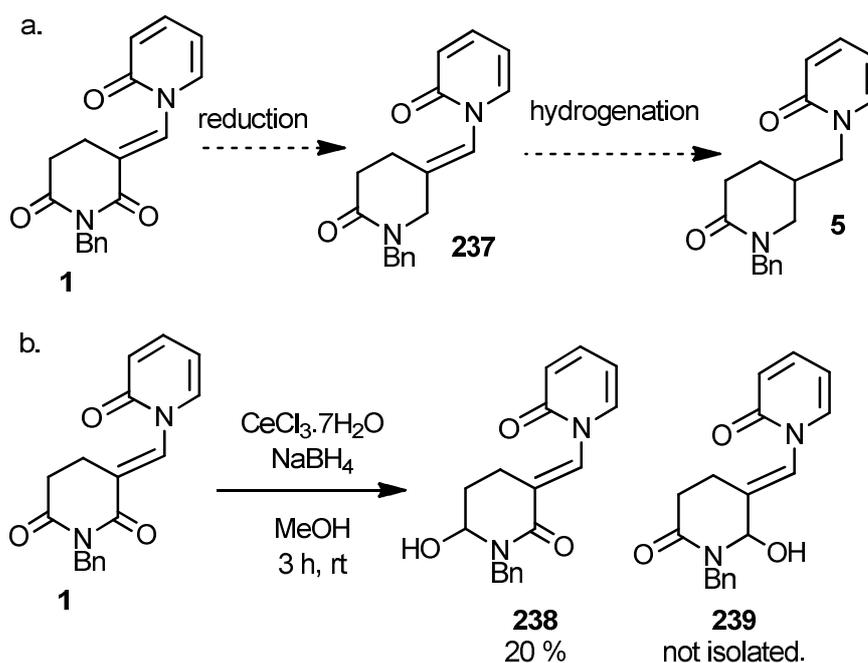


Scheme 2.1.11: a. Hydrogenation of (*R*)-**5** for HPLC analysis;  
b. Synthesis of racemic standard (±)-**235**

Unfortunately, HPLC analysis showed that the ee of compound **5** was only 20 %. Its precursor, compound **218** had an ee of 90 %. This showed that partial racemisation had taken place during the imide reduction.<sup>122</sup> A similar result was obtained following the LiAlH<sub>4</sub> mediated reduction of imide (*S*)-**218** (95 % ee) at – 78°C: following the formation of the α-hydroxylactam and subsequent reduction with Et<sub>3</sub>SiH and TFA, lactam **5** was obtained in 35 % yield and 13 % ee (the same indirect ee determination method by HPLC was used through reduction and analysis of **235**). The reducing agents BH<sub>3</sub>.SMe<sub>2</sub>, NaCNBH<sub>3</sub>, DIBAL-H and NaBH(OAc)<sub>3</sub> were unsuccessful for this reduction.

### Luche reduction of enamide **1**.

In a final effort to prepare lactam **5** without a loss of enantioselectivity, a second approach was considered via the synthesis and hydrogenation of alkene **237** (Scheme 2.1.12a). This alkene possessed the required functionality for efficient asymmetric reduction. It was thought that this alkene could be reached via the reduction of enamide **1**. Reduction was attempted with NaBH<sub>4</sub> and HCl but was unsuccessful; however treatment with CeCl<sub>3</sub>·7H<sub>2</sub>O and NaBH<sub>4</sub> following Luche type conditions<sup>136</sup> resulted in the formation of the unwanted isomer, α-hydroxylactam **238**. Other reduction products were identified in the crude reaction mixture (<sup>1</sup>H NMR) but α-hydroxylactam **238** was the only isolatable product, and the desired compound was not identified in any form.



Scheme 2.1.12: a. Potential synthesis and hydrogenation of alkene **237**; Luche type reduction of **1**.

Successive purification (silica gel chromatography, followed by preparative reverse phase HPLC, Waters XBridge Prep C<sub>18</sub> OBD column) provided α-hydroxylactam **238** in 20 % yield as colourless needles which were analysed by X-ray crystallography to confirm the structure, which is shown in Figure 2.1.4. The higher

stability of the carbonyl within the conjugated enamide system over the isolated carbonyl may have favoured reduction of the non-conjugated carbonyl bond.

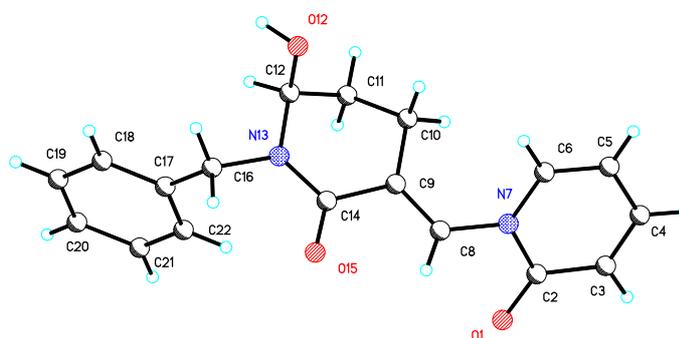
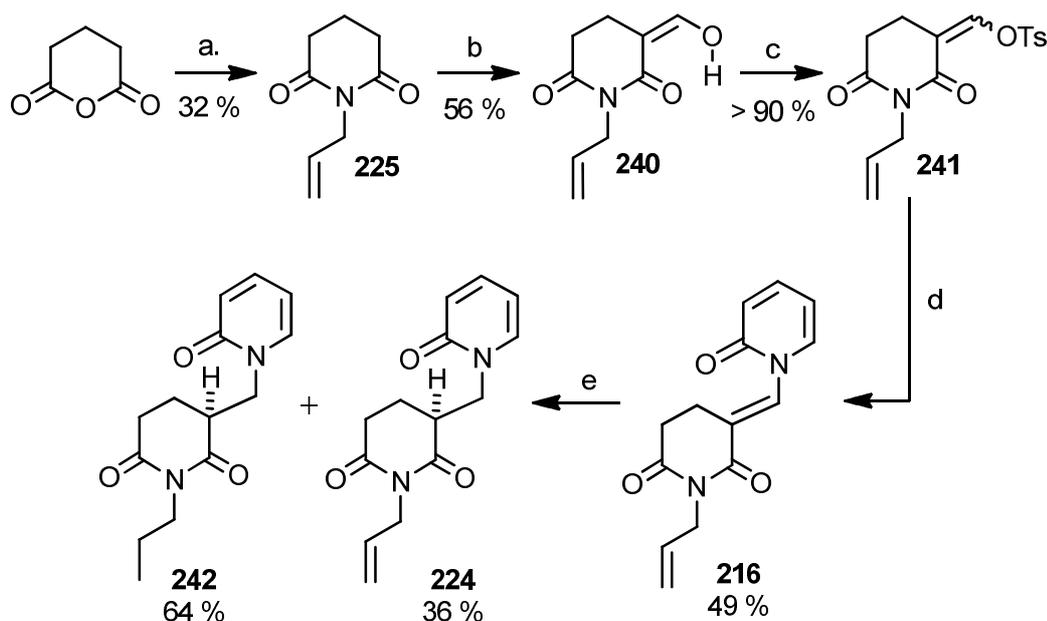


Figure 2.1.4: X-ray crystallographic structure of **238**.

#### *Section 2.1.4: The Attempted Synthesis of (-)-Sparteine.*

The synthesis of sparteine precursor, enamide **216** was carried out through a variation of the cytosine precursor route, using *N*-allyl glutarimide **225** as starting material. The synthesis is shown in Scheme 2.1.13.

Following the synthesis of alkene **216**, the AH was found to result in formation of an inseparable mixture of what was characterised to be the overreduction product **242** and the desired reduction product **224** in 64 % and 36 % yields respectively (as determined by  $^1\text{H}$  NMR).<sup>137</sup>



**Reagents and conditions:** a. i.  $\text{NET}_3$ , Allyl amine, THF, reflux, 2 d; ii.  $\text{CH}_3(\text{CO})\text{Cl}$ , 1 d  
 b.  $\text{HCO}_2\text{Et}$ , cat. EtOH, NaH,  $\text{Et}_2\text{O}$ , 0 °C to rt, 18 h; c.  $\text{NET}_3$ , TsCl, 0°C to rt, 1h; d.  
 2-hydroxypyridine,  $\text{NET}_3$ , toluene, 110 °C, 20 h; e. 3 mol %  $[\text{Rh.EtDuPHOS}]$ , 25 bar  $\text{H}_2$ ,  
 30 °C, 5 d.

Scheme 2.1.13: Synthesis and hydrogenation of **216**

Consequently, no further time was spent trying to optimise this hydrogenation. By this stage in the project, it also became clear that the substrate used in this route would probably also have undergone the same epimerisation that had occurred in the cytosine synthesis, preventing the proposed asymmetric synthesis.

#### *Summary and conclusions.*

On one note, the AH of enamide **1** was highly successful, achieving the formation of glutarimide **218** in up to 94 % ee. This work was subsequently published.<sup>178</sup> A formal synthesis of cytosine was achieved, but the inability of glutarimide to undergo cyclisation, and the late stage epimerisation upon conversion to lactam **5** prevented the asymmetric synthesis from being achieved. These same underlying problems combined with overreduction of the allyl group also prevented the success of the asymmetric synthesis of sparteine.

#### *Section 2.1.5: Future Work.*

##### *The proposed synthesis and hydrogenation of pyridone 2.*

At this point in the project, the focus moved towards a second strategy for completing an asymmetric formal synthesis of cytosine, through the formation of the precursor lactam **5**. This strategy required a 5-substituted pyridone bearing a proximal coordinating group to be asymmetrically reduced in high enantioselectivity, to give a product that could be converted to the cytosine precursor. More specifically, the synthesis and AH of pyridone **2** was considered (see Scheme 2.3.1). If successful, the resulting 5-substituted lactam **274** could be converted to the cytosine precursor lactam **5** through a known route. A more detailed explanation of this proposal and the results and discussion are given in Section 2.3.

##### *The synthesis of bispiperidine 6.*

With the formation of lactam (*S*)-**228** in 98 % ee, reduction to the saturated piperidine is a unique method of forming 5-substituted piperidine **6**. This work is continued in Section 2.4.

##### *ATH of enamide 1 and 216.*

Before moving on to the newly proposed research topics discussed in the last two paragraphs, the next section in this chapter will briefly cover an ATH study of the enamides **1** and **216**.

## Section 2.2: ATH of Enamides, $\beta$ -(Acylamino)acrylates, Tetramic acids and 5-Acetylracil.

Due to the highly polarised alkene bond within enamides **1** and **216**, during the course of this study, these compounds were also considered as potential substrates for alkene ATH. There are numerous examples of the transfer hydrogenation of alkenes in the literature<sup>138</sup>; however, there are few asymmetric examples.<sup>139 140</sup> This may have provided an alternative route to the formation of their corresponding 5-substituted glutarimides. This topic led on to the second and third parts of this section, in which the ATH of related  $\beta$ -substituted  $\alpha,\beta$ -unsaturated carbonyl derivatives (**243**, **244**, Figure 2.2.1) was also carried out. In the final section, the ATH of 5-acetylracil **245** was carried out. This work was not directly related to the work outlined in this introduction, but the unexpected result was interesting and seemed to be related to the subject of the transfer hydrogenation of alkene bonds. This section begins with an interesting result obtained involving the ATH of enamides **1** and **216** which were both active to reduction by the catalyst.

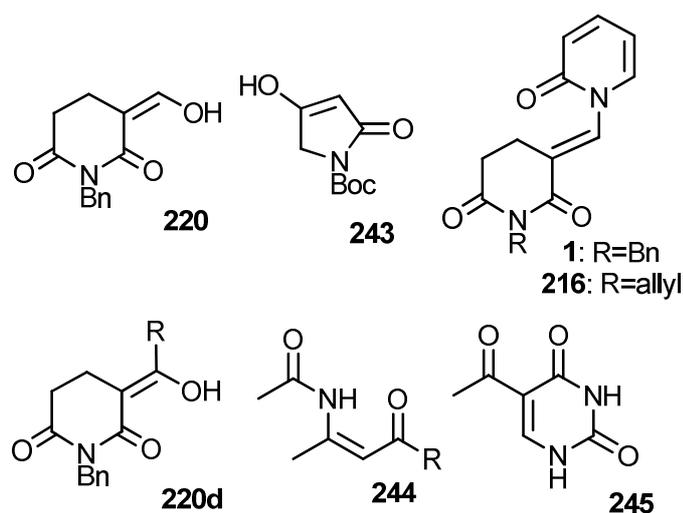


Figure 2.2.1: Compounds considered in this section.

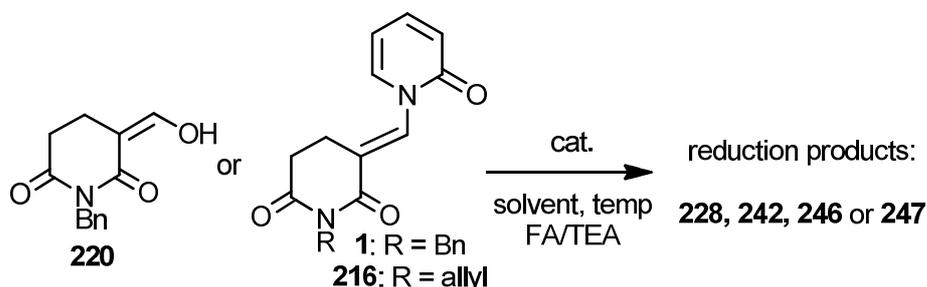
### *Section 2.2.1: ATH of Enamides.*

When the ATH of **1** was carried out with 3 mol % (*R,R*)-RutethTsDPEN **248**, full conversion to glutarimide **228** (Figure 2.2.2) was observed over a period of 5 days, with varying solvents: tBuOH, IPA and ethanol (Scheme 2.2.1 and 2.2.2, Table 2.2.1, entries 2, 3 and 4). In one case (entry 4), the ee of the sample was determined, however the sample was found to be racemic (for details of the chiral separation, see Section 2.1.2). To determine if this absence of ee may have been the result of subsequent epimerisation following the formation of the chiral centre in high ee, a control experiment was carried out. A sample of (*R*)-**228** (95 % ee) in ethanol and FA/TEA was stirred for 5 days (the same conditions as the results from Table 2.2.1), after which the ee of the sample was reanalysed to show no significant change. This confirmed that the ee of the reaction was in fact 0 % and that subsequent loss of ee had not occurred during the reaction. Two mechanistic possibilities for this reduction are shown later in this section, which provide an explanation for the lack of enantioselectivity.

When methanol was used as solvent in the reduction of allyl derivative **216** (entry 1), ring opening occurred, forming **247** alongside an impure sample of reduction product **242**, in an approx. 1:1 ratio. This was most likely to have resulted from FA/TEA catalysed methanolysis of the imide group, although ruthenium Lewis acid based catalysts are known.<sup>141</sup>

Interestingly, a small enantioselectivity was observed in the reduction of enol imide **220**. The ATH of enol imide **220**, resulted in complete conversion to alcohol **246** in 31 % ee (the absolute configuration was not determined) (chiral separation was

determined by Chiralpak IA, hexane : IPA 95:1, flow rate = 1 mL/min) (entries 6 and 7) following a reaction time of 16 h at 28 °C.



Scheme 2.2.1: ATH of enamides **1**, **216** and **220**.

Table 2.2.1: ATH of enamides.

entry	substrate <sup>a,b</sup>	cat./mol %	sol.	time	temp. (°C)	prod.	Conv.	ee <sup>d</sup>
1	<b>216</b>	( <i>R,R</i> )- <b>248</b> 2 mol%	MeOH	3 d	30	<b>242</b> <b>247</b>	1:1 >99	- -
2	<b>1</b>	( <i>R,R</i> )- <b>248</b> 3 mol%	tBuOH	5 d	30	<b>228</b>	>99	-
3	<b>1</b>	( <i>R,R</i> )- <b>248</b> 3 mol%	IPA	5 d	30	<b>228</b>	>99	-
4	<b>1</b>	( <i>R,R</i> )- <b>248</b> 3 mol%	EtOH	5 d	rt	<b>228</b>	>99	0 %
5	<b>1</b>	<b>249</b> 2 mol%	EtOH	5 d	28	<b>228</b>	>99	-
6	<b>220</b>	( <i>R,R</i> )- <b>248</b> 2 mol%	MeOH	16 h	28	<b>246</b>	>99	32 %
7	<b>220</b>	( <i>S,S</i> )- <b>248</b> 2 mol%	MeOH	16 h	28	<b>246</b>	>99	32 %

a. 0.6 M; b. 0.5 cm<sup>3</sup> FA/TEA / mmol SM; c. determined by <sup>1</sup>H NMR; d. determined by chiral HPLC.

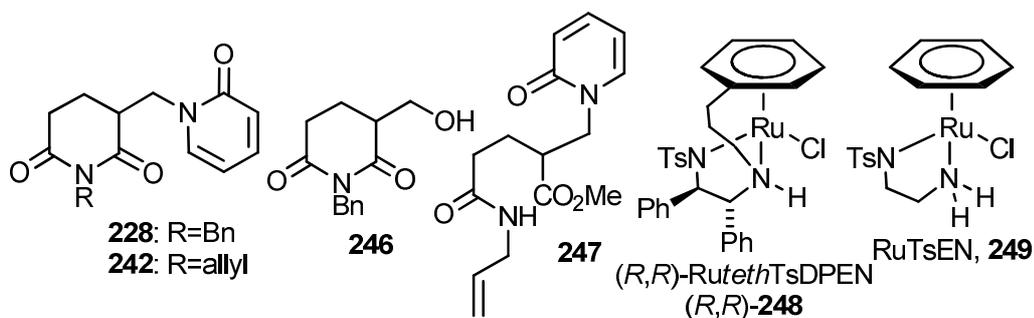
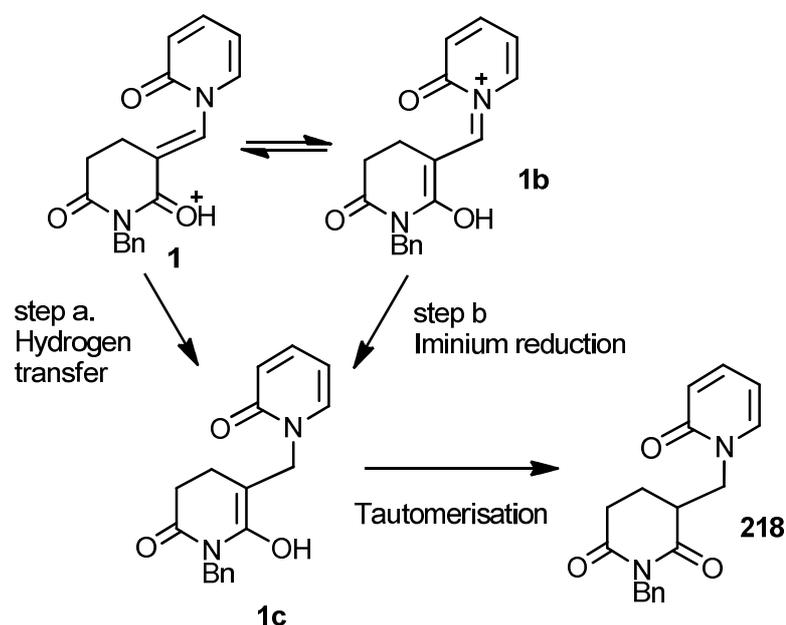


Figure 2.2.2: ATH products and catalysts.

### Discussion.

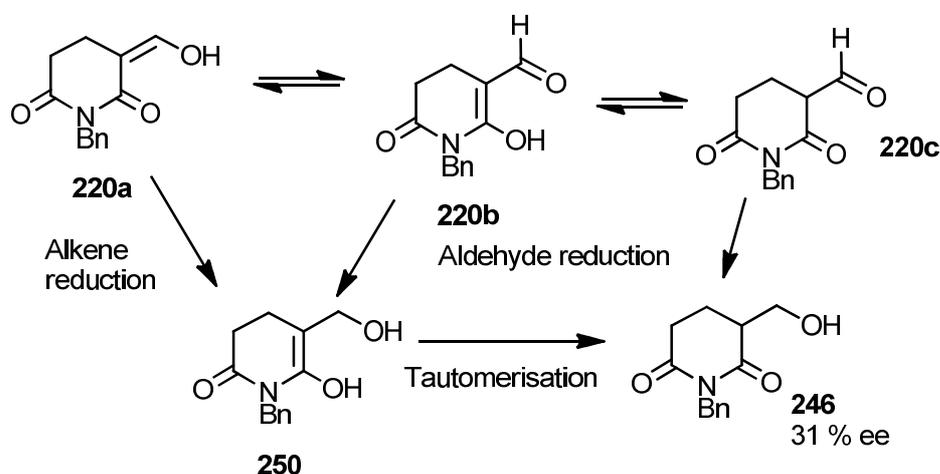
There are two possible ways in which reduction of **1** could take place (Scheme 2.2.3): 1) 1,4-conjugate hydrogen transfer may take place which has been reported for similarly polarised alkenes.<sup>139</sup> 2) Reduction proceeds through the resonance form **1b** (step b). In both steps, enol **1c** would be formed, which may then undergo tautomerisation to give the product **218**. Some cases in the literature have reported

directed asymmetric protonations. From these results the exact mechanism is not evident.



Scheme 2.2.3: two possible mechanisms for the reduction of **1**.

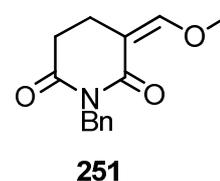
Enol imide **220a** can also exist in the tautomeric forms **220b** and **220c** (Scheme 2.2.4). All three of these isomers may potentially undergo reduction by the catalyst.



Scheme 2.2.4: Possible mechanisms for the reduction of tautomers **220a**, **220b** and **220c**.

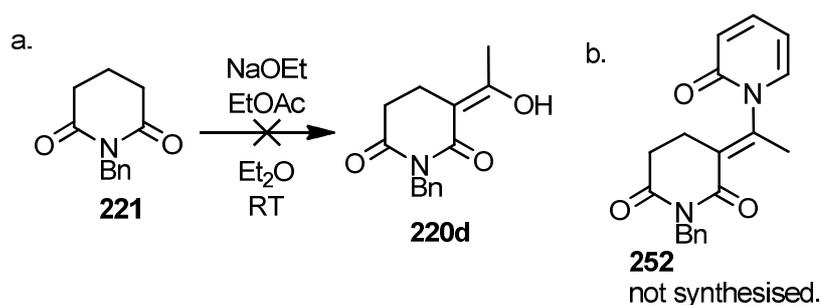
Reduction of **220a** or **220b** would both result in formation of enol **250**, which may subsequently undergo tautomerisation to give the product **246**. Alternatively the reduction of tautomer **220c** may take place through a kinetic resolution (KR) resulting in the formation of product **246**.

The low ee obtained in the formation of **246** may have resulted from a poorly controlled asymmetric protonation of **250** or from the KR of **220c**. However since seeing **218** was formed racemically via the corresponding enol **1c**, the comparison between **250** and **1c** could be made to suggest that tautomerisation of **250** by this route would also be unselective. This would suggest that the origin of the low enantioselectivity was from the reduction of **220c**. But not enough evidence is available for any firm conclusion to be made. The ATH of enol ether **251** was considered, however the compound could not be prepared.



*Summary.*

The natural progression of this work would have led to the synthesis and ATH of  $\beta$ -substituted derivatives of **220d** or **252**, in order to create a new chiral centre proximal to the alcohol. The synthesis of **220d** was attempted following a modified procedure of forming **220a**, using ethyl acetate (Scheme 2.2.5), but this was unsuccessful and prevented this series from being assessed.



Scheme 2.2.5: a. Attempted synthesis of **220d**; b. potential  $\beta$ -substituted analogue of **1d** which was not possible.

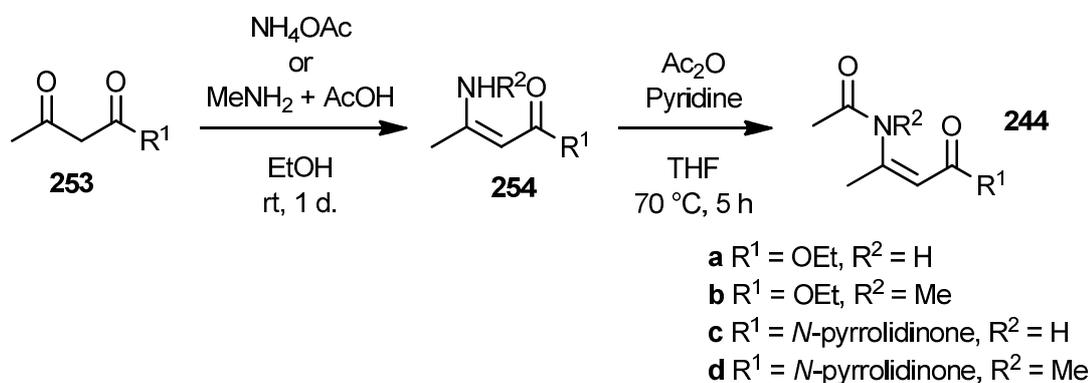
Instead, two alternative compound types were considered as  $\beta$ -substituted ‘surrogates’ of the enamides **1** and **220**. These were aminoacrylates (analogous to enamide **1**) and tetramic acids (analogous to enamide **220**). The synthesis and ATH of these two compound types are described in the next two sections.

### Section 2.2.2: Synthesis and ATH of $\beta$ -(Acylamino)acrylates.

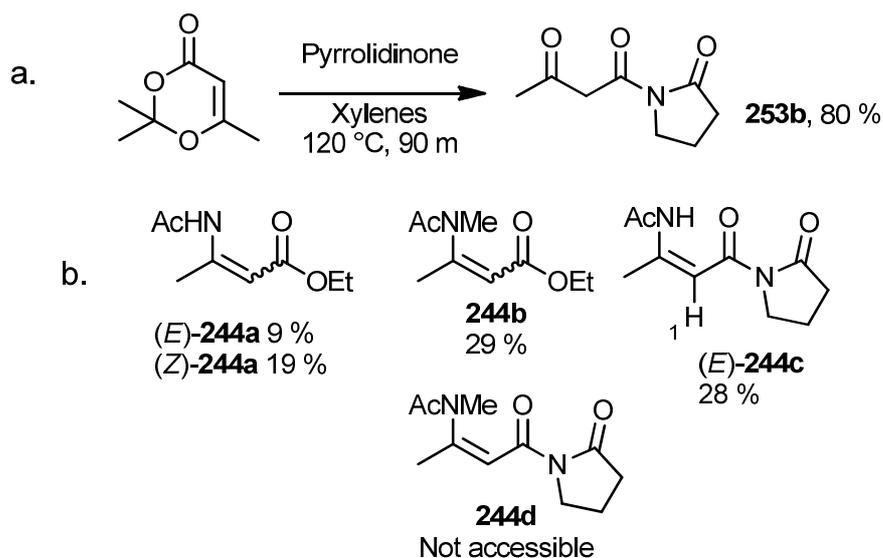
$\beta$ -(Acylamino)acrylates were considered due to their  $\alpha,\beta$ -unsaturated- $\beta$ -acyl-carbonyl conjugated system which was similar to the  $\alpha,\beta$ -unsaturated- $\beta$ -*N*-pyridone-imidyl conjugated system present in enamide **1**. The asymmetric pressure hydrogenation of amino acrylates is a well established field and was reviewed in the introduction. The ATH of structurally similar activated alkenes was carried out by Xue *et al.* with Noyori's catalyst with modest enantioselectivity.<sup>142</sup> Reductions of  $\beta$ -(acylamino)acrylates have not been reported by ATH. In this section, the synthesis and ATH of a range of  $\beta$ -(acylamino)acrylates was briefly carried out with the catalyst, *RutethTsDPEN* **248**.

#### Synthesis of $\beta$ -(acylamino)acrylates.

The  $\beta$ -(acylamino)acrylates were conveniently synthesised by a known procedure<sup>143b</sup> involving the condensation of an ammonium salt to a  $\beta$ -keto-carbonyl (**253**) to form an intermediate enamine (**254**) (Scheme 2.2.6). This intermediate was subsequently acetylated to give a mixture of the *E/Z*  $\beta$ -(acylamino)acrylates, **244**. Isomers **244a**, were formed via this procedure using  $\beta$ -keto-carbonyl **253a**. Isomers (*E*)-**244a** and (*Z*)-**244a** were isolated by silica gel chromatography in 9 % and 19 % yields respectively (Scheme 2.2.7).



Scheme 2.2.6: General procedure for the synthesis of  $\beta$ -(acylamino)acrylates.



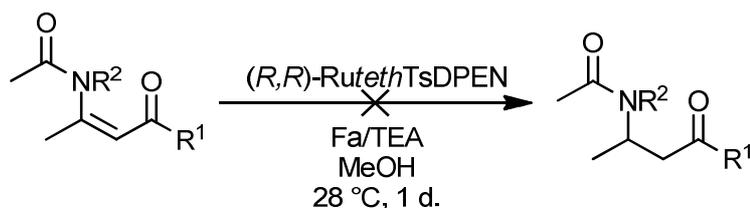
Scheme 2.2.7: a. Synthesis of  $\beta$ -keto imidopyrrolidine; b. yields of obtained  $\beta$ -(acylamino)acrylates.

$\beta$ -Keto amidopyrrolidine **253b** was synthesised in 80 % yield via a 2 step procedure involving the nucleophilic ring opening reaction of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one by pyrrolidine (Scheme 2.2.7a).<sup>144</sup> Using **253b** in the condensation – acylation sequence (Scheme 2.2.6), only the (*E*)-isomer of imidopyrrolidine (*E*)-**244c** was isolated in 28 % yield. An nOe <sup>1</sup>H NMR study indicated an interaction between H<sub>1</sub> and the CH<sub>3</sub> protons, supporting *E* geometry. Condensation and subsequent acylation of **253a** with methylamine and acetic acid enabled NMe derivative **244b** to be accessed in 29 % yield. Formation of **244d** via direct methylation of (*E*)-**244a** was not possible using NaH and MeI reagents, or through the condensation – acylation of **253b** with methylamine and acetic acid.

#### *ATH of aminoacrylates.*

The ATH of the amino acrylates was carried out with (*R,R*)-RutethTsDPEN (*R,R*)-**248** (Scheme 2.2.8).  $\beta$ -(acylamino)acrylates (*E*)-**244a** and (*Z*)-**244a** were both inactive to ATH. It was considered that the ester group did not induce sufficient polarisation of the alkene bond to enable hydrogen transfer. This led to the replacement of the ester group by an imido pyrrolidine group resulting in (*E*)-**244c**;

however this compound also was not reduced when treated with the catalyst at 28 °C or at a prolonged time of 3 d at 40 °C and in neat FA/TAE. The effect of any NH bonding interaction upon the stability of the alkene bond of (*E*)-**244a** and (*Z*)-**244a** was also considered, leading to the synthesis and ATH of methylated derivative **244b**. This compound was not reduced with the catalyst.



Scheme 2.2.8: Conditions used for the ATH of  $\beta$ -(acylamino)acrylates.

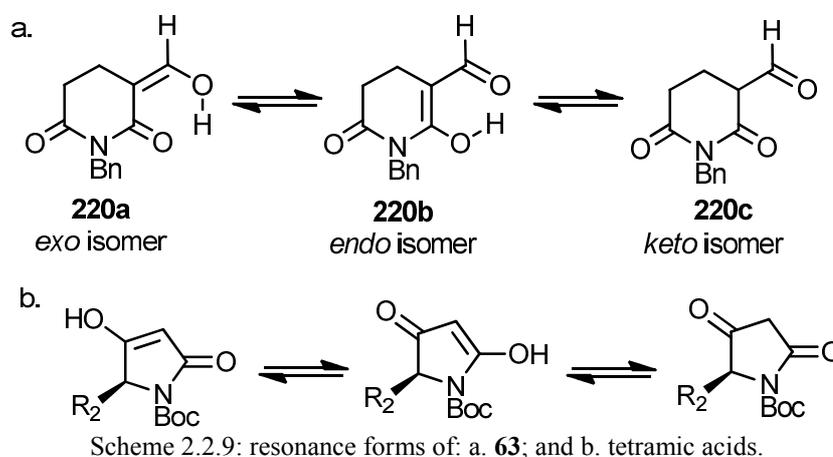
### Conclusions.

In conclusion, none of the  $\beta$ -(acylamino)acrylates studied reduced by ATH using the Ru(II) tethered catalyst. An explanation may be that the alkene bond is not sufficiently polarised<sup>142</sup> to react with the catalyst, and that the conjugated system present in these compounds was not comparable to enamide **1**.

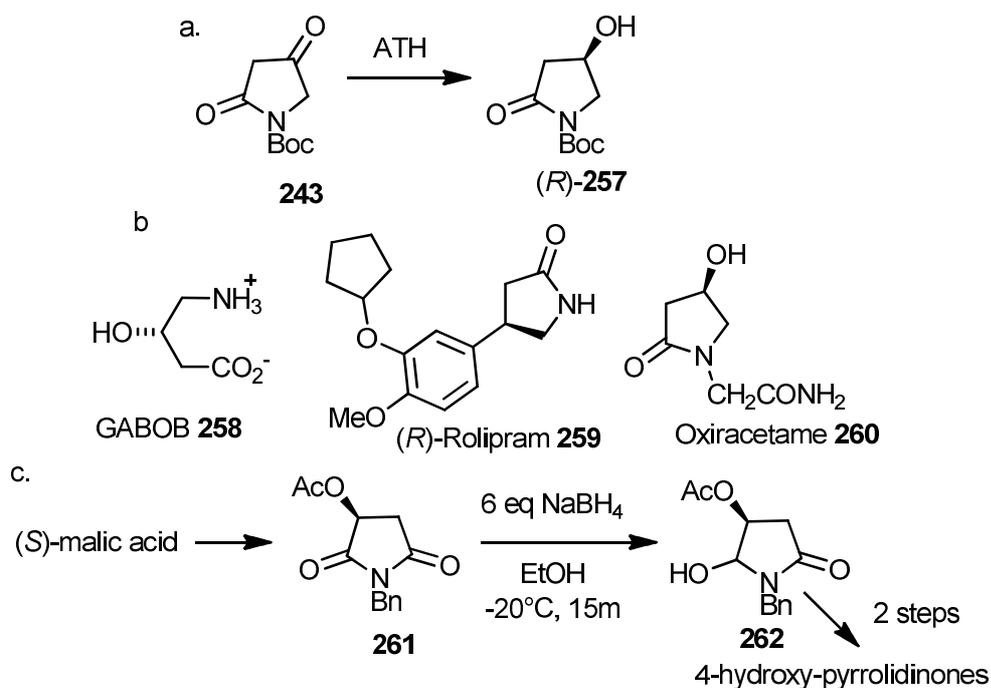
### Section 2.2.3: Synthesis and ATH of *N*-Boc Tetramic Acids.

Following the ATH of enamide **220**, in this section tetramic acids were investigated as  $\beta$ -substituted ‘surrogates’ of enamide **220** due to their similar tautomeric  $\beta$ -keto- $\gamma$ -lactam conjugated system which was similar to the  $\beta$ -keto-glutarimidyl conjugated system present in enamide **220** (Scheme 2.2.9). Tetramic acids are substituted at the  $\beta$  position, whereas the corresponding  $\beta$  position of enamide **220** was not substituted. An attempted synthesis of a  $\beta$ -substituted derivative of enamide **220** was unsuccessful (Scheme 2.2.5) which prevented further study into the enantioselective formation of a chiral centre at this position. The ATH of substituted tetramic acids

could result in the enantioselective formation of *N*-Boc 4-hydroxy-pyrrolidinones (*R*)-**257** (Scheme 2.2.10a).

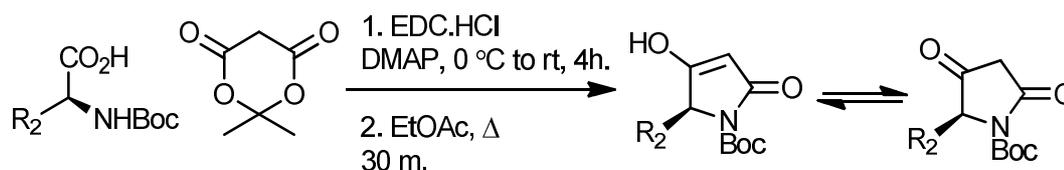


These compounds are precursors to pharmaceuticals such as the antidepressant, (*R*)-Rolipram, **259**<sup>145</sup>; the anticonvulsant, (-)- $\gamma$ -amino- $\beta$ -hydroxybutyric acid, **258** (GABOB)<sup>146</sup>; and Oxiracetam, **260**<sup>147</sup> (Scheme 2.2.10b).<sup>148</sup> Alternative methods for the synthesis of 4-hydroxy-pyrrolidinones involve the reduction of imide **261** (obtained from (*S*)-malic acid) in which **262** is formed with no loss of enantiopurity (Scheme 2.2.10c).<sup>149</sup>



Scheme 2.2.10: a. Reduction of *N*-Boc tetramic acids via ATH; b. Pharmaceuticals potentially derived from *N*-Boc 4-hydroxy-pyrrolidinones; c. Alternative method of synthesis.

*Synthesis of N-Boc tetramic acids.*



Scheme 2.2.11: General synthesis of *N*-Boc tetramic acids.

To accomplish this, a range of tetramic acids were synthesised. There are numerous methods for their synthesis known in the literature,<sup>150</sup> but in this project the procedure reported by Størgaard *et al.* was followed.<sup>186</sup> This procedure utilises Boc-protected amino acids as starting materials in the 2 step synthesis (Scheme 2.2.11). The tetramic acids are known to be formed with retention of chirality. The broad range of protected amino acids available enables the possibility of the synthesis of a wide range of tetramic acids. The *N*-Boc tetramic acids **243**, (*S*)-**264**, (*S*)-**265** and (*R*)-**265** (Figure 2.2.3) were synthesised from *N*-Boc-glycine, *N*-Boc-(*O*Bn)-L-serine and *N*-Boc phenylalanine (both L and D natural and unnatural isomers) respectively, through the coupling of commercially available *N*-Boc amino acids with Meldrum's acid (0°C to rt) in DCM. This resulted in formation of the intermediate adduct **263** (Figure 2.2.3) which was not isolated due to its known instability.<sup>151</sup> Upon heating in ethyl acetate this intermediate undergoes an intramolecular cyclisation and subsequent loss of CO<sub>2</sub> to give the final product. Generally the product was sufficiently pure for further use without purification as prescribed. In some cases decomposition has been reported following silica gel chromatography.

Serine-derived tetramic acid (*S*)-**264** was obtained in 51 % yield (Figure 2.2.3). The compound was found to be prone to decomposition following silica gel chromatography or upon standing for 1 day or more. Glycine-derived tetramic acid **243** was obtained in 51 % yield. Phenylalanine-derived (both L and D) tetramic acids

(*S*)-**265** and (*R*)-**265** were obtained in 54 % and 16 % yields respectively following recrystallisation (ethyl acetate – hexane).

In all cases, variation of the <sup>1</sup>H NMR solvent was found to alter the tautomeric form of the tetramic acid. In deuterated chloroform, the keto tautomer was exclusively present; whereas in deuterated DMSO, the enol tautomer was exclusively present (Scheme 2.2.9).

*O*-Methylated tetramic acid **266** was synthesised in 34 % yield via alkylation of **243** with MeI and AgCO<sub>3</sub> in MeCN at room temperature for 24 h. The product of *C*-alkylation was not isolated from the reaction mixture. Enol methyl ether **266** had not been reported in the literature, but the corresponding free NH derivative is known.<sup>152</sup>

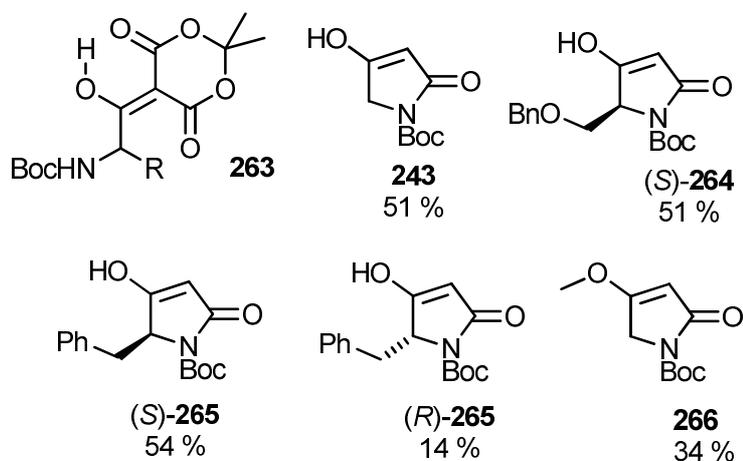
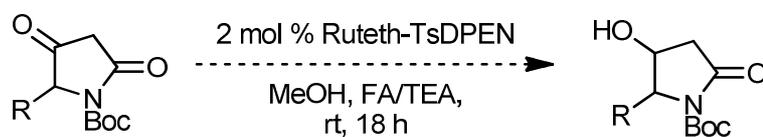


Figure 2.2.3: Isolated yields of *N*-Boc tetramic acids.

#### *ATH of tetramic acids.*

The ATH of **243** was carried out using methanol as solvent and 2 mol % (*R,R*)-RutethTsDPEN, **248** (Scheme 2.2.12). Following 18 h at room temperature, product (*S*)-**257** was obtained in complete conversion (determined by <sup>1</sup>H NMR) (entry 1, Table 2.2.2). Chiral separation was achieved following a literature HPLC method<sup>148</sup>

enabling the determination of ee to be 41 %. The absolute configuration was assigned to *S* based on comparison with literature  $[\alpha]_D$  values.<sup>148</sup>

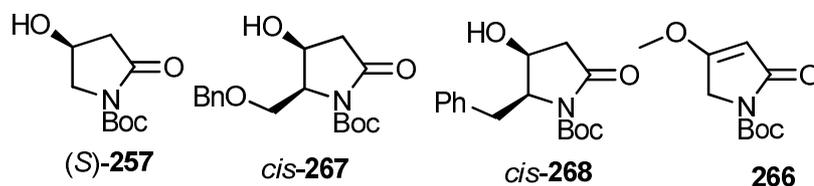


Scheme 2.2.12: ATH of tetramic acids.

Table 2.2.2: ATH of tetramic acids.

entry	tetramic acid <sup>a,b</sup>	R	cat.	de (%) <sup>e</sup>	Ee (%) <sup>c</sup>	Prod. <sup>c,d</sup>
1	<b>243</b>	H	( <i>R,R</i> )- <b>248</b>	N/A	41	( <i>S</i> )- <b>257</b>
2			( <i>S,S</i> )- <b>248</b>	N/A	41	( <i>R</i> )- <b>257</b>
3	<b>266<sup>f</sup></b>	H <sup>f</sup>	( <i>R,R</i> )- <b>248</b>	N/A	N/A	N/A
4	( <i>S</i> )- <b>264</b>	CH <sub>2</sub> OBn	( <i>R,R</i> )- <b>248</b>	100	N/D	<i>cis</i> - <b>267</b>
5			( <i>S,S</i> )- <b>248</b>	100	N/D	<i>cis</i> - <b>267</b>
6	( <i>S</i> )- <b>265</b>	CH <sub>2</sub> Bn	( <i>R,R</i> )- <b>248</b>	100	99	( <i>S,S</i> )- <b>268</b>
7			( <i>S,S</i> )- <b>248</b>	100	>99	( <i>S,S</i> )- <b>268</b>
8	( <i>R</i> )- <b>265</b>	CH <sub>2</sub> OBn	( <i>R,R</i> )- <b>248</b>	100	>99	( <i>R,R</i> )- <b>268</b>
9			( <i>S,S</i> )- <b>248</b>	100	>99	( <i>R,R</i> )- <b>268</b>

a. [SM] = 0.625 M; b. 0.5 cm<sup>3</sup> mmol (w/r to SM); c. determined by chiral HPLC; d. config. assigned by comparison of lit.  $[\alpha]_D$  values; e. *cis* config. determined by <sup>1</sup>H NMR, as prescribed by the lit.<sup>188</sup>; f. methyl enol ether derivative, was obtained via alkylation of **243**; N/A: not applicable; N/D: not determined.



To test whether the reduction occurred via reduction of the enol or keto tautomer of **243**, it was necessary to carry out the synthesis and ATH of tetramic acid **266**. If this compound was inert to ATH it would suggest that the reduction had resulted from ketone ATH. This compound was inert to reduction by the catalyst (entry 3, Table 2.2.2), suggesting the reduction of **243** occurs via reduction of the keto tautomer.

The low level of enantioselectivity obtained from the ATH of **243** may have resulted from the sterically undemanding environment. The ketone is also not proximal to

functionalisation about the heterocyclic ring. This prompted ATH of the more sterically hindered tetramic acids **264** and **265**.

The NaBH<sub>4</sub> mediated reduction of **264**<sup>153</sup> and **265**<sup>188</sup> has been reported to proceed with complete stereocontrol, forming the *cis*-product only. There has been dispute over the diastereoselectivity of the reaction which required precise conditions to achieve 100 % dr.<sup>188</sup> The dr was studied by Kraus *et al.* who assigned each diastereomer by the *OH* signal of the <sup>1</sup>H NMR spectrum (DMSO).<sup>188</sup>

In this study it was found that ATH of **264** with (*R,R*)-RutethTsDPEN proceeded with complete stereocontrol, forming only one diastereomer (entry 4). This was as determined by <sup>1</sup>H NMR through appearance of only one *OH* signal (as specified in the last paragraph).<sup>188</sup> The diastereomer was assumed to be the *cis* product **267** in analogy with the corresponding NaBH<sub>4</sub> mediated reduction of **264**. Reaction of **264** with (*S,S*)-RutethTsDPEN also resulted in the formation of one diastereomer, assigned as the *cis* product *cis*-**267** (entry 5). These assignments of configuration have been made on the basis that the starting material was enantiomerically pure and the product consisted of only one diastereomer, assigned as the *cis* product.

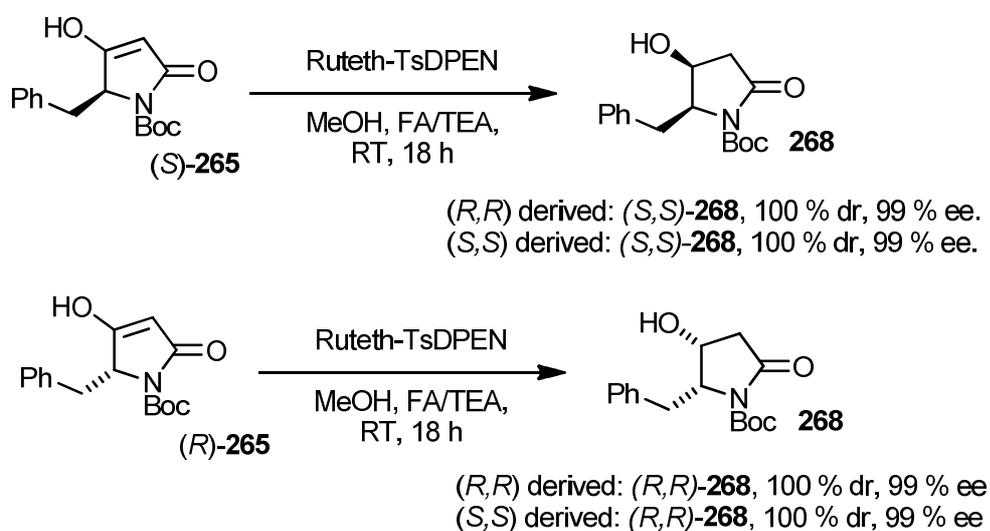
These results were independent of the isomer of catalyst used – both (*R,R*) and (*S,S*) catalysts reacted with **264** to give exclusive formation of the *cis* product **267**, suggesting that the reduction proceeded via a substrate controlled reduction. However, the  $[\alpha]_D$  values of the two products of **267** formed from the (*R,R*) and (*S,S*) isomers of the catalyst were not found to be of the same magnitude with each other ( $[\alpha]_D = 27$  and  $78$  respectively) or the literature value<sup>100</sup> ( $[\alpha]_D^{20} + 59$  (c1.00,

MeOH)). From a substrate controlled reduction, this would be required. It was considered that this could be an indication that the ee of the two samples of **267** were different. A feasible explanation for this may be that during the reduction, a dynamic kinetic resolution (DKR) involving epimerisation at C (1) could result in the formation of both enantiomers of the *cis* product. A study by Oba *et al.* had shown that the NaBH<sub>4</sub> mediated reduction of **264** had occurred without epimerisation and retention of enantiopurity.<sup>153b</sup> However it seemed important to determine the ee of these samples.

Determination of ee required a racemic standard. This required the opposite enantiomer starting material which was derived from the unnatural amino acid, D-Boc serine, however this compound was not commercially available which was problematic. The unnatural isomer, D-Boc phenylalanine was however available and so for simplicity, the task of determining the ee of the reduction products was to be carried out through the ATH of the model compounds, L- and D- derived tetramic acids (*S*)-**265** and (*R*)-**265**. This was more advantageous than alternative synthetic methods, as full characterisation data was available for the reduction products of **265**.<sup>153</sup>

The ATH of both enantiomers of **265** was carried out with both isomers of the catalyst. ATH of (*S*)-**265** and (*R*)-**265** with (*R,R*)-*Ruteth*TsDPEN proceeded with complete stereocontrol, each forming one diastereomer which in both cases was assigned as the *cis*-product (in analogy with the literature NaBH<sub>4</sub> reduction), (*S,S*)-**268** and (*R,R*)-**268** respectively (entries 6 and 8, Scheme 2.2.13). ATH of (*S*)-**265** and (*R*)-**265** with (*S,S*)-*Ruteth*TsDPEN, formed the *cis*-products (*S,S*)-**268** and (*R,R*)-

**268** respectively (entries 7 and 9). Chiral HPLC separation of these products was achieved (Chiralpak IC, heptane : IPA 1:1, flow rate = 1 mL/min) enabling the ee to be determined as 99 % in each case. The literature optical rotation values matched the reduction products in each case, confirming that the configuration assignments were correct. These results indicated that the reduction proceeded with retention of enantiopurity and that a DKR had not occurred. The reductions were the result of substrate control, independent of the isomer of catalyst.



Scheme 2.2.13: ATH of  $(S)$ - and  $(R)$ - **265** with  $(R,R)$ - and  $(S,S)$ -RutethTsDPEN.

### Conclusion.

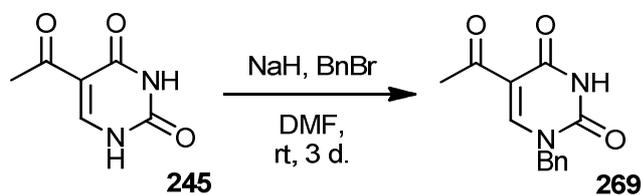
Tetramic acids were chosen as  $\beta$ -substituted  $\alpha,\beta$ -unsaturated imido surrogates of the enol imide **1**. The synthesis and ATH of a range of tetramic acids was carried out in one case with low enantioselectivity (41 % ee ( $S$ )). The *O*-methylated tetramic acid **266** was found to be inert to ATH indicating that the reduction proceeded via the keto form. For the 2-substituted tetramic acids, the reductions were found to proceed by substrate control with complete stereoselectivity.

*Section 2.2.4: ATH of 5-Acetyluracil.*

In a study unrelated to this chapter, the ATH of 5-acetyluracil **245** and *N*-benzyl 5-acetyluracil **269** was investigated to enable comparison to other heterocyclic methyl ketones such as pyridyl methyl ketones. There are not any direct ATH examples of substrates of this functionality. Primarily of interest was the enantioselectivity of the ketone reduction. Reductions of heterocycles of this type have not been reported. It was of interest to know the enantioselectivity of this reaction. It was found that the alkene bond of this compound as well as the ketone was reduced.

*Synthesis of N-benzyl 5-acetyluracil.*

5-Acetyluracil was benzylated by treatment with NaH in DMF (Scheme 2.2.14). Using a sub-stoichiometric ratio of electrophile to starting material, slow dropwise addition of benzyl bromide was carried out to favour mono-alkylation.



Scheme 2.2.14: alkylation of 5-acetyluracil.

Following recrystallisation from methanol, *N*-benzyl-5-acetyluracil, **269** was obtained in 39 % yield as crystalline white needles which underwent X-ray diffraction to confirm the structure (Figure 2.2.4), thus confirming that alkylation had occurred exclusively on *N* (7A). Full characterisation data is shown in Appendix II.

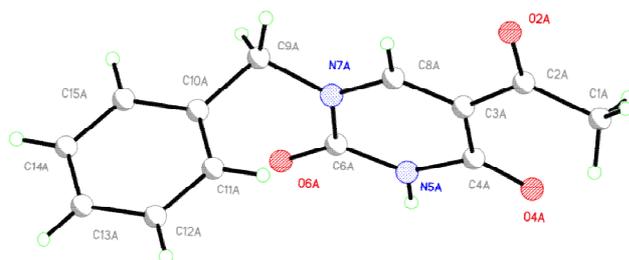
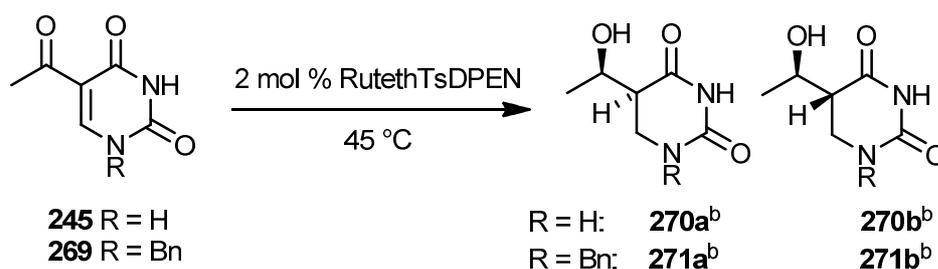


Figure 2.2.4: X-ray crystal structure of **269**.

*ATH of 5-acetyluracil and N-benzyl 5-acetyluracil.*

The ATH of **245** was carried out with the catalyst (*R,R*)-RutethTsDPEN, **248** (Scheme 2.2.15). Neat FA/TEA was used as solvent at a substrate concentration of 2M. The results are shown in Table 2.2.3. Following a reaction time of 17 h at room temperature, **245** underwent 100 % conversion to the fully reduced diastereomers **270a** and **270b** in a ratio of 3.1 : 1 (entry 1, Table 2.2.3). It is important to note, that the configuration of **271a** and **271b** was not determined and has been included for illustration purposes only. Interestingly, both the alkene and ketone bonds were reduced, creating two adjacent chiral centres. The reaction yielded the product as a light yellow solid, containing an inseparable mixture of the diastereomers which could not be separated by silica gel chromatography due to the high polarity of the compound. Chiral separation was not possible via gas chromatography (GC) or HPLC. To aid chiral HPLC separation (potentially by reducing polarity), analysis of the benzylated product **271** was instead performed through the use of *N*-benzyl 5-acetyluracil, **269**. It is important to again note, that the configuration of **271a** and **271b** was not determined and has been included for illustration purposes only. Catalyst structures may be seen in Appendix IV.

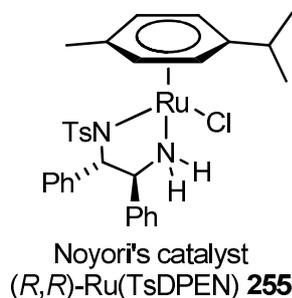


Scheme 2.2.15: ATH of **245** and **269**.

Table 2.2.3: ATH of **245** and **269**.

entry	ketone <sup>a</sup>	R	cat. <sup>c</sup>	mol %	time (h)	conv. (%) <sup>b</sup>	a/b (%) <sup>b</sup>	Ee a (%) <sup>c</sup>	Ee b (%) <sup>c</sup>
1	<b>245</b>	H	( <i>R,R</i> )- <b>248</b>	2	17	100	3.1:1	N/D	N/D
2	<b>269</b>	Bn	<b>249</b>	6	20	100	1:1	N/A	N/A
3	<b>269</b>	Bn	( <i>R,R</i> )- <b>255</b>	6	20	100	1.3:1 <sup>d</sup>	55	36
4	<b>269</b>	Bn	( <i>R,R</i> )- <b>248</b>	0.8	20	100	4:1 <sup>d</sup>	92	33
5	<b>269</b>	Bn	( <i>S,S</i> )- <b>248</b>	0.8	20	100	4:1 <sup>d</sup>	86	49

a. [SM] = 2M, b. determined by <sup>1</sup>H NMR (the exact configuration was not determined and has been included for illustration purposes only); c. determined by chiral HPLC; d. the same major diastereomer was identified by <sup>1</sup>H NMR in these reactions; e. see Appendix IV for catalyst structures; N/D: not determined; N/A: not applicable.



The ATH of **269** was carried out with *Ruteth*TsDPEN **248**, (*R,R*)-RuTsDPEN, (*R,R*)-**255** and racemic TH catalyst, RuTsEN **249**. Catalysts **249** and (*R,R*)-**255** were used in a higher loading (6 mol %) to achieve full conversion within the time scale of catalyst (*R,R*)-*Ruteth*TsDPEN (20 h). In all cases, conversion and dr were determined by <sup>1</sup>H NMR. Use of catalyst (*R,R*)-**248** resulted in formation of **271a** and **271b** in a 1:1 ratio and 100 % conversion (entry 2), as an inseparable mixture of diastereomers. Substrate **269** was reduced with formation of **271a** and **271b** in a 1.3:1 ratio and 100 % conversion (entry 3). Chiral HPLC separation of the mixture

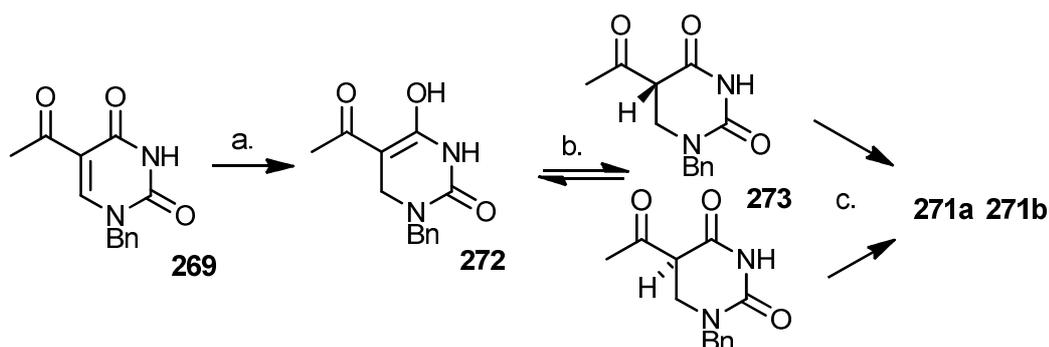
of the diastereomers was achieved (Chiralpak IA, hexane : IPA 9 : 1, flow rate = 1 mL/min) using the racemic reduction product (**a** : **b** 1:1) obtained from racemic catalyst **249** as a racemic standard to confirm the position of peaks. As the **a** : **b** ratio had been determined by <sup>1</sup>H NMR, it was possible to assign the chiral HPLC peaks to the correct pairs of enantiomers. This enabled the ee of diastereomers **271a** and **271b** to be determined as 55 % and 36 % respectively. The use of catalyst (*R,R*)-**248** resulted in the formation of **271a** and **271b** in 4 : 1 ratio with 92 % and 33 % ee respectively (entry 4) (Chiralpak IA, hexane : IPA 9 : 1, flow rate = 1 mL/min). The use of catalyst (*S,S*)-**248** resulted in the formation of **271a** and **271b** in 4 : 1 ratio with 86 % and 49 % ee respectively (entry 5) (Chiralpak IA, hexane : IPA 9 : 1, flow rate = 1 mL/min). These GC traces have been included for comparison in Appendix III.

Comparison of the results obtained from ATH with Noyori's catalyst (*R,R*)-**255** and *Ruteth*TsDPEN(*R,R*)-**248** (entry 3 and 4) show that the same diastereomer **271a** is formed in the majority in each case. Interestingly, comparison of the HPLC retention times for each isomer (see Appendix III) show that for **271a**, the same major enantiomer is formed. However, for **271b**, the major enantiomer from each catalyst is the opposite. These results highlight subtle differences in selectivity of the two catalysts, resultant from the presence of the three carbon tether in *Ruteth*TsDPEN, even though the catalysts both operate by the same reduction mechanism and share an equivalent asymmetric environment. Comparison of the results obtained from ATH with opposite enantiomers of *Ruteth*TsDPEN, (*R,R*)-**248** and (*S,S*)-**248** (entry 4 and 5) show that each catalyst favours the same diastereomer **271a**. However the opposite enantiomer catalyst forms the opposite major enantiomer of both

diastereomers. By comparison of the HPLC retention times, it is clear that for each diastereomer, changing the enantiomer of catalyst will favour the formation of the opposite enantiomer: i.e. For **271a** the (*R,R*)-**248** catalyst leads to the major isomer at  $R_t$  43.5 min., and the minor isomer at  $R_t$  75.3 min; whereas (*S,S*)-**248** leads to the minor isomer at  $R_t$  44.1 min., and the major isomer at  $R_t$  75.9 min. A similar affect is observed for **271b**. The configuration of diastereomers **271a** and **271b** was not determined and has been included for illustration purposes only.

#### *Discussion of mechanism.*

It is possible to gain some insight into a potential mechanism of this process, from these results. As each diastereomer was present in differing ee in each reduction, this indicates that ketone reduction could not have occurred first. Instead, conjugate reduction must have occurred first, resulting in formation of the enol intermediate **272** (step a, Scheme 2.2.16) which would tautomerise to give ketone **273** (step b). The subsequent ketone reduction of ketone **273a** or **273b** may then proceed via a DKR or KR, potentially leading to differing asymmetric inductions for each enantiomer of ketone, and the subsequent formation of diastereomers **271a** and **271b** (step c).<sup>154</sup> This explanation is supported by the observed difference in ee for each diastereomer. Attempts to independently form ketone **273** via partial reduction of **269** were unsuccessful, preventing further study.

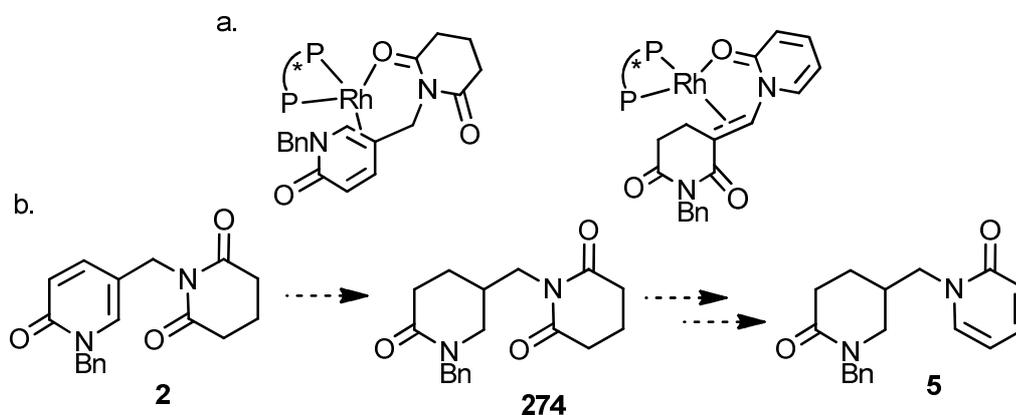


Scheme 2.2.16: Mechanism for the reduction of **269**.

## Section 2.3: 2<sup>nd</sup> Generation Formal Synthesis of Cytisine: AH of Pyridone 2.

### Section 2.3.1: Introduction.

In this section, a 2<sup>nd</sup> generation formal approach to cytisine was carried out through the AH of pyridone **2**. The product of this hydrogenation, the 5-substituted lactam **274**, may be converted to the cytisine precursor lactam **5** through a known route (Scheme 2.3.1b). Following the known structural requirements for enantioselective hydrogenation, pyridone **2** was considered to bear these necessities. The proximal glutarimide carbonyl group to the pyridone group would be anticipated to enable effective coordination of the catalyst, resulting in an enantioselective reduction of the alkene (Scheme 2.3.1b). In the introduction, the AH of pyridone **67** (see Section 1.2.4) proceeded with low enantioselectivity, however this compound did not have any proximal coordinating group, and only one catalytic system was used.



Scheme 2.3.1: a. Proposed coordination modes of **2** and **1**; b. formation of **5** from **2**.

This work was motivated by the availability of an extensive screen of chiral ligands (up to 200) and rhodium, ruthenium and iridium catalysts through collaboration with AstraZeneca. The full retrosynthetic approach and full synthesis is described in Section 2.3.2. As discussed in the introduction, the enantioselective synthesis of  $\delta$ -lactams has not been described in detail. If successful, this methodology could also potentially be modified for use in the asymmetric synthesis of other 5-substituted  $\delta$ -lactams.

*AH of alternative 5-substituted pyridones.*

In this section, the AH of a number of 5-substituted pyridones was also carried out in attempt to prepare the corresponding 5-substituted lactams, which are also synthetically useful as precursors to cytosine and in other applications. The AH of the structurally similar  $\alpha,\beta$ -unsaturated  $\delta$ -lactam, **110** was described in Section 1.3.2 (Scheme 1.14a).

This section is split between two parts: the first part will consist of the main subject of this section, the synthesis and hydrogenation of pyridone **2**. In the second part, the AH of a range of 5-substituted pyridones is described.

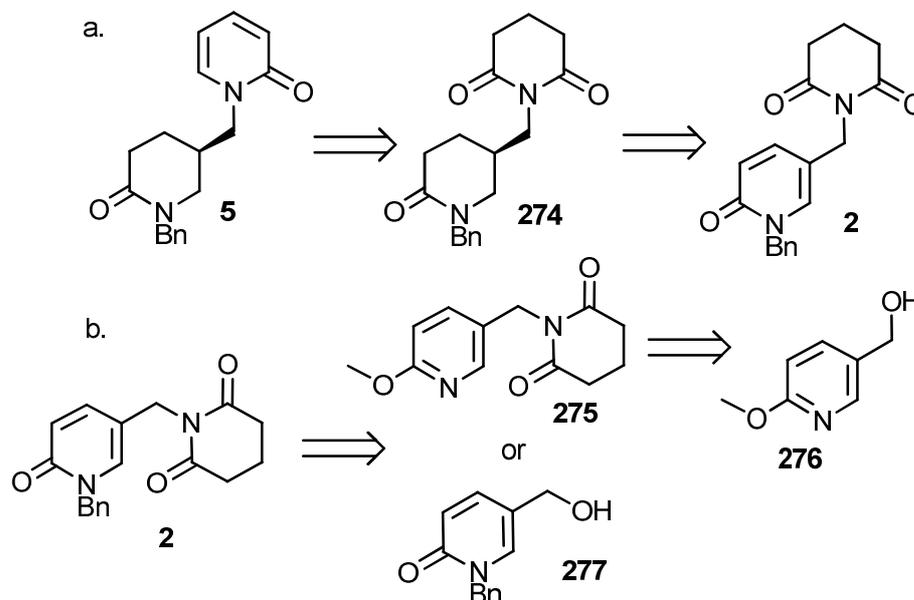
*Section 2.3.2: Synthesis and AH of Pyridone 2.*

During Section 1, the AH of  $\alpha,\beta$ -unsaturated imide **1** resulted in the highly enantioselective formation of imide **228**. However, the asymmetric synthesis of cytosine could not be completed by this route, due to late state epimerisation and subsequent loss of ee following conversion of imide **228** to the cytosine precursor **5**. To complete the asymmetric synthesis, an alternative strategy was required. In this section, the AH of pyridone **2** was studied, as a potential entry to the cytosine precursor **5**. Lactam **274**, the product of AH may also be readily converted to cytosine precursor **5** through the method outlined in the retrosynthesis is below.

*Retrosynthesis.*

The intended retrosynthetic approach to cytosine precursor **5** is shown in Scheme 2.3.2. Cytosine precursor **5** should be accessible from imide **274** by the conversion of the imide group to the pyridone through the three step method detailed by Sivaguru

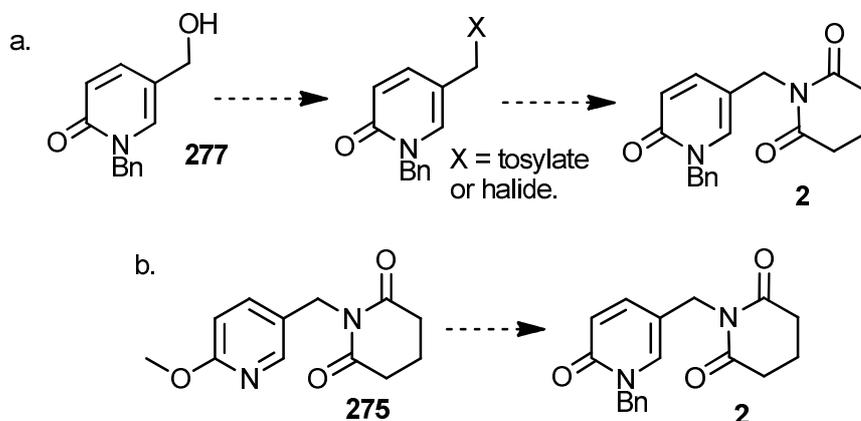
*et al.*<sup>155</sup> Imide **274** may be obtained from pyridone **2** via AH, potentially through the proposed mode of coordination (Scheme 2.3.2a). Pyridone **2** may be accessed from two possible compounds: pyridone **277** or methoxypyridine **275** which itself may be obtained from alcohol **276** via Mitsunobu coupling.



Scheme 2.3.2: Retrosynthesis of cytosine precursor, **5**.

#### Synthesis of pyridone **2**.

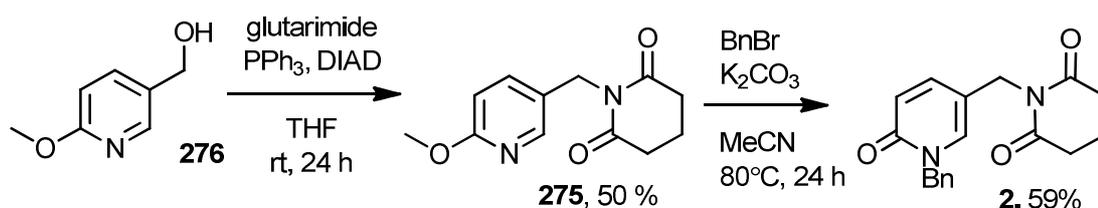
Initially the coupling of pyridone **277** with glutarimide was considered as the primary approach to **2** (Scheme 2.3.3a); however, a second approach involving the synthesis and benzylation of pyridine **275** was immediately more successful, yielding the desired hydrogenation substrate.



Scheme 2.3.3: a. Attempted substitution of pyridone **277**; b. alkylation of **275**.

Conversion to the desired pyridone **2** was attempted by converting **277** to the corresponding bromide or tosylate, followed by subsequent reaction with glutarimide (Scheme 2.3.3a), however the corresponding bromide or tosylate could not be formed which made this approach unsuccessful.

Alternatively, it was possible to complete synthesis of the desired hydrogenation substrate via pyridine **275**. Pyridine **275** was formed by the coupling of pyridine **276** with glutarimide under Mitsunobu conditions<sup>156</sup> (50 % yield, Scheme 2.3.4). It was possible to convert pyridine **275** to the corresponding pyridone **2** by treatment with benzyl bromide.



Scheme 2.3.4: synthesis of hydrogenation substrate **2**.

Following recrystallisation from ethanol, hydrogenation substrate **2** was obtained in 59 % yield as a colourless powder. Further recrystallisation provided crystals which underwent X-ray diffraction to give confirm the structure (Figure 2.3.1), thus confirming that alkylation had occurred exclusively on *N*(8). Full characterisation data is shown in Appendix II.

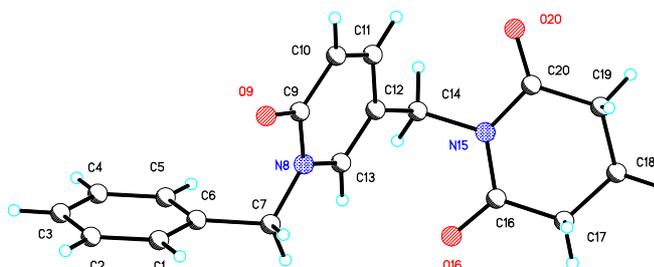
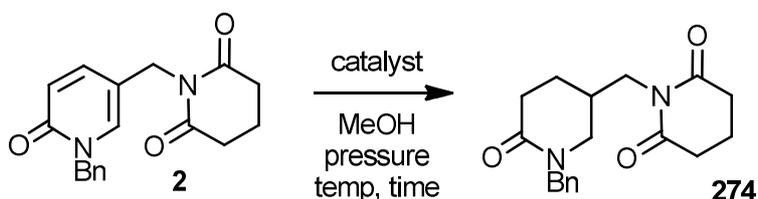


Figure 2.3.1: X-ray crystal structure of **2**.

### AH of pyridone **2**.

The hydrogenation of pyridone **2** was carried out using a range of homogeneous and heterogeneous catalysts (Scheme 2.3.5, Table 2.3.1). Catalyst structures may be seen in Appendix IV. Pyridone **2** reacted with Pd / C under atmosphere of hydrogen to give ring opened product pyridone **278** in 57 % yield (entry 1). No reduction products were isolated. Ring opening was avoided using platinum oxide in ethanol for 6 h at room temperature, to give the desired lactam **274** in 100 % conversion (entry 2). Scaling up this reduction (1.0 – 1.5 g) under the same conditions lead to incomplete conversion to the product.

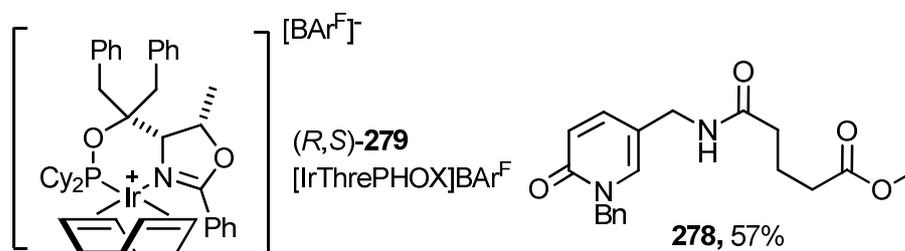


Scheme 2.3.5: AH of pyridones **2**.

Table 2.3.1: AH of pyridones **2**.

entry	cat.	scale (mg)	mol %	temp/ (°C)	time (h)	P. (bar)	conv. (%)
1	Pd / C	185	5	rt	18	1 <sup>c</sup>	N/A <sup>d</sup>
2 <sup>a</sup>	PtO <sub>2</sub>	40	10	30	6	1 <sup>c</sup>	100
3 <sup>a</sup>	PtO <sub>2</sub>	1140	5	rt	18	5	95 <sup>e</sup>
4	( <i>R,R</i> )- <b>229</b>	30	5	40	72	30	54 <sup>f</sup>
5	( <i>R</i> )- <b>37a</b>	20	5	30	6	50	100 <sup>f</sup>
6 <sup>b</sup>	( <i>R,S</i> )- <b>279</b>	20	1	rt	2	50	0

a. EtOH as solvent; b. DCM as solvent; c. run under a balloon of hydrogen; d. ring opened product **278** was isolated; e. obtained yield; f. the sample was found to be racemic.



$\text{BAR}^{\text{F}} = \text{B}(3,5\text{-di(trifluoromethyl)phenyl})_4$

Running the hydrogenation at higher temperatures (40°C) resulted in formation of unwanted side products which were inseparable from the desired product. Limited

evidence suggested that debenzylation of the product was occurring. Running the reduction at an elevated pressure of 5 bar at room temperature for 18 h was reproducibly found to give the desired product in high yield following purification (silica gel chromatography) typically in 90 – 95 % yield (entry 3).

Chiral separation of **274** was achieved (Chiralpak IB, hexane : IPA 8 : 2, flow rate = 1.0 mL/min). This sample was used as a racemic standard in chiral HPLC for subsequent AHs. Partial conversion to lactam **274** was observed using (*R,R*)-Rh-Et-DuPhos (*R,R*)-**229** following a prolonged reaction time of 72 h at 40 °C under 30 bar of hydrogen (entry 4). The ee of the sample was found to be 0 %. (*R*)-Ru(OAc)<sub>2</sub>(BINAP) (*R*)-**37a** (see p 19 for catalyst structure) was remarkably active, resulting in 100 % conversion to **274** following 6 h at 30 °C under 50 bar of hydrogen. Again, the sample was found to be racemic. No activity was observed with (*R,S*)-IrThrePHOX, (*R,S*)-**279**.

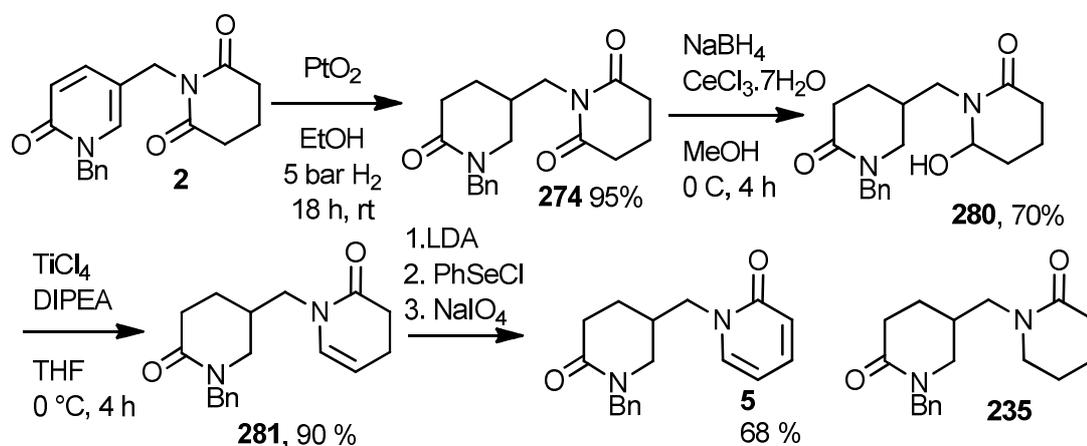
Through collaboration with AstraZeneca, the AH of pyridone **2** underwent an extensive asymmetric ligand screen with ruthenium and rhodium catalysts. Due to unfortunate circumstances which lead to the closure of the research facility, it has not been possible for these results to be made available for presentation in this thesis. It was however reported that of all the ligands screened, no significant chiral induction was observed in any case.

This absence of any enantioselectivity with any of the ligands screened was a real set back. This shows that the predicted coordination mode was not successful in directing enantioselectivity. It was suggested that the absence of any

enantioselectivity observed in the AH of pyridone **67**, was due to the tautomeric forms of the structure (Section 1.2.4).<sup>42</sup> The AH of pyridines is generally known to result in poor enantioselectivity,<sup>52</sup> with the exception of a few key examples,<sup>53</sup> and this may be an explanation for the results observed here.

### Section 2.3.3: Completion of the Synthesis.

Nonetheless, with lactam ( $\pm$ )-**274** in hand, the formal synthesis of racemic cytosine was continued following the three step method of Sivaguru (Scheme 2.3.6).<sup>155</sup> Treatment of lactam ( $\pm$ )-**274** with sodium borohydride and cerium chloride gave  $\alpha$ -hydroxylactam **280** in 70 % yield as an inseparable mixture of diastereomers which could not be adequately purified. It was not possible to distinguish between the two isomers by <sup>1</sup>H NMR. Further evidence supporting the assignment was obtained following the treatment of **280** with Et<sub>3</sub>SiH and TFA, which resulted in its conversion to lactam **235**. The use of the *N*-acyliminium chemistry of **280** was briefly considered,<sup>157</sup> however it was reported that in similar experimentation with  $\alpha$ -hydroxy- $\delta$ -lactams, conversion to the corresponding  $\gamma,\delta$ -unsaturated- $\delta$ -lactam was always observed as a major product.<sup>158</sup>



Scheme 2.3.6: Conversion of pyridone **2** to cytosine precursor **5**.

Advantageously, treatment of  $\alpha$ -hydroxylactam **280** with titanium chloride and DIPEA mediated the formation of the enamide **281**.<sup>159</sup> This method was favoured over the use of methanesulfonyl chloride and NEt<sub>3</sub> which resulted in co-formation of inseparable side products.<sup>158</sup> To complete the synthesis, oxidation of the enamide to the pyridone was required. Although this transformation had been reported in the literature with phenyl selenyl chloride<sup>155</sup>, initially, less toxic alternatives to selenium were investigated, albeit unsuccessful. Reaction with Br<sub>2</sub> or I<sub>2</sub> was attempted. The oxidants, MnO<sub>2</sub> and benzoquinone were also tried. Transition metal mediated transfer dehydrogenation was attempted with the reagents Pd/C, [Ir(COD)dppp], platinum black, and Raney nickel; in each case with cyclohexene as co-solvent to act as a hydrogen acceptor. However, none of these approaches were successful. Instead, the oxidation was achieved by the originally planned selenide oxidation – elimination method.<sup>155</sup> Treatment of the lithium enolate of **281** (formed with LDA) with phenyl selenyl chloride at -78°C resulted in formation of the intermediate selenide which was then subjected to oxidation with NaIO<sub>4</sub> in a solution of THF : MeOH : H<sub>2</sub>O 18 : 6 : 2, resulting in a sample containing a mixture of the desired pyridone **5** and an unidentified product. This procedure was carried out at a small scale (15 mg) which prevented adequate purification and isolation of **5**. This was not repeated, due to the results of the asymmetric ligand screen and time constraints.

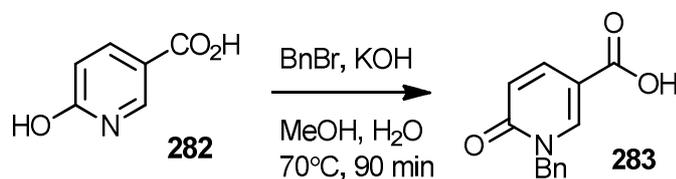
#### *Section 2.3.4: Synthesis and AH of 5-Substituted Pyridones.*

In this part of the section, the AH of a number of 5-substituted pyridones was carried out in attempt to achieve an enantiomerically enriched 5-substituted lactams. These pyridones were conveniently synthesised from the equivalent 5-substituted 2-methoxypyridine or 5-substituted 2-hydroxypyridine by known procedures involving

the *N*-alkylation and subsequent demethylation / deprotonation. Two different methods were used depending on the starting material used. Alternative synthesis methods involve the acid hydrolysis of substituted 2-fluoropyridines.<sup>160</sup>

#### *Pyridone 283.*

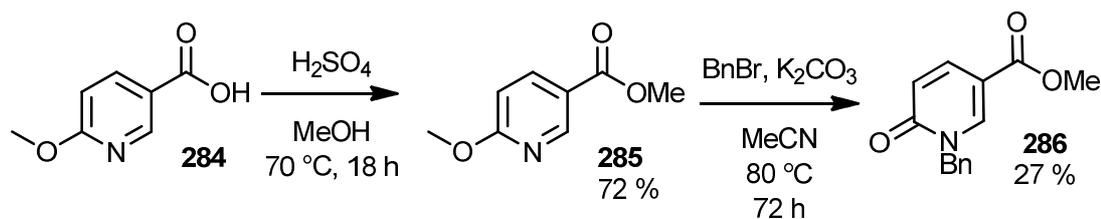
Pyridine **283** underwent reaction with benzyl bromide in the presence of KOH in methanol and water following a reaction time of 90 min at 70 °C (Scheme 2.3.7). The crude material obtained from the reaction was not sufficiently pure and contained traces of other alkylation products which could not be isolated or characterised. Instead of conventional purification, a portion of the crude material (290 mg) (for practical reasons only a fraction was used) was purified by preparative reverse phase HPLC ((Phenomenex Gemini-NX axia Prep C<sub>18</sub> OBD column) to give analytically pure **283** (211 mg).



Scheme 2.3.7: Alkylation of 5-substituted 2-hydroxypyridine **282**.

#### *N*-benzylpyridone-5-carboxylate **286**.

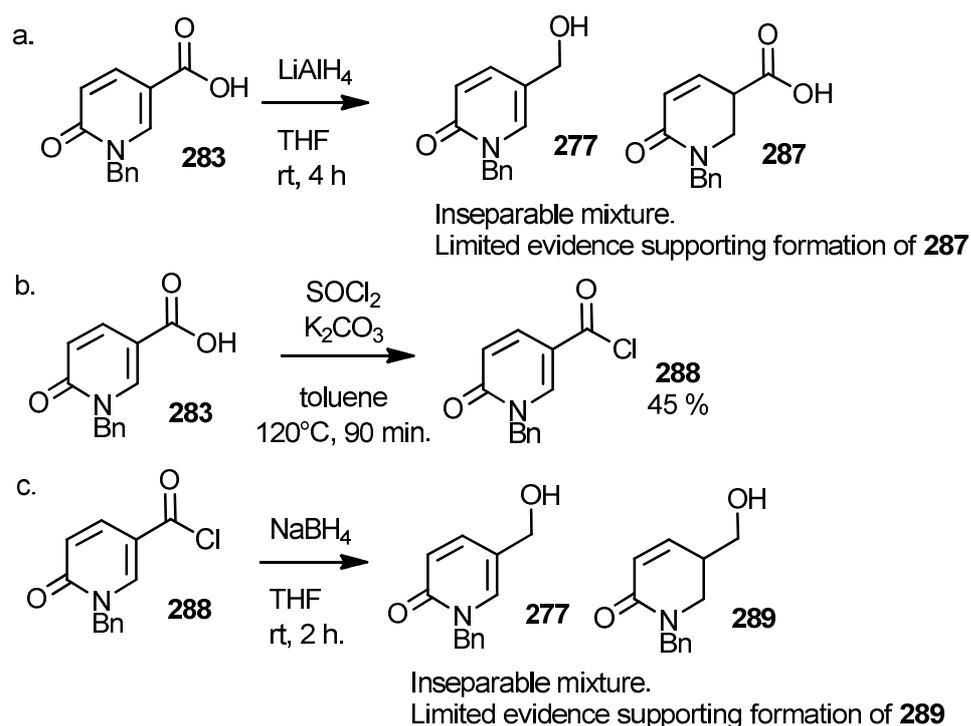
Pyridone **286** was synthesised in two steps from methyl nicotinate, **284**. Esterification of methyl nicotinate **284** was achieved with H<sub>2</sub>SO<sub>4</sub> and methanol (72 % yield, Scheme 2.3.8). Alternatively, the product, pyridine **285**, could be purchased from an affordable commercial source. Pyridine **285** underwent reaction with benzyl bromide in the presence of K<sub>2</sub>CO<sub>3</sub> in acetonitrile following 47 h at 80°C to give methyl *N*-benzylpyridone-5-carboxylate **286** in 29 % yield.



Scheme 2.3.8. Synthesis of pyridone **286** from pyridine **284**.

*N*-benzyl-5-hydroxymethylpyridone **277**.

Initially the synthesis of pyridone **277** was attempted by reduction of pyridones **283** or **288** (Scheme 2.3.9); however in both cases this was hampered by the apparent co-formation of multiple reduction products which could not be removed from the desired product. Following reduction of pyridone **277**, limited evidence by MS suggested that formation of conjugate reduction product **287** had also occurred (Scheme 2.3.9a).

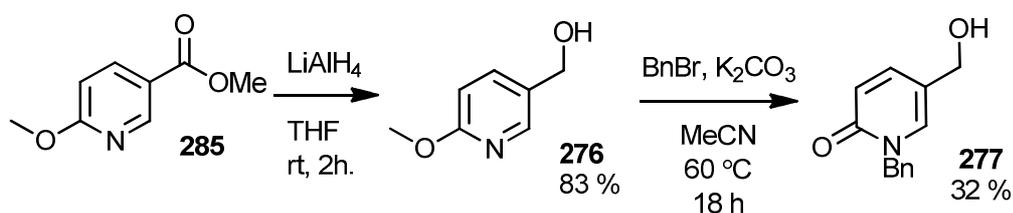


Scheme 2.3.9: (a) Reduction of pyridone **283** with  $\text{LiAlH}_4$ ; (b) formation of acid chloride **288**; (c) reduction of acid **288** with  $\text{NaBH}_4$ .

Alternatively, pyridone **283** was converted to acyl chloride **288** (Scheme 2.3.9b) which was subsequently reduced with  $\text{NaBH}_4$  by the method of Thomas *et al.* However, this procedure was not reproducible and resulted in multiple reduction

products which could not be removed from the desired product.<sup>161</sup> Limited evidence by MS suggested the formation of conjugate reduction product **289** (Scheme 2.3.9c).

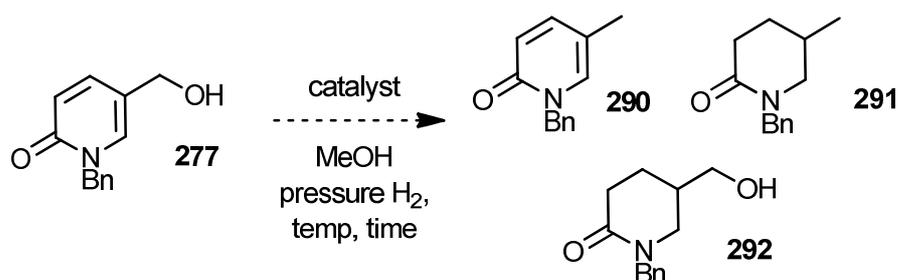
For these reasons, an alternative synthesis of pyridone **277** was completed via the two step sequence from pyridine **285**, shown in Scheme 2.3.4. Reduction of ester **285** was performed with LiAlH<sub>4</sub> to afford pyridine **276** in 83 % yield. Pyridine **276** underwent *N*-alkylation and subsequent *O*-demethylation following 18 h at 60°C. *N*-benzyl-5-hydroxymethylpyridone **277** was obtained in 32 % yield (Scheme 2.3.10). There was some evidence for the presence of other alkylation products in the crude reaction sample however none were isolated and identified. The analysis of alcohol **277** was in agreement with reported data. An nOe <sup>1</sup>H NMR study also showed an interaction between the CH<sub>2</sub>Ph protons and H<sub>3</sub>, supporting *N*-benzylation.



Scheme 2.3.10: Synthesis of *N*-benzyl-5-hydroxymethylpyridone **277**.

#### *AH* of *N*-benzyl-5-hydroxymethylpyridone **277**.

The *AH* of the 5-substituted pyridones was then carried out using a range of homogeneous and heterogeneous catalysts (Scheme 2.3.11, Table 2.3.2). Pyridone **277** was reduced with Pd / C using the H-cube, an automated continuous flow method for hydrogenations with heterogeneous catalysts. Following one pass of a solution of the substrate in methanol (0.25 M) through the H-cube using a 10 % w/w Pd/C cartridge, the C-O cleavage product **290** was isolated in 81 % yield (entry 1).



Scheme 2.3.11: AH of pyridone **277**.

Table 2.3.2: AH of pyridone **277**.

entry	scale (mg)	cat.	mol %	Temp (°C)	time (h)	P. (bar)	prod.	yield (%)
1	100	Pd/C <sup>a</sup>	N/A	rt	N/A	5	<b>290</b>	81
2	30	Pd/BaSO <sub>4</sub>	10	rt	18	5	<b>291</b>	71
3	30	PtO <sub>2</sub>	10	rt	18	5	<b>292</b>	65
4	15	( <i>R,R</i> )- <b>229</b>	2.5	40	20	40	<b>292</b>	50 <sup>b</sup>

a. Reaction performed in the H-cube; b. ee could not be determined by chiral GC or HPLC.

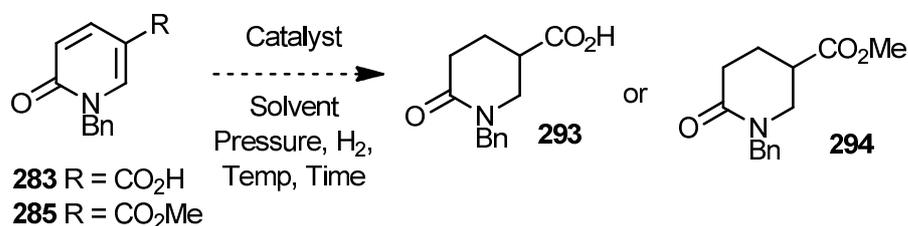
When Pd/BaSO<sub>4</sub> was used, the fully hydrogenated and C-O cleaved product **291** was obtained in 71 % yield (entry 2). The desired hydrogenation of the pyridone group was achieved with PtO<sub>2</sub> resulting in formation of the desired lactam **292** in 65 % yield (entry 3). Asymmetric catalyst (*R,R*)-**229** resulted in partial conversion to lactam **292** (entry 4); however, chiral separation could not be achieved by GC or HPLC. In Section 2.5.4, the ee of the similar lactam ( $\pm$ )-**304** obtained from reduction with (*R,R*)-**229** was determined to be 0 %. The ee of lactam **292** formed in this experiment was thus expected to also be 0 %. This asymmetric synthesis of lactam **292** (95 % ee) has been reported by Park *et al.*, via the phase transfer organo-catalytic mono-alkylation of a malonamide precursor to the lactam.<sup>162</sup>

The difference in reactivity of Pd/C in comparison to Pd/BaSO<sub>4</sub> is unexpected as BaSO<sub>4</sub> is thought to deactivate Pd leading to a poorer catalyst. Comparatively, Pd/C would have also been expected to fully reduce the pyridone ring, also resulting in formation of product **291**. However, as this experiment was run with the H-cube this may be explained by the reduced effective time, following only one pass of the

reaction solution through the system. The formation of **292** with PtO<sub>2</sub> is a good example of the catalyst's chemoselectivity to hydrogenation over hydrogenolysis.<sup>163</sup>

#### AH of pyridones **283** and **285**.

The attempted AH of the 5-substituted pyridones **283** and **285** was carried out using a range of homogeneous and heterogeneous catalysts (Scheme 2.3.12, Table 2.3.3). Pyridone **283** was reduced with Pd / C under forcing conditions (25 bar hydrogen) to give lactam **293** in quantitative yield (entry 1). No reduction was observed with the catalysts (*R*)-Ru(OAc)<sub>2</sub>(BINAP) (*R*)-**37a** or (*R,R*)-Rh-EtDuPhos (*R,R*)-**229** under a variety of conditions (entry 2 and 3). Due to the highly polarised nature of **283**, transfer hydrogenation catalyst (*R,R*)-RutethTsDPEN (*R,R*)-**248** was tested with no success (entry 4). Pyridone **283** was found to be unusually resistant to hydrogenation with these asymmetric catalysts.



Scheme 2.3.12: AH of pyridones **283** and **285**.

Table 2.3.3. AH of pyridones **283** and **285**.

entry	pyridone <sup>a</sup>	cat.	mol %	temp/ (°C)	time (h)	P. (bar)	conv. (%)
1	<b>283</b>	Pd / C	10	30	20	25	> 99 <sup>d</sup>
2	<b>283</b>	( <i>R</i> )- <b>37a</b>	5	30	20	20	0
3	<b>283</b>	( <i>R,R</i> )- <b>229</b>	5	30	20	20	0
4	<b>283</b> <sup>b</sup>	( <i>R,R</i> )- <b>248</b> <sup>c</sup>	2	30	72	N/A	0
5	<b>285</b>	Pd/C	10	40	24	1	29 <sup>d</sup>
6	<b>285</b>	W001-1 <sup>e</sup>	3.2	40	120	40	0
7	<b>285</b>	W002-1 <sup>e</sup>	3.2	40	120	40	0
8	<b>285</b>	T001-1 <sup>e</sup>	3.2	40	120	40	0
9	<b>285</b>	T002-1 <sup>e</sup>	3.2	40	120	40	54
10	<b>285</b>	( <i>R,R</i> )- <b>229</b>	3	40	120	40	75
11	<b>285</b>	( <i>R,S</i> )- <b>279</b>	3	40	120	40	0

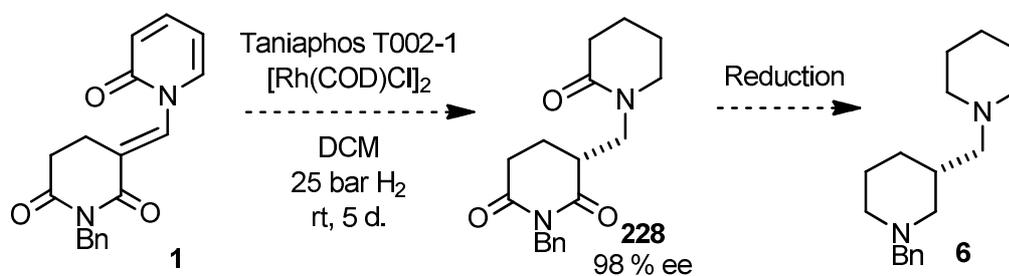
a. Reactions with **283**: 30 mg scale. Reactions with **285**: 40 mg scale; b. 50 mg scale; c. determined by chiral HPLC; d. isolated yield; e. used with [Rh(COD)Cl]<sub>2</sub> (3 mol % w/r to Rh).

Pyridone **285** was readily reduced with Pd / C under a balloon of hydrogen to give lactam **294** in complete conversion, although it was obtained at a low yield (29 %) following repeated purification (silica gel chromatography) which was required due to its use as a racemic standard. Chiral separation of **294** was achieved (Chiralpak IA, hexane : IPA 85 : 15, flow rate = 1 mL/min). The Walphos ligands W001-1 and W00-2-1; and Taniaphos ligands, T001-1 and T002-1 were used (3.2 mol %) in AHs with the precatalyst Rh(COD)Cl]<sub>2</sub> (3.0 mol % w/r to Rh) and pyridone **2** (entry 6-9). Taniaphos T002-1 was the only active ligand resulting in 54 % conversion to **294** in 0 % ee (entry 9). (*R,R*)-RhDuPHOS, (*R,R*)-**229** resulted in 75 % conversion to **294** in 0 % ee (the chiral HPLC method was shown above). No activity was observed with the catalyst (*R,S*)-IrThrePHOX, (*R,S*)-**279**, although iridium catalysts of this type are known to be deactivated by strongly coordinating substrates (entry 11).<sup>164</sup> The asymmetric homogeneous catalysts studied required forcing conditions to achieve reduction. As the reduction products found were found to be racemic, further optimisation to achieve full conversion was not attempted.

## Section 2.4: Synthesis of (1-Benzyl-3-(piperidin-1-ylmethyl)piperidine): AH of Pyridone 3.

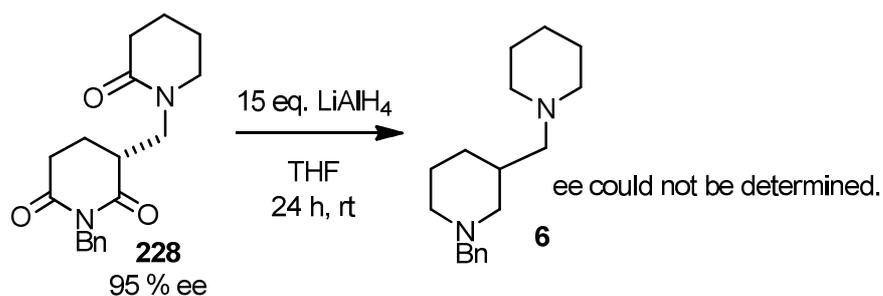
### Section 2.4.1: Reduction of Imide 228.

This work carries on from Section 1, following the successful AH of enamide **1** with Taniaphos T002-1 and  $[\text{Rh}(\text{COD})\text{Cl}]_2$  which resulted in the formation of lactam (*S*)-**228** in 98 % ee (Table 2.1.3, p 72). Further reduction to the fully saturated compound, 1-benzyl-3-(piperidin-1-ylmethyl)piperidine **6** (bispiperidine) was seen as a desirable method of forming enantiomerically enriched 5-substituted piperidines (Scheme 2.4.1).



Scheme 2.4.1: Synthesis of bispiperidine **6** from imide **1**.

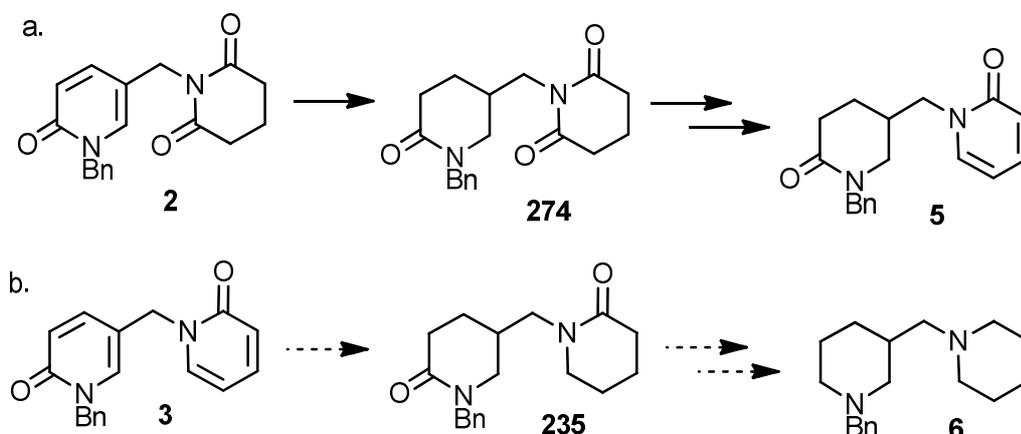
The reduction of imide (*S*)-**228** (95 % ee) was achieved following reaction with an excess (15 eq.) of  $\text{LiAlH}_4$  in THF for 24 h at room temperature (Scheme 2.4.2).<sup>165</sup> A similar glutarimide reduction with  $\text{LiAlH}_4$  from the literature resulted in the formation of the corresponding piperidine with no reported loss of ee.<sup>166</sup> The reduction of **228** would be expected to have proceeded in the same manner, however it was not possible to achieve chiral separation by GC or HPLC to confirm this, which seemed important in light of the loss of ee following the reduction of imide **228** (Section 2.1). This partly motivated the development of a second synthesis of bispiperidine.



Scheme 2.4.2: reduction of imide **228** to bispiperidine **6** with  $\text{LiAlH}_4$ .

*Alternative approach to bispiperidine 6.*

Leading on from Section 3, where the AH of pyridone **2** was used as a key component in the formal synthesis of cytosine precursor **5** (Scheme 2.4.3a), in this section, the AH of pyridone **3** was carried out. In analogy with the rationale for the proposed enantioselective reduction of pyridone **2**, the reduction of pyridone **3** was proposed to bear the known functional requirements for successful AH via the proximal pyridone group which may direct the reduction.



Scheme 2.4.3: a. Synthesis of cytosine precursor **2** from Section 3;  
 b. proposed synthesis of bispiperidine **3** in this section.

This work was largely motivated by the availability of an extensive screen of chiral ligands and rhodium, ruthenium and iridium catalysts which was carried out simultaneously with the screen of pyridone **2** through collaboration with AstraZeneca. As pyridone **3** was synthetically accessible through a similar route to pyridone **2**, the opportunity of having multiple substrates screened was taken and pyridone **3** was also put forward for screening. This was also partly motivated by the

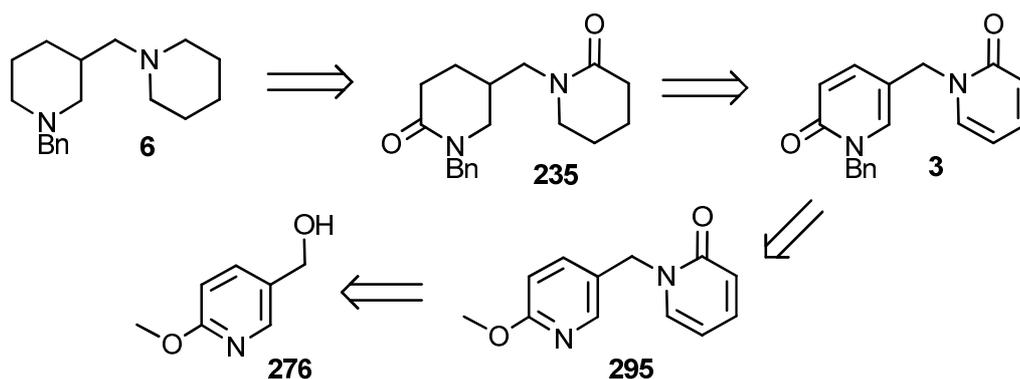
uncertainty of the ee of bispiperidine **6** (formed following reduction of **228**, Scheme 2.4.1). As was for the motive for the AH of pyridone **2**, a route to bispiperidine **6** involving a configurationally stable chiral centre was also desirable. The synthetic use of optically pure 5-substituted lactams and piperidines has been briefly reviewed in Section 1.5, which gives further motive for this work.

### *Summary.*

This section starts with the main subject of this section, the synthesis and hydrogenation of pyridone **3**, and subsequent conversion to bispiperidine **6**. This section then ends with related work involving the synthesis and hydrogenation of 5-membered enamides in attempt to access 5-membered cyclic diamines.

### *Section 2.4.2: Synthesis and AH of Pyridone 3.*

In this retrosynthetic approach, bispiperidine **6** may be directly obtained from bislactam **235**, through reduction of the two amide groups in which the isolated chiral centre has no risk of epimerisation (Scheme 2.4.4). Bislactam **235** is the product of the asymmetric reduction of pyridone **3**. This AH-catalysed reduction of this compound holds the potential for a directing group effect through the pyridone carbonyl as discussed earlier. Hydrogenation substrate, pyridone **3** may be conveniently reached from pyridine **295** via an *N*-alkylation *O*-demethylation sequence. Pyridine **295** may be accessed from alcohol **276** following substitution of the corresponding halide with 2-hydroxypyridine. Due to the thermodynamic preference of *N*-alkylation over *O*-alkylation encountered when initial formation of the pyridone is reversible, chemoselectivity to the desired *N*-pyridone **295** may be achievable possible in this process.<sup>167</sup>



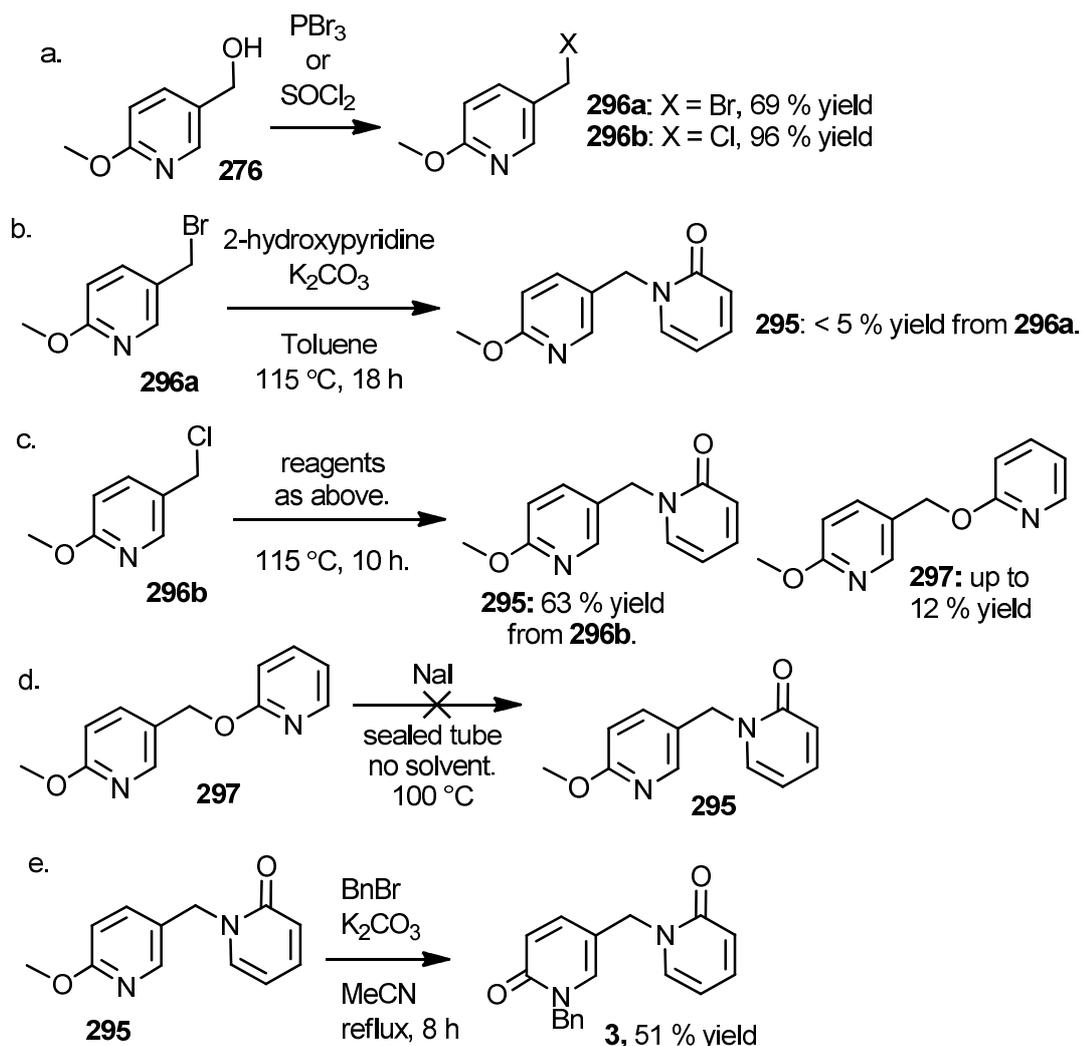
Scheme 2.4.4: Retrosynthetic of bispiperidine **6**.

### *Synthesis of hydrogenation substrate 3.*

For the initial alkylation to form pyridine **295**, halides **296a** and **296b** were considered. Bromide **296a** was formed following treatment of alcohol **276** with  $\text{PBr}_3$  (Scheme 2.4.5a). The crude bromide was used directly in the subsequent reaction with 2-hydroxypyridine and  $\text{K}_2\text{CO}_3$ . Methoxypyridine **295** was obtained in <5 % yield (Scheme 2.4.5b). This low yield was may be due to the lability of bromide **296a** (the compound has also been reported to undergo self polymerisation). Alternatively, chloride **296b** (formed from thionyl chloride) was used for the alkylation reaction. Reaction with 2-hydroxypyridine and  $\text{K}_2\text{CO}_3$  in toluene at 115 °C for 10 h, successfully gave methoxypyridine **295** in 63 % yield as the major isomer, alongside the *O*-substituted isomer, **297** which was isolated in 12 % yield, although this was inconsistent and in some cases it was not isolated (Scheme 2.4.5c). Both isomers were readily separated from each other via silica gel chromatography. Longer reaction times (18 h) resulted in only traces of **297** (observed by  $^1\text{H}$  NMR of the crude reaction mixture). This has been attributed to the reversibility of the reaction and the known thermodynamic preference for alkylation at nitrogen.

It is worth noting the similarity of the  $^1\text{H}$  NMR spectra obtained from *N*-substituted pyridone **295** with that of *N*-substituted enamide **1** (Section 1); and those of *O*-

substituted pyridol **297** with O-substituted enamide **227** (Section 2.1.2). These comparisons are summarised in Appendix I. Their patterns are similar and appear to be indicative of *N*- or *O*- substitution; however the conclusive evidence for each structural assignment was obtained from the X-ray structure of **3**, formed from *N*-substituted imide **295** (see Figure 2.4.1).



Scheme 2.4.5: a. Synthesis of halides **296a** and **296b**; b. formation of **295** from **296a**; c. formation of **295** and **297** from **296b**; d. unsuccessful isomerisation of **297**; e. benzylation of **295**.

Sodium iodide mediated conversion of pyridols to pyridones have been reported.<sup>168</sup> This was attempted following the heating of pyridol **297** with NaI in a sealed tube at 100 °C; however the reaction yielded a complex mixture from which no products could be isolated (Scheme 2.4.5c).

With methoxypyridine **295** in hand, conversion to the corresponding pyridone was carried out. Methoxypyridine **295** readily underwent alkylation with benzyl bromide and  $K_2CO_3$  in acetonitrile at 80 °C for 8 h. Hydrogenation substrate pyridone **3** was obtained in 51 % yield as a colourless power, following recrystallisation from ethanol (Scheme 2.4.5d). Further recrystallisation provided crystals which underwent X-ray diffraction to confirm the structure (Figure 2.4.1).

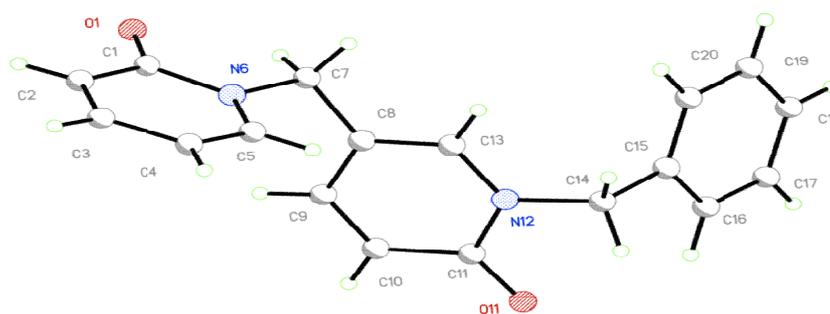
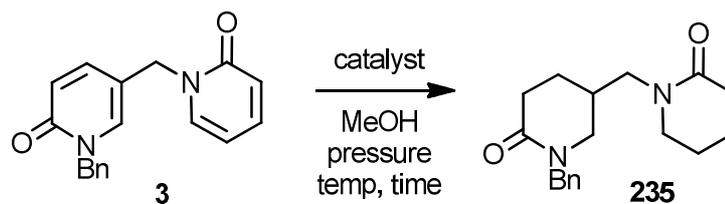


Figure 2.4.1: X-ray crystallographic structure of pyridone **3**.

#### *AH of pyridone 3.*

The hydrogenation of pyridone **3** was carried out using a range of homogeneous and heterogeneous catalysts (Scheme 2.4.6, Table 2.4.1). Pyridone **3** was reduced with Pd / C under a balloon of hydrogen at 30 °C to give lactam **235** in 90 % conversion after 17 h (entry 1). Preferably (due to ease of subsequent purification) reduction was achieved with  $PtO_2$  under a balloon of hydrogen at 30 °C.

At a larger scale of 644 mg, 90 % conversion of the starting material was achieved (as determined by  $^1H$  NMR) after 20 h, providing pure lactam **235** in 75 % yield following silica gel chromatography (entry 2) (for the chiral separation of lactam **235**, see Section 2.1.3).



Scheme 2.4.6: AH of pyridone **3**.

Table 2.4.1: AH of pyridone **3**.

entry	cat.	scale (mg)	mol %	temp/ (°C)	time (h)	P. (bar)	conv. (%)
1	Pd /C	110	5	30	17	1 <sup>b</sup>	90
2 <sup>a</sup>	PtO <sub>2</sub>	644	5	30	20	1 <sup>b</sup>	90 (75 <sup>c</sup> )
3	( <i>R,R</i> )- <b>229</b>	30	5	rt	18	20	40 <sup>d</sup>
4	( <i>R,S</i> )- <b>279</b> <sup>a</sup>	20	1	rt	2	50	0

a. DCM used as solvent; b. run under a balloon of hydrogen; c. % yield after purification; d. the sample was found to be racemic.

Pyridone **3** underwent partial conversion to lactam **235** with (*R,R*)-RhEtDuPhos, (*R,R*)-**229** following a reaction time of 18 h at room temperature under 20 bar hydrogen (entry 3), however the ee of the sample was found to be 0 %. No activity was observed with (*R,S*)-IrThrePHOX, (*R,S*)-**279** (entry 4).

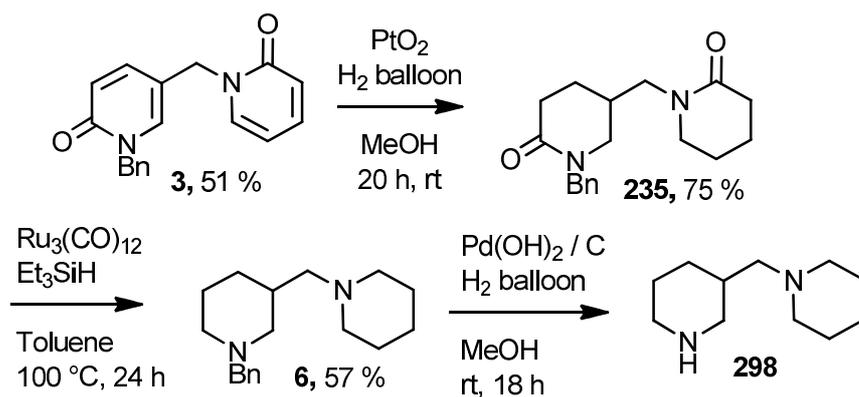
The AH of pyridone **3** underwent an extensive asymmetric ligand screen with ruthenium and rhodium catalysts, through collaboration with AstraZeneca. Unfortunately the same circumstances as detailed in Section 2.3 prevented these results from being made available for presentation in this thesis. It was, however, reported that of all the ligands screened, no significant chiral induction was observed in any case.

Again, this absence of any enantioselectivity with any of the ligands screened was a again a real set back. This shows that the predicted coordination mode was not successful in directing enantioselectivity. As explained in Section 2.3, it is possible

that a poorly controlled asymmetric reduction of the pyridinium tautomer of **3** is taking place, as suggested for similar compounds (see Section 1.2.4).<sup>42</sup>

*Section 2.4.3: Synthesis of (1-Benzyl-3-(piperidin-1-ylmethyl)piperidine) 6.*

With lactam ( $\pm$ )-**235** in hand, the racemic synthesis of bispiperidine was continued (Scheme 2.4.7). Treatment of lactam **235** with LiAlH<sub>4</sub> in THF (0 °C to rt) provided the product **6** in 37 % yield following careful purification (silica gel chromatography, eluent: CHCl<sub>3</sub> – MeOH - NH<sub>4</sub>OH 100:2:1, visualisation by I<sub>2</sub>). This method was not ideal, as a large amount of side products were co-formed which required tedious purification. Alternatively, reduction with Ru<sub>3</sub>(CO)<sub>12</sub> (2 mol %) and Et<sub>3</sub>SiH (7 eq.) in toluene at 100 °C for 18 h resulted a clean crude reaction mixture (<sup>1</sup>H NMR) containing bispiperidine **6** with only traces of side products.<sup>169</sup> In this case an alternative solvent system was used in purification (silica gel chromatography, eluent: ethyl acetate – hexane – triethylamine 10:90:1, visualisation by I<sub>2</sub>) to give product **6** in 57 % yield. Debenzylation of bispiperidine **6** was achieved with Pd(OH)<sub>2</sub> under an atmosphere of hydrogen, following 18 h at room temperature. A sample containing the free amine was isolated through the use of an Isolute-XL SCX amine scavenger thiol resin. The crude reaction mixture was conveniently passed through the resin which was then washed with solvent to remove non basic impurities. The trapped basic compounds on the resin (including the desired product) were then released by washing flushing the resin with a methanolic solution of ~2 % NH<sub>4</sub>OH (for details of use, see the experimental section). A sample containing the amine **298** was obtained showing only a trace of the starting material by <sup>1</sup>H NMR.

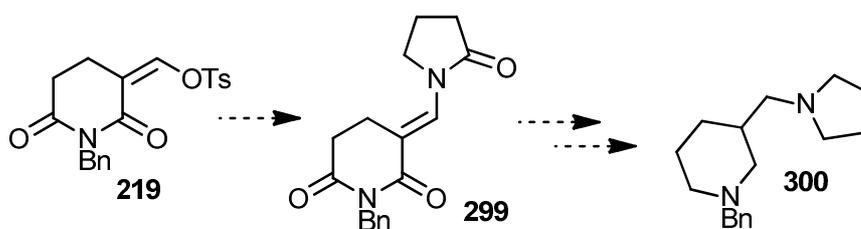


Scheme 2.4.7: Formation of bispiperidine **6** from pyridone **3**.

#### Section 2.4.4: Synthesis and Hydrogenation of Enamide **299**.

Following the synthesis and hydrogenation of enamide **1**, the synthesis of alternative heterocyclic derivatives was briefly investigated, to probe the further utility of this synthetic route to other applications.

Through the use of a different nucleophile in the Michael addition reaction with enamide **219** (see Section 2.1) it may also be possible to access 5-membered enamides such as compounds **299** which could be subsequently converted to the corresponding diamines (**300**) (Scheme 2.4.8).

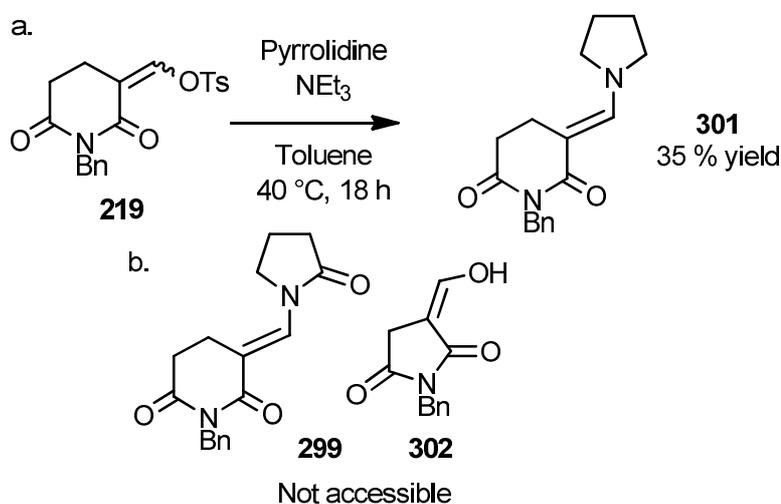


Scheme 2.4.8: Potential synthesis of 5-membered enamides and diamines

#### Synthesis of pyrrolidine derived enamides.

Pyrrolidine **301** was prepared in 35 % yield following treatment of enamide **219** with pyrrolidine and  $\text{NEt}_3$  in toluene at 40 °C for 18 h (Scheme 2.4.9). Treatment of pyrrolidinone with tosylate **219** failed to yield the corresponding pyrrolidinone **301**. An attempted synthesis of enol imide **302** using N-benzyl succinimide as starting

material was unsuccessful, following a modified procedure used for the synthesis of enamide **218** (see Section 2.12).



Scheme 2.4.9: a Synthesis of pyrrolidine **218**; b. unachievable targets **300** and **302**.

Surprisingly, pyrrolidine **301** was inert to pressure hydrogenation with Pd/C and RhEtDuPHOS, (*R,R*)-**229** and transfer hydrogenation with RutethTsDPEN, (*R,R*)-**248**. This is presumably due to the relatively higher stability of the conjugated system of **301** compared to enamide **1**. This may result from relatively higher donation of the pyrrolidine nitrogen lone pair into the conjugated enamide system, in comparison with the corresponding pyridone nitrogen lone pair donation.

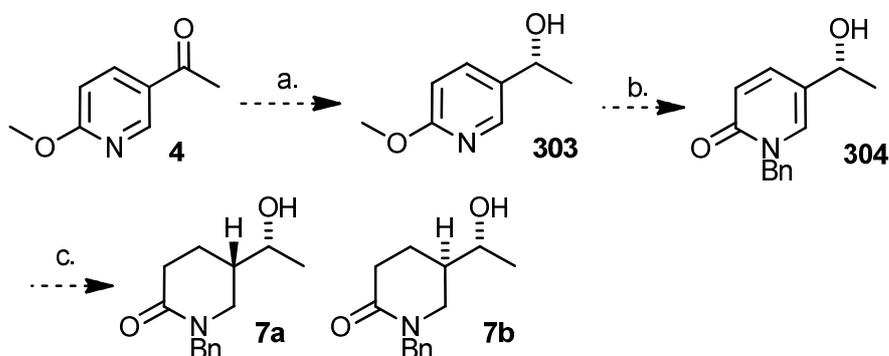
### Conclusions.

Following an extensive ligand screen, the hydrogenation of precursor pyridone **3** did not result in any substantial enantioselectivity. The product of this hydrogenation, lactam **235** was however successfully converted to bispiperidine **6**. The synthesis of enamide, pyrrolidine **3** was completed; however the compound was inert to hydrogenation.

## Section 2.5: Asymmetric Synthesis of Alcohols **7a** and **7b**.

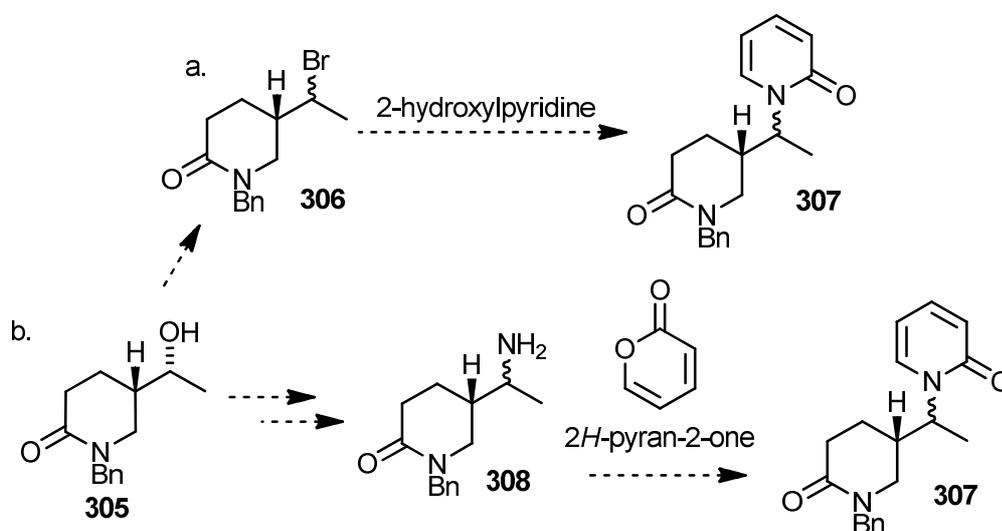
### Section 2.5.1: Introduction.

In sections 1-4, AH and ATH was used as a means of potentially forming enantiomerically enriched 5-substituted lactams specific to the application in the asymmetric formal synthesis of cytosine and bispiperidine **6**. In this section, an indirect method of asymmetrically synthesising a 5-substituted lactam cytosine precursor was attempted, through the conversion of an enantiomerically pure alcohol (formed via ATH) proximal to the 5-lactam position into a pair of diastereomers, from which physical chromatographic separation may be possible. This would result in two diastereomers which were optically enriched at the desired 5- position (although differing in orientation). This is depicted more specifically in Scheme 2.5.1: ATH of pyridyl methyl ketone **4**, may result in the highly enantioselective formation of alcohol **303** (Scheme 2.5.1b, step a). Following conversion to the corresponding pyridone, **304** (step b.), hydrogenation may result in the formation of two diastereomers, **7a** and **7b** which may be separable by chromatography. Each diastereomer would be optically enriched at the desired 5-lactam position, potentially present in the enantiopurity obtained from the initial ketone ATH. There is a further potential for diastereoselectivity in the hydrogenation of pyridone **304** (step c).<sup>176</sup>



Scheme 2.5.1: Potential strategy for the enantiomeric enrichment of 5-substituted lactams – chromatographic separation of diastereomers **7a** and **7b**.

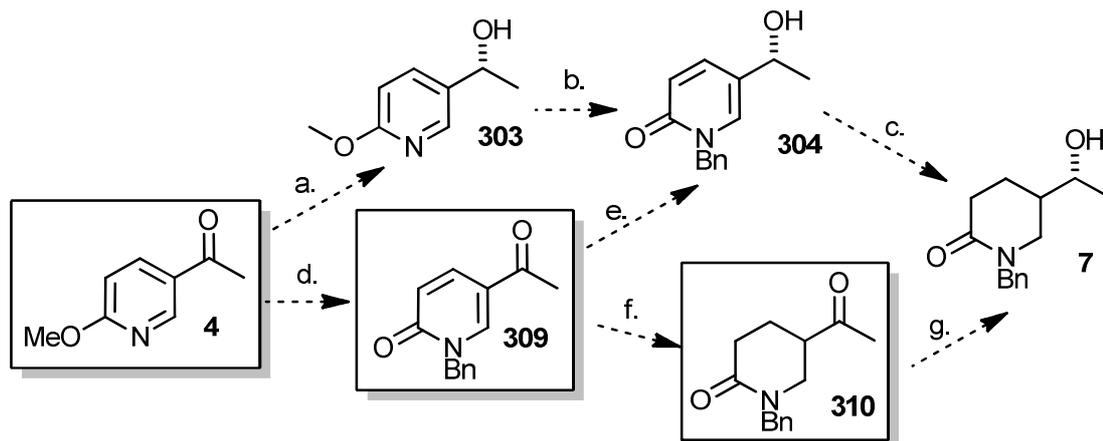
Optically pure lactam **7** may be subsequently converted to a derivative of the cytosine precursor, lactam **5** through substitution with 2-hydroxypyridine (in analogy to Gallagher's method)<sup>63</sup> (step a, Scheme 2.5.2)) or via conversion to the corresponding amine **308**, which may be converted to the pyridone **307** following reaction with 2*H*-pyran-2-one. However, in view of the reviewed pharmacological limitations of structurally modified bispidine derivatives, optically pure 5-substituted lactams are in themselves synthetically useful in other applications.<sup>170</sup>



Scheme 2.5.2: potential utilisation alcohol **7**.

#### *Various methods of forming lactam **7**.*

Additionally to the procedure for reaching lactam **7** shown in Scheme 2.5.1, potentially these are also alternative routes, resulting from alternative orders of sequential transformation steps. Each route would involve a different ketone, expected to be reduced in differing ee, which as well as its synthetic use, may also be mechanistically interesting. These steps are shown in Scheme 2.5.3: 1) a. ketone reduction of **4**; b. conversion to pyridone **304**; c. hydrogenation of pyridone **304**. 2) d. conversion to pyridone **309**; e. ketone reduction of **304**; c. hydrogenation of pyridone **304**; 3) d. conversion to pyridone **309**; f. hydrogenation of pyridone **310**; g. ketone reduction of **310**.



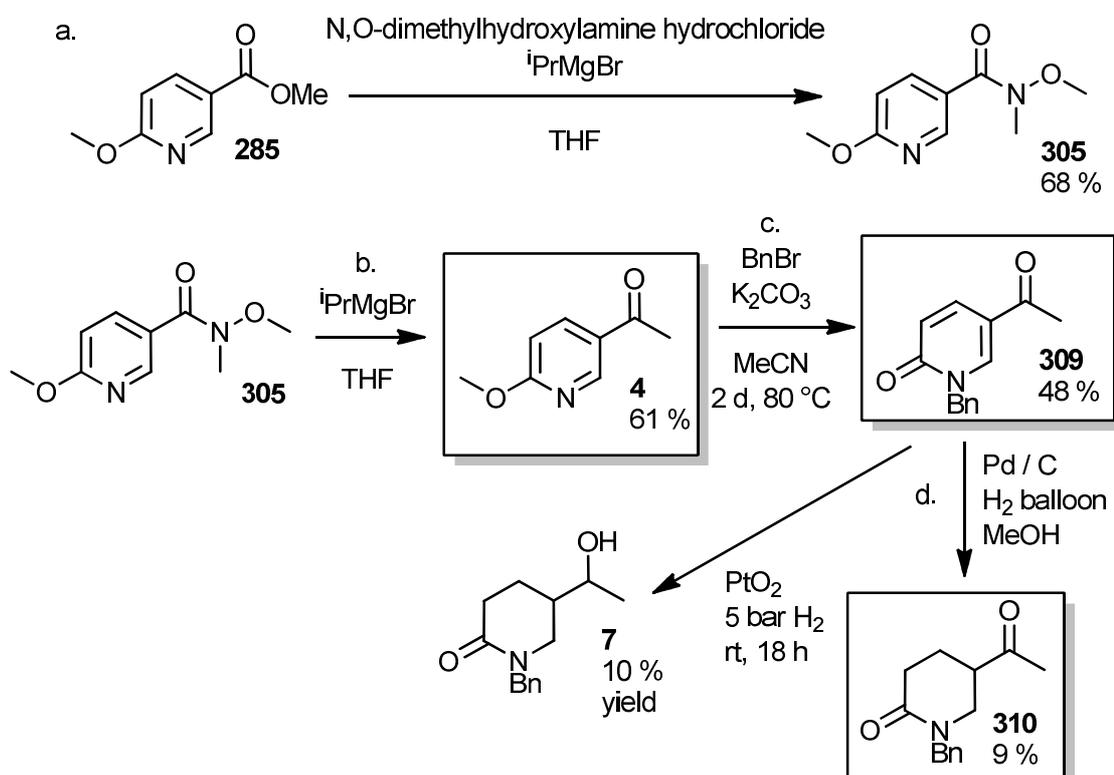
Scheme 2.5.3: Various potential routes to alcohol **7** from **4**; and target ketones **4**, **309** and **310**.

This section is split between three main parts. In the first part, the synthesis and ATH of ketones **4**, **309** and **310** was carried out. Based on these results, a second series of pyridyl alkyl / aryl ketenes were evaluated. In the second part, the synthesis of diastereomers **7a** and **7b** was completed; and in the final section, their application in the synthesis of amines **308a** and **308b** was carried out.

#### *Section 2.5.2: Preliminary Synthesis and ATH of Ketones.*

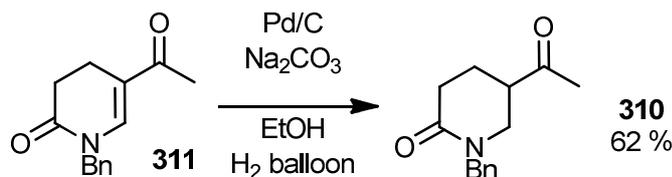
To initiate the work, the synthesis of the key ketones **4**, **309** and **310** was carried out. This required the synthesis of pyridyl methyl ketone **4** utilising the alkylation of Weinreb amide **305**.<sup>171</sup> Weinreb amide **305** was obtained directly from the substitution of *N,O*-dimethylhydroxylamine hydrochloride with methyl methoxynicotinate **285** and isopropyl magnesium chloride in THF (-40 °C to 0 °C, 90 min). Following silica gel chromatography, Weinreb amide **305** was obtained in 68 % yield (Scheme 2.5.5a). Direct alkylation with methyl magnesium chloride gave the pyridyl methyl ketone **4** in 61 % yield, following purification (Scheme 2.5.5b). This yield was obtained reproducibly at reaction scales of ~ 3.5 g. Ketone **4** was commercially available but not affordable for its use as the starting material of a synthesis.

Synthesis of pyridone methyl ketone **309** was achieved via treatment of pyridyl methyl ketone **4** with benzyl bromide in acetonitrile at 80 °C. Pyridone methyl ketone **309** was obtained in 48 % yield, following silica gel chromatography (Scheme 2.5.5c).



Scheme 2.5.5: a. Synthesis of Weinreb amide **305**, and synthesis of ketones **4**, **309**, and **310**.

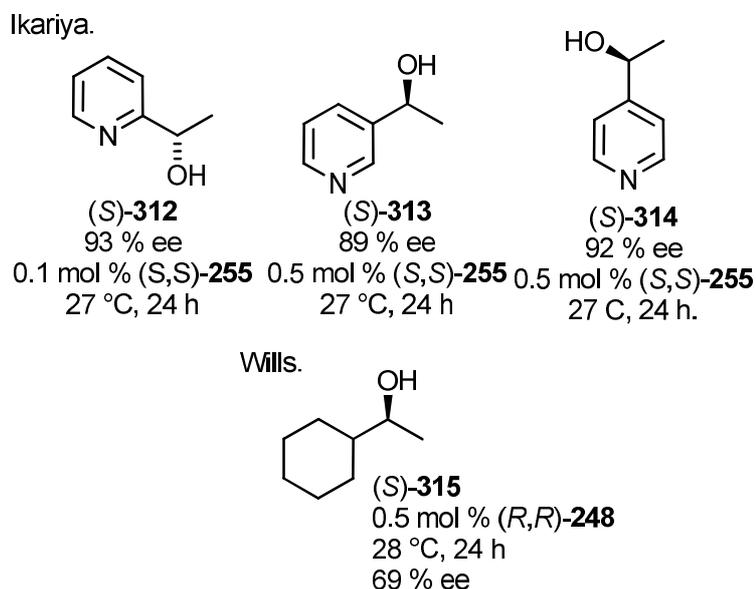
Lactam methyl ketone **310** was obtained via reduction of pyridone methyl ketone **309** with Pd/C under an atmosphere of hydrogen at room temperature. The reaction was unselective and a large amount of side products were observed by <sup>1</sup>H NMR. Repeated purification (silica gel chromatography) was required to isolate the lactam methyl ketone **310** in 9 % yield (Scheme 2.5.5d). The product has been reported in the literature, and alternatively had been obtained from Pd/C reduction of enamide **311** in 62 % yield (Scheme 2.5.6).<sup>197</sup> However, sufficient material was obtained (via the procedure) for subsequent ATH and the literature work did not need to be repeated. Notably, the reduction of **309** with PtO<sub>2</sub> resulted in formation of alcohol **7** in 10 % yield (5 bar H<sub>2</sub>, MeOH, rt, 18 h).



Scheme 2.5.6: Literature synthesis of lactam **310**.

*ATH of pyridine derived ketones.*

The ATH of pyridyl ketones similar in structure to **285**, has been reported with numerous catalysts.<sup>172</sup> Ikariya achieved the reduction of a range of pyridyl alkyl ketones in high enantioselectivity with (*S,S*)-Ru(TsDPEN), **255** (the catalyst structure is shown in Appendix IV). Pyridyl alcohols (*S*)-**312**, (*S*)-**313**, and (*S*)-**314** were obtained in 93 %, 98 % and 92 % ee respectively (Scheme 2.5.8b).<sup>173</sup> Enantiofacial selection during these reductions was comparable to the reduction of aromatic ketones. Optically pure pyridyl ketones have been useful as chiral ligands, auxiliaries, and pharmaceuticals.



Scheme 2.5.6b: Optically pure pyridyl alcohols obtained by ATH with (*S,S*)-**255**, achieved by Ikariya.

The interaction that lactam methyl ketone **310** may have with the catalyst *Ruteth*TsDPEN is uncertain; however, unfunctionalised ketones such as cyclohexyl methyl ketone has been reduced in 69 % ee to form the (*S*) configuration alcohol (*S*)-**315** with (*R,R*)-**248** by Wills.<sup>174</sup>

For this study, the ATH of the pyridyl alkyl ketones was carried out using with *Ruteth*TsDPEN, **248** (Scheme 2.5.9). The stereofacial selection of this catalyst would be expected to be analogous to that of Ru(TsDPEN), **255**. The ATH of ketones **4**, **309** and ( $\pm$ )-**310** was carried out with the catalyst *Ruteth*TsDPEN, **248** (Scheme 2.5.7). Neat FA/TEA was used as solvent at a substrate concentration of 1M in all cases. Ees were determined by chiral GC or HPLC analysis. Racemic samples of the product alcohols formed by reduction with NaBH<sub>4</sub> were used as racemic standards to confirm the position of the isomers in chiral GC / HPLC analysis. The results are shown in Table 2.5.1.



Scheme 2.5.7: ATH of ketones **4**, **309** and **310**.

Table 2.5.1: ATH of ketones **4**, **309** and **310**.

entry	ketone <sup>a</sup>	cat.	time (h)	conv (%) <sup>d</sup>	Prod.	Ee (%)	a : b
1	<b>4</b>	( <i>S,S</i> )	21	100	( <i>S</i> )- <b>303</b> <sup>e</sup>	82 <sup>b</sup>	N/A
2	<b>4</b>	( <i>S,S</i> )	18	100	( <i>S</i> )- <b>303</b>	75 <sup>b,g</sup>	N/A
3	<b>309</b>	( <i>R,R</i> )	20	100	( <i>R</i> )- <b>304</b> <sup>e</sup>	42 <sup>c</sup>	N/A
4	( $\pm$ )- <b>310</b>	( <i>R,R</i> )	24	100	( <i>R,S</i> )- <b>7a</b> <sup>f</sup> ( <i>S,S</i> )- <b>7b</b> <sup>f</sup>	85 <sup>b</sup> 49 <sup>b</sup>	1.5:1 <sup>d</sup>

a. [SM] = 1 M; b. determined by chiral GC; c. determined by chiral HPLC; d. determined by <sup>1</sup>H NMR; e. config. assigned by comparison [ $\alpha$ ]<sub>D</sub> values of an authentic sample; f. config. assigned by comparison of the GC analysis of an authentic sample; g. reaction run at rt and in methanol, [SM] = 0.16 M; N/A: not applicable.

Configurations were determined by comparison of [ $\alpha$ ]<sub>D</sub> values of a known sample, or by comparison of HPLC/GC analysis of a known sample. Following 17 h at room temperature, pyridyl methyl ketone **4** underwent complete conversion to alcohol, (*S*)-**303** in 82 % ee (entry 1, Table 2.5.1, Figure 2.3.2) (CP – ChiraSil – DEX CB, gas: He, T = 170 °C). The ee was slightly lower (75 % ee) when run in methanol at room temperature (entry 2). Pyridone methyl ketone **309** underwent complete conversion to (*R*)-**304** in 42 % ee (entry 3) (Chiralpak IC, hexane : IPA 80 : 20). The absolute

configuration was assigned as *R* following comparison of the HPLC analysis of a known sample of (*R*)-**304** (details of the preparation of (*R*)-**304** are shown in the next section). Reduction of lactam methyl ketone ( $\pm$ )-**310** resulted in formation of diastereomers **7a** and **7b** in a 1.4:1 ratio. In the case of this experiment the two diastereomers were not separated (because of the small scale of the experiment) but directly analysed as a mixture. The dr was determined by  $^1\text{H}$  NMR analysis of the crude product mixture. Chiral separation of the four isomers was achieved by chiral GC: (CP – ChiraSil – DEX CB, gas: H, T = 200 °C). In the following section, a racemic mixture of diastereomers **7a** and **7b** was separated chromatographically to provide two diastereomerically pure racemic samples of ( $\pm$ )-**7a** and ( $\pm$ )-**7b**. This enabled the assignment of the enantiomer pairs (for this experiment), and subsequently the ees and configurations were determined. The ees of **7a** and **7b** (entry 3) were 85 % and 49 % respectively. These chiral GC traces are shown in Appendix IV. The Complete details of how the configurations of **7a** and **7b** have been assigned are fully explained in a later Section 2.5.4.

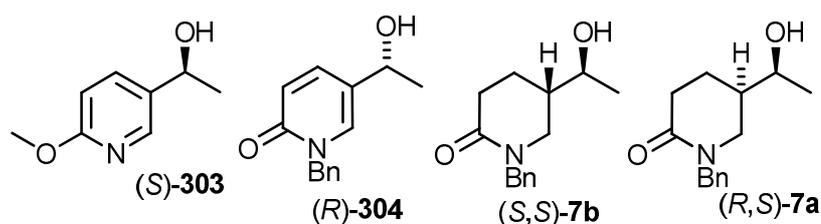


Figure 2.3.2: ATH alcohol products.

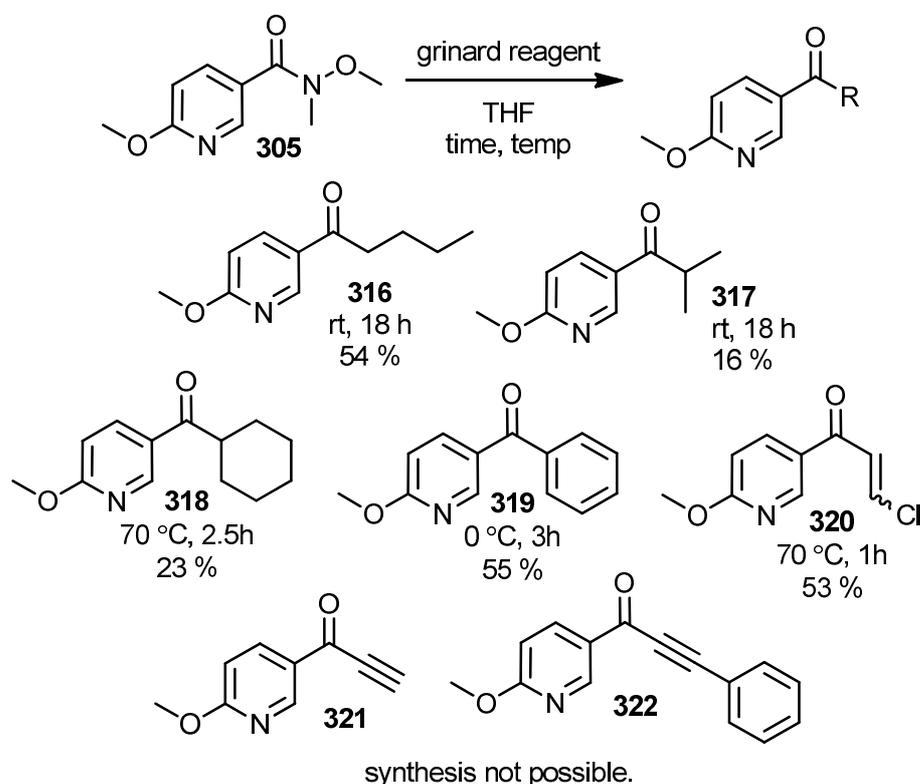
### Discussion.

The absolute configuration of the alcohol product obtained from reduction of ketone **4** with (*S,S*)-**248** is in accordance with what would be expected through the standard reduction mechanism of aryl methyl ketones such as acetophenone. Pyridone ketone **309** appeared to also follow this trend: the use of the (*R,R*) catalyst resulted in the (*R*) alcohol, (*R*)-**304** suggesting that an interaction between aryl C-H and pyridone

group is occurring. Lactam methyl ketone **310** results in the formation of the (*S*) configuration alcohol. This result follows what is expected from the reduction of cyclohexyl methyl ketone.<sup>175</sup>

*Section 2.5.3: Synthesis and ATH of Pyridyl Alkyl / Aryl Ketones.*

With the ATH of pyridyl methyl ketone **4** giving a product of 82 % ee, a further series of alkyl derivatives was studied. This series was chosen over the lactam alkyl series as they may be directly obtained via alkylation of Weinreb amide **305** (Scheme 2.5.5).<sup>171</sup>



Scheme 2.5.8: Weinreb amide alkylation – ketones **316-320**.

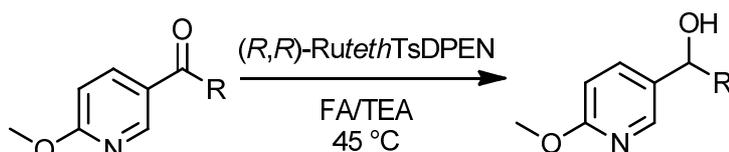
The pyridyl alkyl ketones **316-320** were synthesised via treatment of Weinreb amide **305** with the alkyl magnesium bromide or chloride reagent in a solution of THF at variable temperatures (as stated). Acid work up yielded the ketones following silica gel chromatography. Pyridyl butyl ketone **316** was obtained in 54 % yield following reaction with butyl magnesium bromide at room temperature for 18 h. Pyridyl

phenyl ketone **319** was obtained in 55 % yield following reaction with phenyl magnesium bromide at 0°C for 3 h. Secondary alkyl Grignard reagents, cyclohexyl- and isopropyl- magnesium bromide were lower yielding – isopropyl ketone **317** was obtained in 16 % yield (room temperature, 18 h); and cyclohexyl ketone **318** was obtained in 23 % yield (70 °C, 2.5 h). The use of fresh Grignard reagent, lengthening of the reaction time, or increased reaction temperature did not result in an increased yield for these ketones.

Interestingly, in an attempt to form acetylenic ketone **321**, with ethynyl magnesium bromide, only the corresponding vinyl chlorides, **320** were obtained in 53 % yield ( $Z/E = 2.7/1$ , determined by  $^1\text{H}$  NMR) (acetylenic ketone **321** was not identified from the reaction mixture). This presumably occurred during the quenching of the reaction with HCl. Alternatively, the synthesis of phenylacetylenic ketone **322** was attempted via alkylation with lithium phenylacetylenide (formed via treatment of phenylacetylene with  $n\text{BuLi}$ ); however the resulting product was found to contain the side-product butyl ketone **316** (formed from unreacted  $n\text{BuLi}$ ) even at a substoichiometric ratio of  $n\text{BuLi}$  to phenylacetylene. This side product could not be adequately removed during purification.

*ATH of pyridyl ketones.*

Neat FA/TEA was used as solvent at a concentration of 2M. Ees were determined by chiral GC (CP – ChiraSil – DEX CB, gas: He) or HPLC analysis of the alcohol or the corresponding acetate derivate. Racemic samples of the product alcohols formed by reduction with NaBH<sub>4</sub> were used as racemic standards to confirm the position of the isomers in chiral GC / HPLC analysis. Results are shown in Table 2.5.2.



Scheme 2.5.9: ATH of ketones **316-320**.

Table 2.5.2: ATH of ketones **316-320**.

entry	ketone <sup>a</sup>	R	time (h) <sup>h</sup>	Prod.	Ee (%)
1	<b>4</b> <sup>b</sup>	methyl	21	( <i>R</i> )- <b>303</b> <sup>i</sup>	83 <sup>e</sup>
2	<b>316</b>	<i>n</i> -butyl	20	( <i>R</i> )- <b>323</b> <sup>j</sup>	76 <sup>e</sup>
3	<b>317</b>	<i>i</i> -propyl	22	( <i>R</i> )- <b>324</b> <sup>j</sup>	53 <sup>d</sup>
4	<b>168</b>	cyclohexyl	24	( <i>R</i> )- <b>325</b> <sup>j</sup>	35 <sup>g</sup>
5	<b>319</b>	phenyl	24	(-)- <b>326</b>	48 <sup>f</sup>
6	<b>320</b>	<i>cis</i> -vinyl chloride	24	( <i>R</i> )- <b>327</b>	N/D
7 <sup>c</sup>	<b>320</b>	<i>cis</i> -vinyl chloride <sup>c</sup>	3.5	(±)- <b>328</b>	N/A

a. [SM] = 2 M in FA/TEA; b. [SM] = 1 M in FA/TEA; c. reaction with NaBH<sub>4</sub> in methanol at rt; d. determined by chiral GC; e. determined by chiral GC of the acetate derivate; f. determined by chiral HPLC; g. determined by chiral HPLC of the acetate derivate; h. completion of reaction confirmed by <sup>1</sup>H NMR; i. config. confirmed by lit. optical rotation reference; j. config. assigned by the expected outcome of the theoretical model; N/A: not applicable; N/D: not determined.

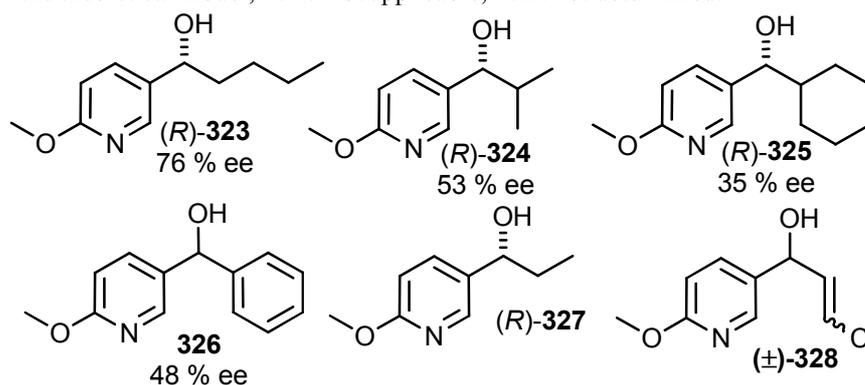
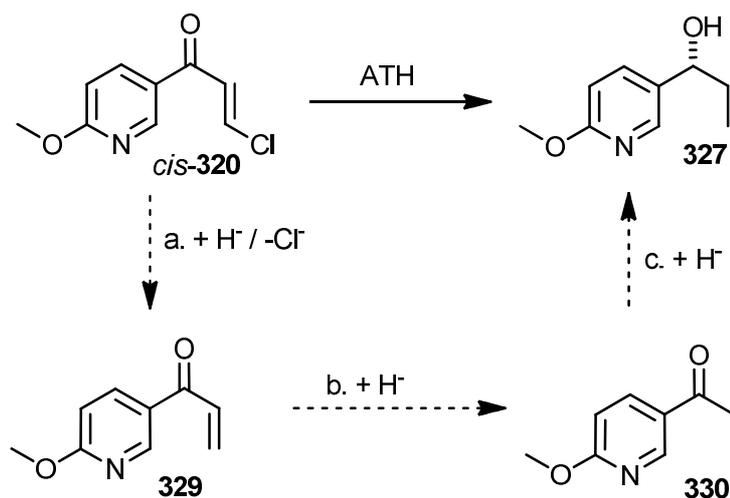


Figure 4: ATH alcohol products.

In all cases the completion of the reduction was confirmed by <sup>1</sup>H NMR. The *n*-alkyl derivatives, methyl ketone **4** and *n*-butyl ketone **316** were reduced in highest enantioselectivity; 83 % and 76 % ee respectively (entries 1 and 2, Table 2.5.2,

Figure 4). In both cases, chiral separation for **323** and **324** was achieved via chiral GC analysis of the acetate derivative. This decrease in ee following increase in alkyl chain length as can be expected.<sup>174</sup> The secondary alkyl ketones, isopropyl ketone **317** and cyclohexyl ketone **318** were reduced in 53 % and 35 % ee respectively (entries 3 and 4). Again, this decrease ee is anticipated and has been reported, following the steric increase of secondary alkyl substituent.<sup>174</sup> In each case the products were assigned the *R* configuration, in analogy with the expected outcome. The reduction of pyridyl phenyl ketone **319** resulted in formation of the product **326** in 48 % ee. Presumably this is the result of one aromatic ring having a slightly more dominating directing affect over the reduction. This compound is known in the literature, however the absolute configuration of the reference was not determined.<sup>205</sup>

Interestingly, *cis* vinyl chloride ketone *cis*-**320** underwent complete reduction to the corresponding saturated ethyl alcohol **327** (entry 6). This product is likely to have been the result of three sequential reductions (Scheme 2.5.10). In step a, 1,4-conjugate reduction and subsequent elimination of the chloride would result in formation of unsaturated ketone **320b**. Further conjugate reduction would result in formation of ethyl ketone **320c** (step b), which again undergoes ketone reduction to give **327**, which may be tentatively assigned as the *R* configuration in analogy with the expected outcome. The ee of this sample was not determined due to time constraints. Interestingly, reduction of *cis*-vinyl ketone **320** with NaBH<sub>4</sub> resulted in the exclusive formation of vinyl chloride **328** – no conjugate reduction was observed.



Scheme 2.5.10: possible sequence of the ATH of *cis*-**320**.

#### Section 2.5.4: Asymmetric Synthesis of Diastereomers **7a** and **7b**.

Following the ketone ATH results, pyridyl methyl ketone **4** was chosen for the large scale synthesis of diastereomers **7a** and **7b**, due to its relatively higher enantioselectivity during ATH. To aid the explanation, the synthesis will be split between two parts: in the first, a racemic synthesis will be shown, which is subsequently followed by the asymmetric synthesis.

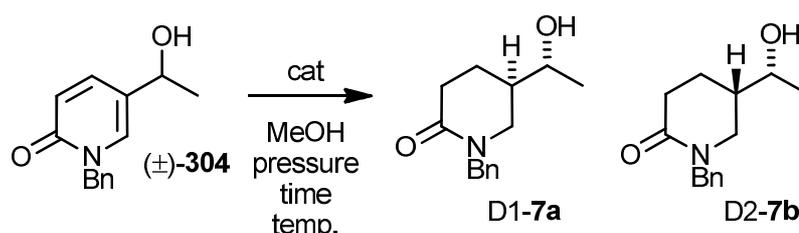
##### *Racemic synthesis of **7a** and **7b**.*

A larger scale reduction of pyridyl methyl ketone (scale) with achieved following reduction with NaBH<sub>4</sub> in methanol at room temperature for 3 h, resulting in formation of alcohol **303** in quantitative yield (Scheme 2.5.12). This material was sufficiently pure for use without further purification. Alcohol **303** readily underwent alkylation with benzyl bromide and K<sub>2</sub>CO<sub>3</sub> in acetonitrile at 80 °C for 24 h to give the pyridone **304** in 63 % yield following purification (silica gel chromatography).

##### *Hydrogenation of pyridone **304**.*

The homogeneous hydrogenation of racemic pyridone ( $\pm$ )-**304** carried out in attempt to diastereoselectively form **7a** and **7b** (Scheme 2.5.11, Table 2.5.3, entry 1-3);

however it was only in one case (*R,R*)-Rh-EtDuPhos, (*R,R*)-**229**, entry 2) that any conversion was obtained although with no diastereoselectivity. In the case of this reaction, the starting material was recovered from the reaction, and its ee was determined to be 0 %, indicating that no KR had occurred (for the chiral separation of pyridone **304**, see Section 6.5.1). Crabtree's iridium based catalyst **335** was unreactive towards the starting material.<sup>176</sup>

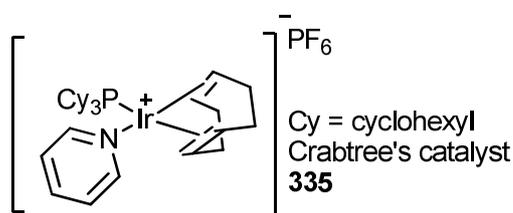


Scheme 2.5.11: hydrogenation of **304**.

Table 2.5.3: Hydrogenation of **304**.

entry	cat.	mol %	temp (°C)	time (h)	P. (bar)	conv. (%) <sup>a</sup>	7a:7b <sup>a</sup>
1	( <i>R</i> )- <b>37a</b>	2	40	20	40	0	N/A
2	( <i>R,R</i> )- <b>229</b>	2	40	20	40	40	1
3	<b>335</b>	2.5	rt	18	1	0	N/A

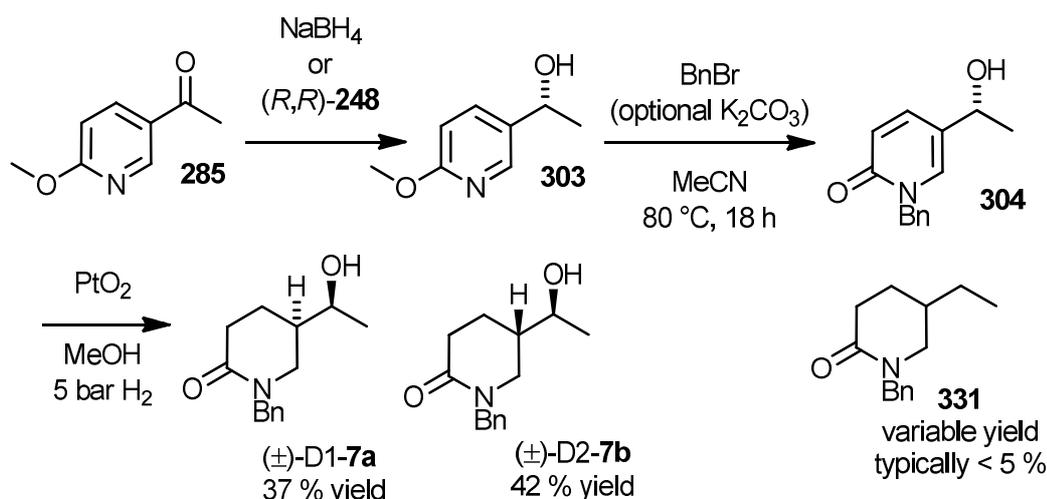
a. determined by <sup>1</sup>H NMR



#### Gram scale hydrogenation of pyridone **304**.

Following the desired chemoselectivity to hydrogenation over hydrogenolysis observed for the PtO<sub>2</sub> reduction of pyridone **277** (Section 2.3.4, p 112); the hydrogenation of pyridone **304** was carried out with PtO<sub>2</sub> in methanol under 5 bar of hydrogen (Scheme 2.5.12). In the majority of experiments, diastereomers D1-**7a** and D2-**7b** were obtained as major products, with only traces of the C-OH cleavage product, ethyl lactam **331** (as determined by <sup>1</sup>H NMR). However in one case, **331** was isolated in 14 % yield (this is detailed in following section). For the case of this

reported reduction, diastereomers **7a** and **7b** were isolated in 37 and 42 % yield respectively following careful purification (silica gel chromatography, 1 to 3 % MeOH in DCM, visualisation by KMnO<sub>4</sub>). Interestingly, it was only in the methanol – DCM solvent system that resolution of the diastereomers was achieved; ethyl acetate and petroleum ether gave no resolution at any mixture ratio. Diastereopurity was confirmed by GC analysis of the crude reaction mixture (before purification) to be 31 % de (CP – ChiraSil – DEX CB, gas: H, T = 185 °C). These samples were later used as racemic standards in chiral analyses of the asymmetric synthesis of the alcohols. For explanation, the two racemic diastereomers from now will be referred to as (±)-D1-**7a** and (±)-D2-**7b** with respect to the order of elution during chromatography.



Scheme 2.5.12: Synthesis of diastereomers **7a** and **7b** via ketone **4**.

Conveniently, (±)-D1-**7a** solidified upon standing to form a waxy solid. Further recrystallisation (DCM – hexane) provided crystals which underwent X-ray diffraction to confirm the structure (Figure 5a). The quality of the X-ray data was sufficient enough for the relative orientation of the two chiral centres to be determined. This crystal sample was racemic, and the two enantiomers are clearly visible in the X-ray structure. This X-ray structure (Figure 5a) corresponds to the depicted schematic structure, (Figure 5b) which may be described as *syn* with respect

to the relative configuration each of the two adjacent hydrogen atoms. Accordingly, ( $\pm$ )-D2-7b has assigned as the *anti* isomer, as depicted in Scheme 2.5.13b.

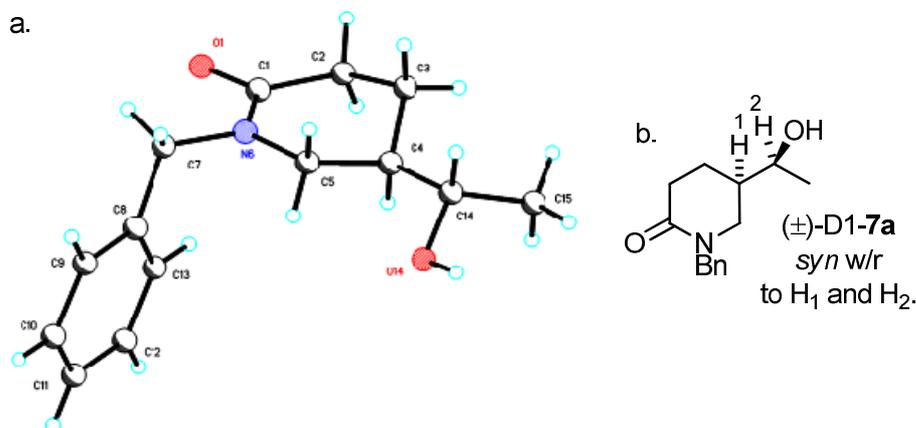


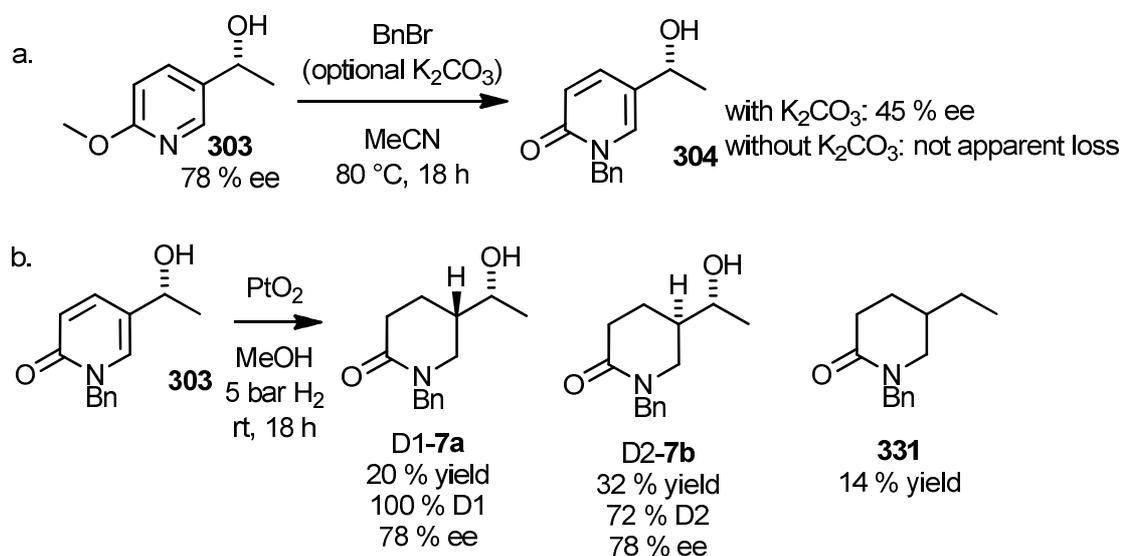
Figure 5: a. X-ray structure of D1-7a; b. corresponding schematic structure of ( $\pm$ )-D1-7a.

#### *Asymmetric synthesis.*

With the racemic samples, ( $\pm$ )-D1-7a and ( $\pm$ )-D2-7b in hand which could serve as racemic standards in GC analysis, the asymmetric synthesis of alcohol **303** was carried out. The ATH of ketone **4** at higher scale (1.0 g) proceeded to give pyridine (*R*)-**303** in 95 % yield following removal of the catalyst (silica gel chromatography) with a slight loss of enantioselectivity at 78 % ee.

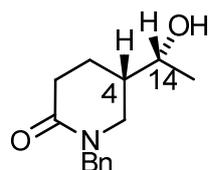
Pyridine (*R*)-**303** readily underwent alkylation with benzyl bromide and K<sub>2</sub>CO<sub>3</sub> in acetonitrile at 80 °C for 24 h to give the pyridone (*R*)-**304** in 71 % yield following purification (silica gel chromatography) (Scheme 2.5.13a) however the sample suffered from loss of enantiopurity, and the ee was determined as 45 % (the chiral separation of **304** was stated in the last section). The use of K<sub>2</sub>CO<sub>3</sub> in the alkylation was therefore questioned. It was previously considered feasible that the base may be required during the *O*-demethylation step of this process and the control experiment had not been carried out as the conditions had been taken from a patent procedure. Repeating the experiment in the absence of K<sub>2</sub>CO<sub>3</sub> resulted in formation of (*R*)-**304**

in 63 % yield. The ee of this sample was not directly determined, but following hydrogenation it was found to be of 78 % ee.



Scheme 2.5.13: a. Alkylation of enantiomerically enriched **303**; b. reduction of **304** with  $PtO_2$ .

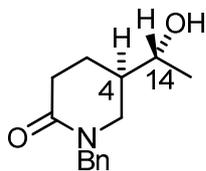
Hydrogenation of pyridine **304** with  $PtO_2$  resulted in formation of alcohols D1-**7a** and D2-**7b**, however a relatively higher level of hydrogenolysis had occurred (Scheme 2.5.13b). Following purification, D1-**7a** and D2-**7b** were isolated in 20 % and 32 % yield respectively, alongside lactam **331** in 14 % yield. The diastereopurity of D1-**7a** and D2-**7b** were independently determined by GC to be: 100 % **7a**; and 72 % **7b** respectively. The ees of D1-**7a** and D2-**7b** were independently determined to be 78 % and 78 % ee respectively, using the racemic standards described in the previous section. The absolute configuration of both diastereomers at C (14) is known to be *R* (they were derived from alcohol (*R*)-**303**). As the relative configuration of D1-**7a** had been determined by X-ray crystallography in the previous section, the following assignments were made accordingly: (*S,R*)-D1-**7a**; (*R,R*)-D2-**7b**. This is illustrated in Scheme 2.5.14.



**D1-7a**  
sys config. (X-ray)  
78 % ee

C (14): *R*  
assigned via precursor, (*R*)-**303**.

C(4): *S*  
sys w/r to C(14) (determined by X-ray.)



**D2-7b**  
*anti* config. (in analogy with D1)  
78 % ee

C (14): *R*  
assigned via precursor, (*R*)-**303**.

C(4): *R*  
*anti* w/r to C(14) (in analogy with D1).

Scheme 2.5.14: Reasoning for the configuration assignments of D1-7a and D2-7b.

#### *Configuration assignment of ATH products from Section 6.5.1.*

Comparison of the GC trace of these samples with the ATH product resulting from the reduction of lactam methyl ketone (section 2.5.2, Table 2.5.1, entry 3) enabled the configuration assignment of the ATH products. This comparison is shown in Appendix III. Pyridone **304** (Table 2.5.1, entry 2) was also assigned as *R* configuration following comparison of the chiral HPLC trace).

#### *Section 2.5.5: Synthesis of Bromides (D1)-306a and (D2)-306b.*

In this section, transformation of alcohol **7** to the desired cytosine precursor lactam **307** was attempted by two methods. In the first, direct alkylation with the corresponding bromide was attempted in analogy with Gallagher's method.<sup>68</sup> In the second, coupling of the corresponding amines **308a** and **308b** was attempted with 2*H*-pyran-2-one.

The substitution chemistry of alcohols D1-7a and D2-7b with 2-hydroxypyridine was first investigated, however these were unreactive with a number of reagents.

Coupling under Mitsunobu conditions <sup>156a</sup> during test reactions with dimethyl malonate as nucleophile were unsuccessful. No reaction occurred following reaction of 2-hydroxypyridine with the corresponding triflate, formed *in situ* via reaction of **7** with triflic anhydride. Only reaction with PBr<sub>3</sub> was successful.

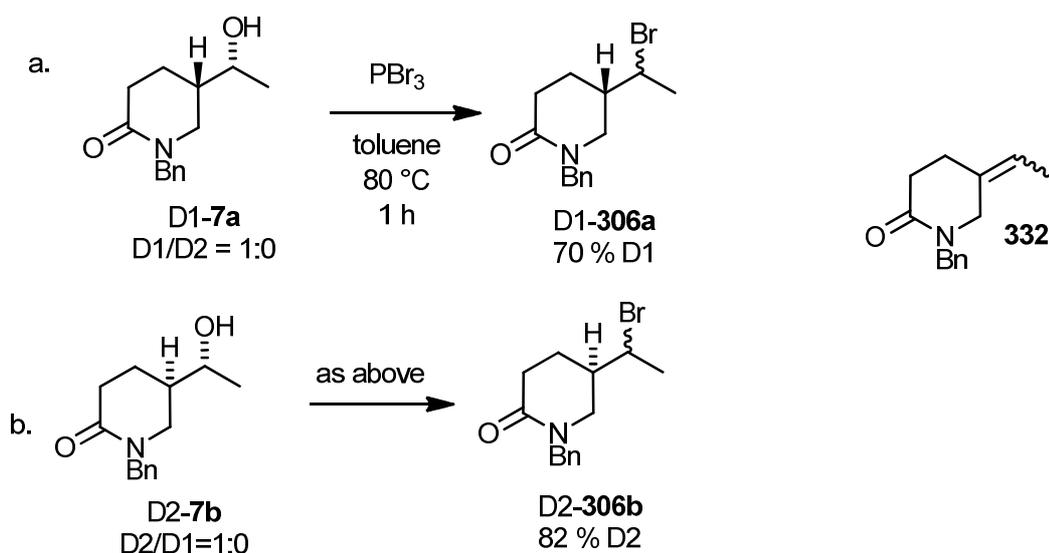
*Bromination of alcohols 7a and 7b.*

Reaction with PBr<sub>3</sub> was successful, providing the corresponding bromide **306**. Diastereomerically pure racemic samples of (±)-D1-**7a** and (±)-D2-**7b** underwent reaction with PBr<sub>3</sub> in separate reactions (Scheme 2.5.15a). (±)-D1-**7a** (100 % D1) was treated with PBr<sub>3</sub> in toluene at 80 °C resulting in the formation of a mixture of the corresponding bromide diastereomers **306** (70 % D1, as determined by <sup>1</sup>H NMR). It was possible to diastereomerically enrich the samples via silica gel chromatography, which enabled clean <sup>1</sup>H NMR spectra of the major diastereomer bromide, to be obtained (15 % yield, 68 % D1). For simplicity, this sample was labelled (D1)-(±)-**306** to indicate that it was obtained from D1-**7a**.

D2-**7b** (100 % D2) was treated with PBr<sub>3</sub>, again resulting in formation of a mixture of the corresponding bromide diastereomers **306** (82 % D2, as determined by <sup>1</sup>H NMR). Following purification it was again possible to diastereomerically enrich the sample providing clean <sup>1</sup>H NMR spectra of the major diastereomer bromide. In this case the sample (D2)-(±)-**306** was obtained in 39 % yield. The <sup>1</sup>H NMR spectra of the two enriched diastereomer samples (D1)-(±)-**306** and (D2)-(±)-**306** were distinguishable showing that although in each case a mixture was obtained, during purification the two samples had been enriched in different isomers.

In each case, the diastereomerically pure starting material gave a mixture of the two diastereomer products. It is not possible to make conclusions on the mechanism of these reactions because two independent processes may simultaneously be occurring; formation of the bromide via an  $S_N1$  mechanism would result in loss of de. But interconversion of the product bromide via substitution of the bromide **306** with  $Br^-$  could also occur during the reaction, also resulting in loss of de. For this reason, the relative configurations of the diastereomers have not been assigned. What appeared to be the elimination product, alkene **332** was also identified in the crude reaction mixture of these bromides (alkene **332** is described in the next section).

Racemic synthesis:

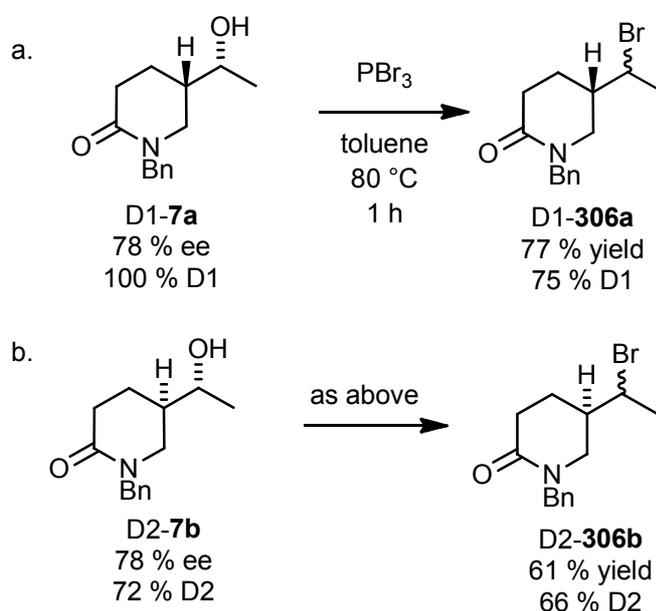


Scheme 2.5.15: Bromination of racemic D1-7a and D2-7b.

An asymmetric synthesis of bromides D1-**306a** and D2-**306b** was carried out. D1-**7a** (78 % ee, 100 % D1) underwent reaction with  $PBr_3$  to give a crude sample containing D1-**306a** in 77 % yield (75 % D1, as determined by  $^1H$  NMR) (Scheme 2.5.16a). Additionally, D2-**7b** (78 % ee, 72 % D2) underwent reaction to give a sample containing D2-**306b** in 61 % yield (67 % D2) (Scheme 2.5.16b). In this case the sample was not purified but used directly in subsequent experimentation. Notably the optical rotation of these samples, D1-**7a** and D2-**7b** had differing signs.

For reasons stated, the configuration of the diastereomers at C (14) could not be accurately determined, however as the samples were enantiomerically enriched, the configuration at C (5) would have been retained upon the transformation from the precursor alcohol. These have been assigned in each case. As the C (5) is configurationally stable, no epimerisation and loss of ee would be expected during these transformations, and so the ee has been assigned as that of the starting material alcohol.

Asymmetric synthesis:

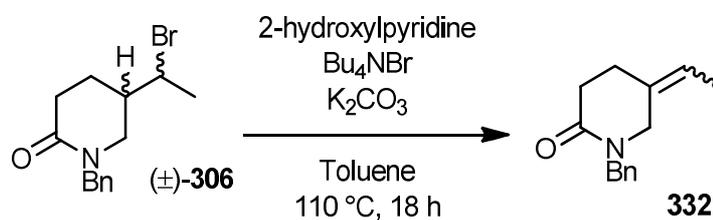


Scheme 2.5.16: Bromination of enantiomerically enriched D1-7a and D2-7b.

*Attempted pyridone coupling.*

Bromide **306** underwent reaction with 2-hydroxypyridine,  $\text{K}_2\text{CO}_3$  and  $\text{Bu}_4\text{NBr}$  in toluene in analogy with the conditions used for by Gallagher to minimise elimination and favour N-substitution over O-substitution (Scheme 2.5.17).<sup>68</sup> However, substitution was not observed and only an impure sample containing what was characterised to be the elimination product **332** was isolated from the reaction. This absence of substitution can be explained by the relatively more sterically hindered

secondary electrophilic centre position to Gallagher's bromide which also suffered from elimination during the reaction.



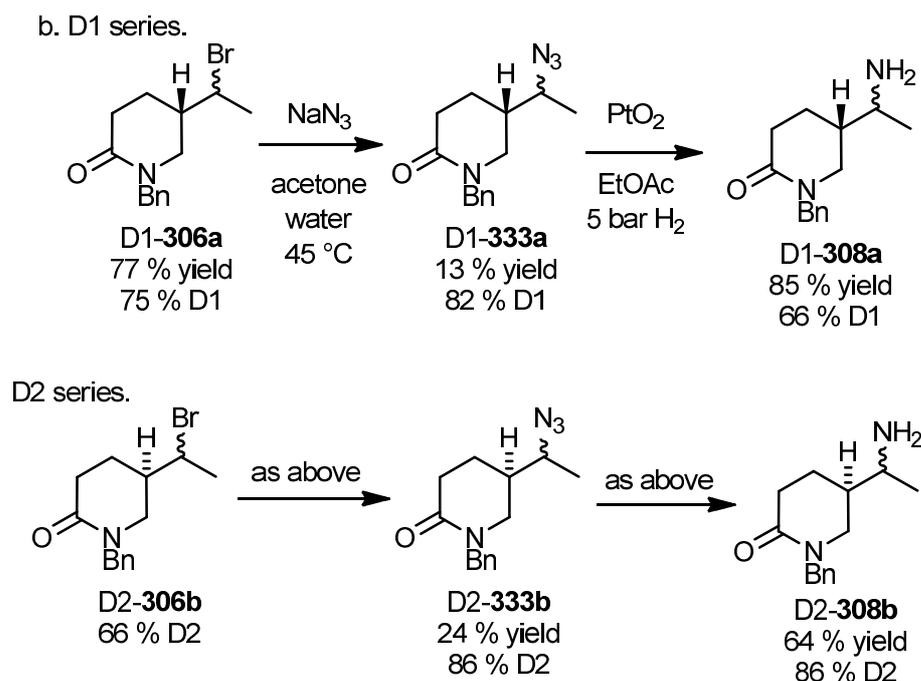
Scheme 2.5.17: Attempted substitution with 2-hydroxypyridine.

#### Section 2.5.6: Synthesis of Amines **308a** and **308b**.

Direct pyridone formation via amines **308a** and **308b** was then attempted through formation of the corresponding azide. It was not possible to directly convert alcohols **7a** or **7b** to the corresponding azide with the reagent, DPPA. Reaction of bromides **306a** and **306b** was however successful.

A sample of diastereomerically enriched bromide D1-**306a** (75 % D1) was treated with NaN<sub>3</sub> in acetone and water at 45 °C. The reaction resulted in what appeared to be a significant amount of decomposition (as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture), resulting in an impure mixture of the corresponding azide diastereomers, D1-**333a** (13 % yield, 82 % D1) (Scheme 2.5.18a).

The corresponding reaction of the D2 series bromide, D2-**306b** (66 % D2) showed less sign of decomposition and the azide was obtained much higher purity. In this case, an enriched sample of the diastereomers, D2-**333b** was obtained in 24 % yield (86 % D2) following purification (silica gel) (Scheme 2.5.18).



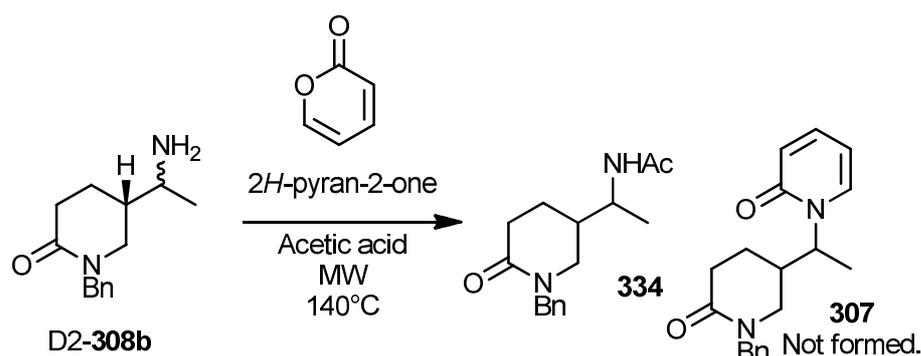
Scheme 2.5.18: a. D1-series: formation of amine D-1-**308a**; b. D2 series: formation of amine D2-**308b**.

Reduction of azide **333** was then attempted by a number of methods: Azide **333** underwent reduction with SnCl<sub>2</sub> in a solution of THF and water; however, poor recovery from the aqueous phase during work up resulted in amine **308** in only 17 % yield (Scheme 2.5.18b). It was found that even at pH 12 the amine was still too soluble in water for effective extraction. Concentration of the aqueous layer did not aid recovery. Alternatively, reduction with PPh<sub>3</sub> in THF followed by subsequent hydrolysis was successful, but resulted in formation of an inseparable mixture of the amine **308** and Ph<sub>3</sub>PO. Reduction with PtO<sub>2</sub> in ethyl acetate under 5 bar hydrogen was found to be the most effective method of reduction – the solvent was simply removed following the reaction. A drawback was limited activity of the catalyst; complete conversion to the amine could not be achieved although it was possible to isolate the amine from the reaction mixture by use of an Isolute-XL SCX amine scavenger thiol resin. Through this method, a sample of azide D1-**333a** (82 % D1) underwent reduction by this method to give D1-**308a** in 85 % yield (66 % D1);

however the sample was in poor yield due to the inseparable contamination from starting material, azide D1-**333a** (Scheme 2.5.18b). Reduction with the D2 series resulted in a clean sample of the amine. Azide D2-**333b** was reduced with PtO<sub>2</sub> to give amine D2-**308b** in 62 % yield (86 % D2) following purification (thiol resin). In each case, the ee of each azide and amine was assigned to be that of the alcohol starting material (78 % ee).

*Attempted pyridone formation.*

The conversion of amine **308** to the pyridone was attempted via treatment with 2*H*-pyran-2-one, following a patent procedure (Scheme 2.5.19).<sup>177</sup> The amine was heated in acetic acid at 140 °C for 3h under microwave irradiation resulting in the formation of what appeared to be the corresponding amide **334** (<sup>1</sup>H NMR). The only evidence for the formation of the desired pyridone was the [M+ H] adduct signal, observed by MS. This procedure was repeated five times but it was not possible to achieve this transformation with compound **308**. The use of a diluted AcOH solution (1 : 9 AcOH : MeCN) was not successful.



Scheme 2.5.19: Attempted pyridone **307** formation with 2*H*-pyran-2-one.

## Section 2.6: Conclusion.

The enantioselective synthesis of the diastereomers alcohol **7a** and **7b** was successful through the ATH of ketone **4**. The diastereomers were obtained in 78 % ee with no loss of ee following conversion from pyridine **303**. The relative and absolute configurations were also determined via X-ray crystallography and optical rotation respectively. These alcohols were converted to the corresponding amines **308a** and **308b** although it was unfortunately not possible to reach pyridone **307** via reaction with 2*H*-pyran-2-one. However, as previously discussed, these 5-substituted lactams are synthetically useful in other applications.

Through the AH of enamide **1**, synthesis of the 5-substituted glutarimide **218** was achieved in high enantioselectivity.<sup>178</sup> Unfortunately, this compound could not be utilised in an asymmetric synthesis of cytosine due to late stage epimerisation following reduction to the lactam, although the formal synthesis was achieved.

An extensive ligand screen for the AH of pyridones **2** and **3** unfortunately failed to provide an enantioselective synthesis of 5-substituted lactams. Nonetheless, a second formal synthesis of cytosine precursor **5** was achieved. A synthetic route to the compound bispiperidine **6** was also developed.

The asymmetric synthesis and complete characterisation of the diastereomers **7a** and **7b** was achieved in 78 % ee, via the ATH of pyridine methyl ketone **4**. Unfortunately it was not possible to convert the alcohols to the cytosine precursor derivative **307**. However, a co-running theme throughout this project was the underlying methodology of enantioselectively forming 5-substituted lactams, of which there is little report in the literature. In completing the asymmetric synthesis of 5-substituted lactams alcohols **7a** and **7b**, this objective has been achieved.

### Section 3: Experimental Procedures.

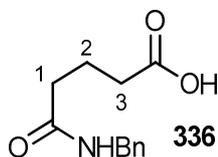
General information.

All reactions unless otherwise stated were run under an atmosphere of nitrogen in glassware (round bottomed flasks or Schlenk tubes). Room temperature refers to ambient room temperature (20-22 °C), and 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by thin layer chromatography (TLC) using aluminium backed silica gel 60 (F254) plates which were visualised using UV254 nm; and PMA, potassium permanganate and ninhydrin dips as appropriate. Flash column chromatography was carried out routinely using 60 Å silica gel (Fluorochem). NMR spectra were recorded on Bruker DPX-300 (300 MHz), DPX-400 (400 MHz), DRX-500 (500 MHz), AV III -600 (600 MHz) and AV II-700 (700 MHz) instruments. Chemical shifts are reported in  $\delta$  units, parts per million.  $^1\text{H}$  NMR spectra run in  $\text{CDCl}_3$  are downfield from TMS;  $^1\text{H}$  NMR spectra run in solvents other than  $\text{CDCl}_3$ , and all  $^{13}\text{C}$  NMR spectra are referenced to the solvent signal. Coupling constants ( $J$ ) are measured in Hertz. IR spectra were recorded on a Nicolet Model Avatar 320 FTIR fitted with a Specac golden gate single reflection diamond attenuated total reflection top plate. Mass spectra were recorded on a Bruker Esquire2000 (ESI) mass spectrometer. Determinations of ee were measured by HPLC or GC. Optical rotations were measured on an AA-1000 polarimeter. Hydrogen gas (99.995 % minimum) was supplied by BOC. Hydrogenations were carried out in a Parr bench-top hydrogenator (0.3 L). HMQC, DEPT and COSY NMR experiments were routinely used in the analysis of new compounds, to assist the assignment of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. When these methods are crucial for characterisation and the assignment of NMR spectra, they have been shown in Appendix I.

### Section 3.1: Procedures from Section 2.1.

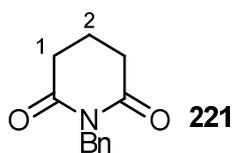
#### Section 3.1.1: Synthesis and Hydrogenation of Enamide 1.

##### 5-(Benzylamino)-5-oxopentanoic acid, **336**.



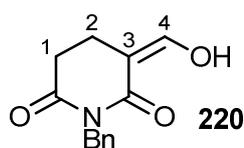
This compound has been reported but not fully characterised.<sup>179</sup> Glutaric anhydride (1.26 g, 11.04 mmol) was added to NEt<sub>3</sub> (1.54 cm<sup>3</sup>, 11.05 mmol) in THF (40 cm<sup>3</sup>) at 0 °C. Benzylamine (1.21 cm<sup>3</sup>, 11.08 mmol) in THF (40 cm<sup>3</sup>) was added dropwise over 1 h at 0 °C. The mixture was heated to 75 °C and left stirring for 24 h before hydrochloric acid (1 M, 40 cm<sup>3</sup>) was added. Following extraction with ethyl acetate (3 x 55 cm<sup>3</sup>), the organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the crude carboxylic acid **336** (2.34 g, 10.58 mmol, 96 % yield) as a white solid; (found (ESI): M<sup>+</sup> + Na, 244.0944. C<sub>12</sub>H<sub>15</sub>NNaO<sub>3</sub> requires M, 244.0944);  $\nu_{\max}$  3303 (OH st.), 3031 (aryl CH st.), 1693 (C=O st.), 1638 (NH st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 7.36-7.25 (5H, m, ArH), 5.81 (1H, s, NH), 4.42 (2H, d, *J* 5.5, CH<sub>2</sub>), 2.44 (2H, t, *J* 7.0, H<sub>3</sub>), 2.31 (2H, t, *J* 7.0, H<sub>1</sub>), 1.99 (2H, quin, *J* 7.0, H<sub>2</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 177.68 (CO), 172.32 (CO), 137.95 (Ar), 128.75 (Ar), 127.83 (Ar), 127.61 (Ar), 43.71 (CH<sub>2</sub>Ar), 35.21 (C<sub>3</sub>), 33.00 (C<sub>1</sub>), 20.68 (C<sub>2</sub>); m/z (ESI) 222.0 (M<sup>+</sup> + 1). No further purification was carried out.

*1-Benzylpiperidine-2,6-dione 221.*



This compound has been reported and fully characterised.<sup>180</sup> 5-(Benzylamino)-5-oxopentanoic acid **336** (2.34 g, 10.58 mmol) was added to acetyl chloride (60 cm<sup>3</sup>) and heated to 65 °C. The mixture was left stirring for 10 h before the mixture was allowed to cool to room temperature. Acetyl chloride was removed under reduced pressure and the crude material was purified by column chromatography (70/30 hexane / ethyl acetate) to give glutarimide **221** (1.93 g, 9.50 mmol, 90 %);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 7.35-7.32 (5H, m, ArH), 4.95 (2H, s, CH<sub>2</sub>), 2.68 (4H, t, *J* 6.5, H<sub>1</sub>), 2.41 (2H, quin, *J* 6.5, H<sub>2</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 173.48 (CO), 136.81 (Ar), 128.81 (Ar), 128.31 (Ar), 127.38 (Ar), 42.57 (CH<sub>2</sub>Ar), 32.80 (C<sub>1</sub>), 17.03 (C<sub>2</sub>); *m/z* (ESI) 204.0 (M<sup>+</sup> + 1), 226.0 (M<sup>+</sup> + 23).

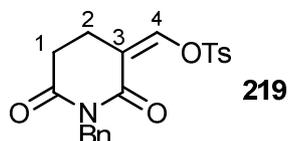
*(Z)-1-Benzyl-3-(hydroxymethylene)piperidine-2,6-dione 220.*



Under an inert atmosphere, dry ethanol (1.60 cm<sup>3</sup>, 27.40 mmol) was added dropwise to a suspension of 60 % NaH in oil (1.10 g, 27.50 mmol) in Et<sub>2</sub>O (32.0 cm<sup>3</sup>) at 0 °C and left stirring for 20 min or until evolution of hydrogen had ceased. In a second flask, 1-benzylpiperidine-2,6-dione **221** (2.0 g, 9.85 mmol) and ethyl formate (1.35 cm<sup>3</sup>, 16.78 mmol) in Et<sub>2</sub>O (32.0 cm<sup>3</sup>) were transferred dropwise to the first flask over 1 h at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h before the solution was extracted with water (2 x 40 cm<sup>3</sup>). The aqueous

extracts were acidified with dil. HCl (aq), followed by extraction with Et<sub>2</sub>O (3 x 50 cm<sup>3</sup>). The organic extract was washed with saturated aqueous sodium hydrocarbonate, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the product **220** (1.86 g, 8.05 mmol, 82 % yield); (found (ESI): M<sup>+</sup> + H, 232.0964. C<sub>13</sub>H<sub>14</sub>NO<sub>3</sub> requires M, 232.0968);  $\nu_{\max}$  3250 (OH st.), 3033 (aryl CH st.), 1714 (C=O st.), 1670 (C=O st.), 1643 (C=C st.), 1143 (amide III) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 12.27 (1 H, d, *J* 12.3, OH), 7.41 - 7.21 (5 H, m, ArH), 7.18 (1 H, d, *J* 12.3, H<sub>4</sub>), 4.98 (2 H, s, CH<sub>2</sub>Ph), 2.67 (2 H, t, *J* 7.3, H<sub>1</sub>), 2.47 (2 H, t, *J* 7.3, H<sub>2</sub>);  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>) 171.71 (CO), 171.37 (CO), 160.88 (C<sub>4</sub>), 136.98 (Ar), 128.53 (Ar), 128.42 (Ar), 127.45 (Ar), 100.18 (C<sub>3</sub>), 42.41 (CH<sub>2</sub>Ar), 32.54 (C<sub>1</sub>), 19.73 (C<sub>2</sub>); *m/z* (ESI) 232.0 (M<sup>+</sup> + 1).

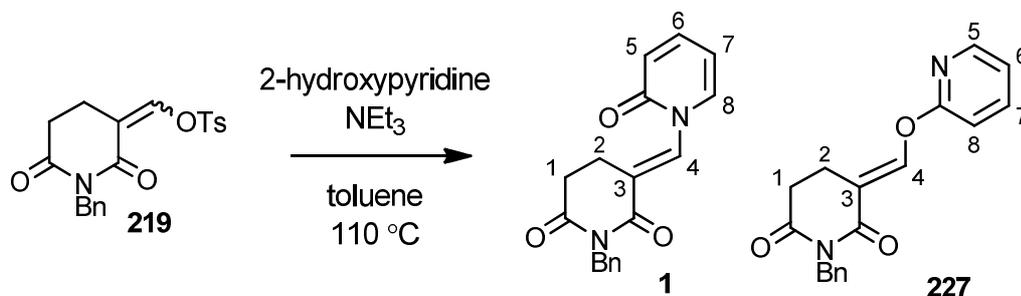
(1-Benzyl-2,6-dioxopiperidin-3-ylidene)methyl-4-methylbenzene sulfonate **219**.



Under nitrogen, (*Z*)-1-benzyl-3-(hydroxymethylene)-piperidine-2,6-dione **220** (0.859 g, 3.72 mmol) was added to a solution of NEt<sub>3</sub> (0.62 cm<sup>3</sup>, 4.45 mmol) in dry DCM (22.0 cm<sup>3</sup>) and cooled to 0 °C. A solution of *p*-toluenesulfonyl chloride (0.851 g, 4.46 mmol) in dry DCM (22.0 cm<sup>3</sup>) was added to first mixture and the mixture was allowed to warm to room temperature and stirred for 1 h before saturated aqueous ammonium chloride (30 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 30 cm<sup>3</sup>), the organic extracts were washed with aqueous sodium hydrogen carbonate (3 x 20 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the product **219** (1.323 g, 3.44 mmol, 92 % yield) as a brown solid; Mp 136 – 140 °C; (found (ESI): M<sup>+</sup> + H, 386.1056. C<sub>20</sub>H<sub>20</sub>NO<sub>5</sub>S requires M, 386.1057);  $\nu_{\max}$  3039

(aryl CH st.), 1721 (C=O st.), 1635 (C=C st.), 1175 (amide III)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.83 (2H, m, ArH), 7.73 (1H, s, H<sub>4</sub>), 7.39 (2H, m, ArH), 7.34-7.23 (5H, m, ArH), 4.96 (2H, s, CH<sub>2</sub>), 2.60-2.54 (4H, m, H<sub>1,2</sub>), 2.47 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 170.82 (CO), 164.62 (CO), 145.93 (Ar), 144.30 (C<sub>4</sub>), 136.38 (Ar), 131.16 (Ar), 128.22 (Ar), 127.89 (Ar), 127.64 (Ar), 126.91 (Ar), 115.08 (C<sub>3</sub>), 42.64 (CH<sub>2</sub>Ar), 30.60 (C<sub>1</sub>), 21.19 (CH<sub>3</sub>), 17.00 (C<sub>2</sub>);  $m/z$  (ESI) 386.1 ( $\text{M}^+ + 1$ ).

(*E*)-1-Benzyl-3-((2-oxopyridin-1(2H)-yl)methylene)piperidine-2,6-dione **1** and *O*-substituted isomer **227**.



Under nitrogen, (1-benzyl-2,6-dioxopiperidin-3-ylidene)methyl-4-methylbenzene sulfonate **219** (1.32 g, 3.43 mmol) was added to a solution of 2-hydroxypyridine (0.98 g, 10.30 mmol) and  $\text{NEt}_3$  (1.67  $\text{cm}^3$ , 11.98 mmol) in dry toluene (42.0  $\text{cm}^3$ ). The mixture was heated to 110 °C and left stirring for 20 h. Following concentration under reduced pressure and purification by column chromatography (10/90 hexane/ethyl acetate), the product **1** (0.687 g, 2.23 mmol, 65 % yield) was obtained as a solid; Mp 138 – 144 °C; (found (ESI):  $\text{M}^+ + \text{H}$ , 309.1235.  $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_3$  requires  $\text{M}$ , 309.1234);  $\nu_{\text{max}}$  3020 (aryl CH st.), 1720 (C=O st.), 1660 (C=O st.), 1630 (C=C st.), 1580 (C=C st.), 1520 (C=C st.), 1250 (amide III)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.97 (1 H, s, H<sub>4</sub>), 7.43-7.35 (3 H, m, ArH, H<sub>6</sub>), 7.34-7.22 (3 H, m, ArH), 7.10 (1 H, dd,  $J$  6.9, 1.8, H<sub>8</sub>), 6.62 (1 H, d,  $J$  9.3, H<sub>5</sub>), 6.24 (1 H, td,  $J$  6.9, 1.3, H<sub>7</sub>), 5.04 (2 H, s,

$CH_2$ ), 2.78-2.64 (4 H, m,  $H_{1,2}$ );  $\delta_C$  (101 MHz,  $CDCl_3$ ) 170.86 (CO), 165.16 (CO), 161.51 (CO), 140.25 ( $C_6$ ), 136.75 (Ar), 136.34 ( $C_4$ ), 135.50 ( $C_8$ ), 128.73 (Ar), 128.33 (Ar), 127.46 (Ar), 124.50 ( $C_3$ ), 121.90 ( $C_5$ ), 106.39 ( $C_7$ ), 43.37 ( $CH_2Ar$ ), 31.40 ( $C_1$ ), 20.91 ( $C_2$ );  $m/z$  (ESI) 309.1 ( $M^+ + 1$ ), 331.1 ( $M^+ + 23$ ). Following recrystallisation of a sample of **1** (EtOH), crystals suitable for crystallography were grown and underwent X-ray diffraction to confirm the structure. Full details of the structure are shown in Appendix II.

Initially, at shorter reaction times, the *O*-substituted isomer **227** was also isolated in varying yields from the reaction mixture following column chromatography (hexane-50/50 hexane / ethyl acetate) and recrystallisation (EtOH) as a colourless crystalline product; (found (ESI):  $M^+ + H$ , 309.1248.  $C_{18}H_{17}N_2O_3$  requires  $MH^+$ , 309.1234);  $\nu_{max}$  3020 (aryl CH st.), 1710 (C=O st.), 1690 (C=O st.), 1660 (C=C st.), 1580 (C=C st.), 1250 (amide III)  $cm^{-1}$ ;  $\delta_H$  (500 MHz,  $CDCl_3$ ) 8.82 (1 H, s,  $H_4$ ), 8.25 (1 H, dd,  $J$  5.3, 1.3,  $H_5$ ), 7.75 - 7.71 (1 H, m,  $H_7$ ), 7.44-7.15 (5 H, m,  $ArH$ ), 7.13-7.09 (1 H, m,  $H_6$ ), 6.94 (1 H, d,  $J$  8.3,  $H_8$ ), 5.04 (2 H, s,  $CH_2$ ), 2.84-2.79 (2 H, m,  $H_1$ ), 2.75-2.70 (2 H, m,  $H_2$ );  $\delta_C$  (126 MHz,  $CDCl_3$ ) 172.21 (CO), 166.84 (CO), 148.47 ( $C_4$ ), 147.45 ( $C_5$ ), 139.83 ( $C_7$ ), 137.50 (Ar), 128.77 (Ar), 128.34 (Ar), 127.29 (Ar), 120.25 ( $C_6$ ), 111.30 ( $C_8$ ), 43.01 ( $CH_2Ar$ ), 31.76 ( $C_1$ ), 17.75 ( $C_2$ );  $m/z$  (ESI) 309.1 ( $M^+ + 1$ ), 331.1 ( $M^+ + 23$ ). Following recrystallisation of a sample of **227** (EtOH), crystals suitable for crystallography were grown and underwent X-ray diffraction to confirm the structure. Full details of the structure are shown in Appendix II.

In further experiments, long reaction times (20 h as opposed to 10 h) were found to result in an absence of *O*-substituted product **227** (Table 1). To determine if the *N*-

product **1** was a thermodynamically favoured product, a separate isomerisation experiment was carried out. A mixture of **1**, **227**, and 2-hydroxypyridine were combined under the same reaction conditions and found to form only the N-substituted product. This suggests that isomerisation occurs between the two O- and N- compounds, forming the thermodynamically favoured product, **1**.

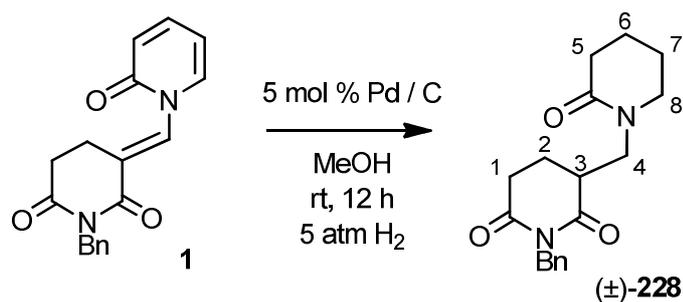
**Table 1:** Yields of products **1** and **227**.

entry	scale / g	N-prod. <b>1</b> (%)	O-prod. <b>227</b> (%)	reaction time (h).
1	0.45	14	25	10
2	0.45	32	12	10
3	0.28	75	0	20
4	1.32	65	0	20
5	4.18	48	0	20
6	1.54	62	0	20

*Procedure for the isomerisation of N- and O- substituted Compounds*

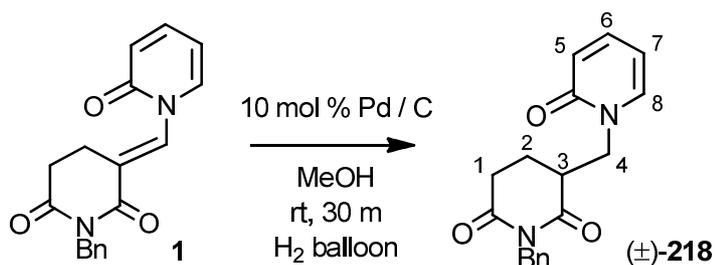
Under nitrogen, NEt<sub>3</sub> (0.15 cm<sup>3</sup>, 1.08 mmol) was added to a mixture containing **1** (67 mg, 0.217 mmol), **227** (44 mg, 0.143 mmol), and 2-hydroxypyridine (42 mg, 0.442 mmol) in dry toluene (3.0 cm<sup>3</sup>). The mixture was heated to 110 °C for 20 h with stirring. Removal of the solvent by reduced pressure gave the crude product which contained the N-substituted product **1** as the major product, and only a trace of the O- substituted product **227** (as determined by <sup>1</sup>H NMR analysis).

*1-Benzyl-3-((2-oxopyridin-1-yl)methyl)piperidine-2,6-dione* ( $\pm$ )-**228**.



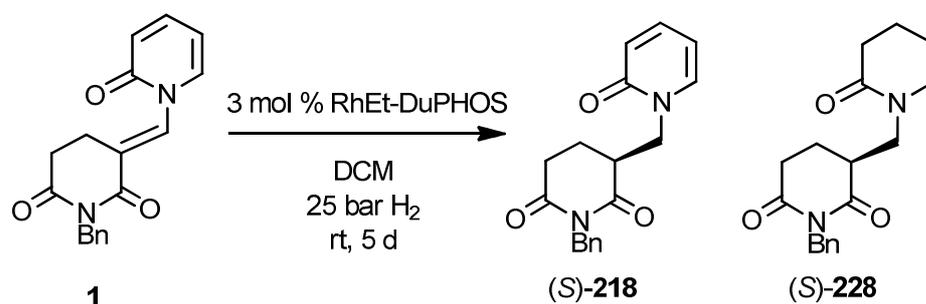
Under nitrogen, a solution of (*E*)-1-benzyl-3-((2-oxopyridin-1(2*H*)-yl)methylene)-piperidine-2,6-dione, **1** (50.0 mg, 0.162 mmol) and palladium on charcoal (10 % Pd w/w, 8.6 mg, 8.08 x 10<sup>-3</sup> mmol) in dry MeOH (2.50 cm<sup>3</sup>) was hydrogenated at room temperature under 5 bar hydrogen overnight. The catalyst was removed by filtration with celite and the reaction mixture was passed through a short silica gel column (10/90 hexane / ethyl acetate) to yield the crude product, ( $\pm$ )-**228** (46 mg, 0.146 mmol, 90 % yield) as a colourless waxy solid; found (ESI): M<sup>+</sup> + Na, 337.1522. C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>NaO<sub>3</sub> requires M, 337.1500);  $\nu_{\max}$  3031 (aryl CH st.), 1721 (C=O st.), 1670 (C=O st.), 1629 (C=C st.), 1163 (amide III) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.37-7.20 (5 H, m, ArH), 4.99-4.90 (2 H, m, CH<sub>2</sub>), 3.87 (1 H, dd, *J* 13.8, 7.7, H<sub>4A</sub>), 3.59 (1 H, dd, *J* 13.8, 5.8, H<sub>4B</sub>), 3.32 - 3.43 (1 H, m, H<sub>8A</sub>), 3.23-3.13 (1 H, m, H<sub>8B</sub>), 2.85 - 2.97 (2 H, m, H<sub>3</sub>, H<sub>1A</sub>), 2.66-2.55 (1 H, m, H<sub>1B</sub>), 2.42-2.33 (2 H, m, H<sub>5</sub>), 2.08-1.97 (1 H, m, H<sub>2A</sub>), 1.85-1.66 (5 H, m, H<sub>2B,6,7</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 173.53 (CO), 172.07 (CO), 170.59 (CO), 137.10 (Ar), 128.58 (Ar), 128.30 (Ar), 127.34 (Ar), 48.90 (C<sub>8</sub>), 47.52 (C<sub>4</sub>), 42.90 (CH<sub>2</sub>Ar), 40.97 (C<sub>3</sub>), 32.23 (C<sub>1</sub>), 31.58 (C<sub>5</sub>), 23.19 (C<sub>2</sub>), 21.13 (C<sub>6</sub>), 20.71 (C<sub>7</sub>); *m/z* (ESI) 315.2 (M<sup>+</sup> + 1), 337.1 (M<sup>+</sup> + 23).

*1-Benzyl-3-((2-oxopiperidin-1-yl)methyl)piperidine-2,6-dione* ( $\pm$ )-**218**.



A short reaction time allowed partially reduced product **218** to be isolated before subsequent reduction of the pyridone ring occurred. Under nitrogen, a solution of (*E*)-1-benzyl-3-((2-oxopyridin-1(*2H*)-yl)methylene)piperidine-2,6-dione, **1** (30 mg,  $9.74 \times 10^{-2}$  mmol) and palladium on charcoal (21 mg,  $9.9 \times 10^{-3}$  mmol, 5 % Pd / w) in dry MeOH (0.2 cm<sup>3</sup>) and dry DCM (0.2 cm<sup>3</sup>) was hydrogenated at room temperature under a balloon of hydrogen for 30 min before the catalyst was removed by filtration with celite and the reaction mixture was passed through a short silica gel column (hexane / ethyl acetate 1:9) to yield the product, ( $\pm$ )-**218** (20 mg,  $6.5 \times 10^{-2}$  mmol, 66 % yield) as a colourless solid; Mp 124 - 126 °C (found (ESI):  $M^+ + Na$ , 333.1208. C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>3</sub> requires M, 333.1300);  $\nu_{\max}$  3035 (aryl CH st.), 1724 (C=O st.), 1657 (C=O st.), 1584 (C=C st.), 1540 (C=C st.), 1160 (amide III) cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.42 (1 H, dd, *J* 6.8, 1.8, H<sub>8</sub>), 7.37-7.19 (6 H, m, ArH, H<sub>6</sub>), 6.55 (1 H, d, *J* 9.3, H<sub>5</sub>), 6.14 (1 H, t, *J* 6.8, H<sub>7</sub>), 4.97 (1 H, d, *J* 13.8, CH<sub>2</sub>), 4.89 (1 H, d, *J* 13.8, CH<sub>2</sub>), 4.38 (1 H, dd, *J* 13.3, 5.9, H<sub>4A</sub>), 4.16 (1 H, dd, *J* 13.3, 5.9, H<sub>4B</sub>), 3.11 (1 H, dt, *J* 18.1, 5.9, H<sub>3</sub>), 2.85 (1 H, dt, *J* 17.6, 3.5, H<sub>1A</sub>), 2.63 (1 H, m, H<sub>1B</sub>), 2.10 (1 H, m, H<sub>2A</sub>), 1.74 (1 H, dq, *J* 13.1, 4.5, H<sub>2B</sub>);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 173.30 (CO), 171.68 (CO), 162.84 (CO), 139.78 (C<sub>8</sub>), 138.68 (C<sub>6</sub>), 136.92 (Ar), 128.49 (Ar), 128.34 (Ar), 127.39 (Ar), 120.71 (C<sub>5</sub>), 105.89 (C<sub>7</sub>), 50.17 (C<sub>4</sub>), 41.98 (CH<sub>2</sub>Ar), 40.95 (C<sub>3</sub>), 32.24 (C<sub>1</sub>), 21.10 (C<sub>2</sub>); *m/z* (ESI) 311.1 ( $M^+ + 1$ ), 333.1 ( $M^+ + 23$ ).

*AH of enamide 1: (S)-1-benzyl-3-((2-oxopyridin-1(2H)-yl)methyl)piperidine-2,6-dione, 218.*

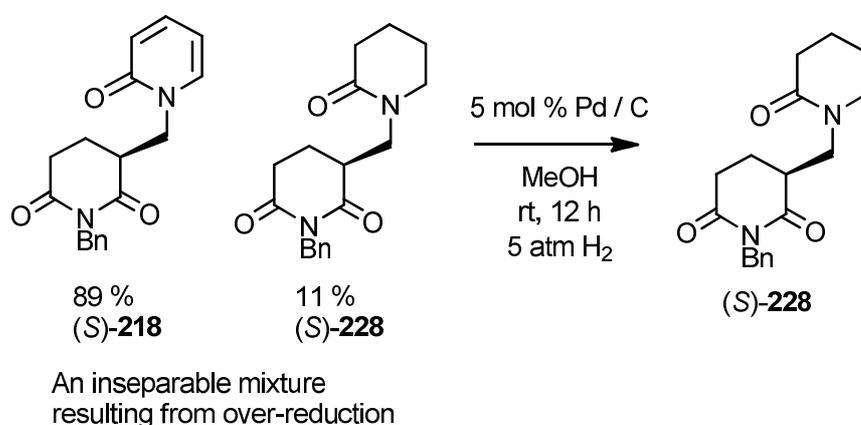


Under nitrogen, a solution of thoroughly dried (*E*)-1-benzyl-3-((2-oxopyridin-1(2*H*)-yl)methylene)piperidine-2,6-dione, **1** (0.78 g, 2.53 mmol) and [Rh(COD)(Et-DuPHOS)]BF<sub>4</sub> (50.7 mg, 76.8 × 10<sup>-3</sup> mmol) in dry DCM (10.14 cm<sup>3</sup>) was degassed three times. The solution was divided equally into five glass test tubes which were used in the hydrogenation procedure. To the stirred solutions, the hydrogenation was performed at 20 °C under 25 bar hydrogen for 5 days. The reaction mixture was passed through a short silica gel column (10/90 hexane / ethyl acetate) to remove the catalyst, yielding product (*S*)-**218** (0.75 g, 2.42 mmol, 96 % yield) as a colourless solid; (Chiracel IA, 25 cm x 4.6 mm column, iPrOH : hexane 15 : 85, 1 mL/min, T = 20 °C, *S* isomer 23.5 min, *R* isomer 55.8 min.) 90 % ee; [α]<sub>D</sub><sup>25</sup> + 11.1 (c1.00 in CHCl<sub>3</sub>). Configuration was subsequently determined by analysis of compound (*R*)-**5**. Full characterisation data was given in the previous section.

On the occasion of this experiment, over-reduction to lactam **228** was not observed. This enabled the ee of **218** to be directly determined by HPLC analysis by the procedure stated above. However, during other experiments, over-reduction was observed in varying conversion. This resulted in the formation of a crude mixture of **218** and **228** which could not be separated by chromatography, and also prevented accurate ee determination. In this case, the ee of **218** was not determined by the

procedure stated above. Instead, the mixture was hydrogenated to **228**, from which the ee was determined by HPLC analysis. The ee of this sample was taken as an indirect indication of the ee of compound **218**. The experimental procedure for this analysis is shown in the next section.

*Procedure for the hydrogenation and subsequent HPLC analysis of inseparable asymmetric reduction mixtures.*



Under nitrogen, a solution of an inseparable mixture of (*S*)-**218** and (*S*)-**228** (89 % and 11 % respectively, as determined by  $^1\text{H}$  NMR analysis; (15.0 mg) and palladium on charcoal (10 % Pd w/w, 2.6 mg,  $2.44 \times 10^{-3}$  mmol) in dry MeOH (1.00 cm<sup>3</sup>) was hydrogenated at room temperature under 5 bar hydrogen overnight. The catalyst was removed by filtration with celite and the reaction mixture was passed through a short silica gel column (10/90 hexane / ethyl acetate) to yield the product, (*S*)-**228** (15 mg, 0.048 mmol) as a colourless waxy solid (full characterisation is listed in the next section); ee was determined by HPLC analysis (Chiracel IA, 25 cm x 4.6 mm column, IPA : hexane 30 : 70, 1 mL/min, T = 15 °C, *S* isomer (major) 10.28 min., *R* isomer (minor) 23.26 min.) 94.5 % ee;  $[\alpha]_{\text{D}}^{25} + 55.1$  (c0.10 in CHCl<sub>3</sub>). Full characterisation data for **228** was given in a previous section. The HPLC of the

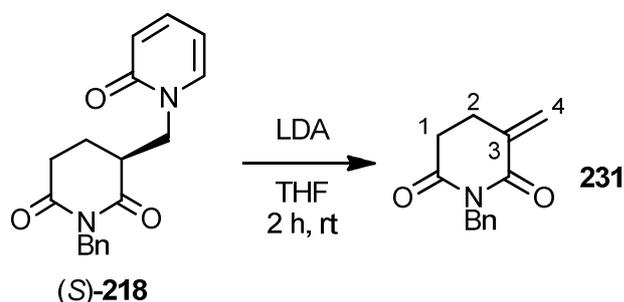
racemic sample (see below) was used to determine the position of the peaks for analysis.

*Procedure for the screening of AH ligands.*

Under nitrogen, a solution of thoroughly dried (*E*)-1-benzyl-3-((2-oxopyridin-1(2*H*)-yl)methylene)piperidine-2,6-dione, **1** (30.0 mg, 0.10 mmol) in dry DCM (0.39 cm<sup>3</sup>) was purged with argon for 30 min before [Rh(COD)Cl]<sub>2</sub> (0.8 mg, 1.6 x 10<sup>-3</sup> mmol) and the ligand (3.0 x 10<sup>-3</sup> mmol) was added. To the stirred solution, the hydrogenation was performed at 30 °C under 25 bar hydrogen for 5 days. The reaction mixture was purified by silica gel column chromatography (hexane - ethyl acetate 1:9) to separate reaction products where applicable, yielding products **218** and / or product **228** as determined by <sup>1</sup>H NMR and analysed for ee by HPLC (conditions as described above). Results are given in Table 2. The highest ee for this transformation was obtained using Taniaphos SL-T002-1 under the same conditions as described above. In this case the ee of exclusive product **228** was 98 % (*R*) and was determined by direct HPLC analysis, following purification by column chromatography: (Chiracel IA, 25 cm x 4.6 mm column, iPrOH : hexane 15 : 85, 1 mL/min, T = 15 °C, *S* isomer (minor) 31.5 min, *R* isomer (major) 57.3 min.) 98 % ee. The configuration was subsequently determined by analysis of compound (*R*)-**5**.

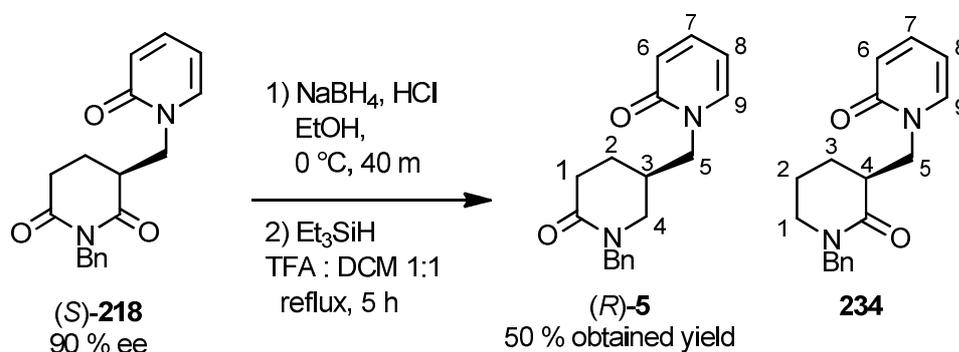
Section 3.1.2: Completion of the Formal Synthesis of (-)-Cytisine

1-benzyl-3-methylidenepiperidine-2,6-dione, **231**.



Under nitrogen, LDA (2M solution in THF, 6  $\mu\text{L}$ ,  $1.20 \times 10^{-2}$  mmol) was added to a solution of 1-benzyl-3-((2-oxopiperidin-1-yl)methyl)piperidine-2,6-dione **218** (90 % ee, 15 mg,  $4.84 \times 10^{-2}$  mmol) in THF (0.5  $\text{cm}^3$ ) and the solution was stirred at room temperature for 2 h before saturated aqueous ammonium chloride (2  $\text{cm}^3$ ) was added. Following extraction with  $\text{Et}_2\text{O}$  (2 x 5  $\text{cm}^3$ ) the organic extracts were dried ( $\text{MgSO}_4$ ), concentrated under reduced pressure and purified by column chromatography (ethyl acetate – hexane 1:1) to give an impure sample containing what was characterised to be **231** (32 mg) as an oil. Data obtained from this mixture:  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.21 - 7.39 (5 H, m, ArH), 6.31 (1 H, d,  $J$  1.2,  $\text{H}_{4\text{A}}$ ), 5.59 (1 H, d,  $J$  1.2,  $\text{H}_{4\text{B}}$ ), 4.99 (2 H, s,  $\text{CH}_2$ ), 2.62 - 2.77 (4 H, m,  $\text{H}_1$ ,  $\text{H}_2$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 173.44 (CO), 171.78 (CO), 137.02 (Ar), 128.83 (Ar), 128.65 (Ar), 127.44 (Ar), 120.87 ( $\text{C}_3$ ), 106.00 ( $\text{C}_4$ ), 50.31 ( $\text{CH}_2\text{Ar}$ ), 43.15 ( $\text{C}_1$ ), 32.35 ( $\text{C}_2$ ).

*(R)*-1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)pyridin-2(1H)-one, (*R*)-**5** and minor isomer **234**.

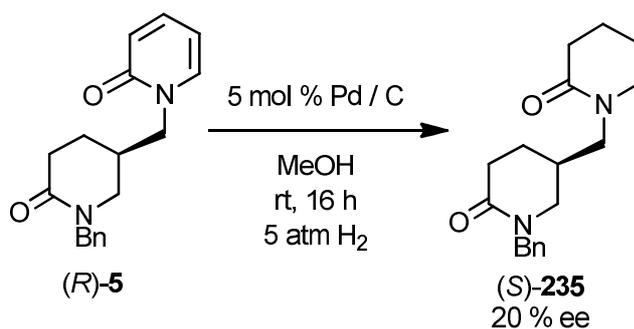


Under nitrogen, a solution of 1-benzyl-3-((2-oxopiperidin-1-yl)methyl)piperidine-2,6-dione, (*S*)-**218** (90 % ee, 200 mg, 0.645 mmol) in dry ethanol (6.0 cm<sup>3</sup>) was acidified to approximately pH 7 with HCl (20 μL, 0.8 M) and cooled to 0 °C. To the stirred solution, NaBH<sub>4</sub> (73 mg, 1.93 mmol) was added portionwise at 10 min intervals. Throughout the reaction HCl (20 μL, 0.8 M) was added in 10 min intervals to maintain the reaction at approximately pH 7. After 40 min, the reaction was neutralised and saturated aqueous sodium hydrocarbonate (10.0 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 5 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the crude intermediate products **232** and **233** (~200 mg) as an oil. Approximate conversion was determined by <sup>1</sup>H NMR analysis. No further purification was attempted. Under nitrogen, Et<sub>3</sub>SiH (512 μL, 3.20 mmol) was added to a solution of the crude intermediate product in TFA (1.14 cm<sup>3</sup>) and dry DCM (1.14 cm<sup>3</sup>). The mixture was heated to 45 °C and stirred for 5 h before saturated aqueous sodium hydrocarbonate (10 cm<sup>3</sup>) was carefully added. Following extraction with DCM (3 x 10 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the major product, (*R*)-**5** (65 mg, 0.220 mmol, 34 % yield from imide (*S*)-**218**) as a colourless oil, following purification by column chromatography (ethyl acetate – methanol

95:5); found (ESI):  $M^+ + Na$ , 319.1417.  $C_{18}H_{20}N_2NaO_2$  requires  $M$ , 319.1417);  $\nu_{max}$  3066 (aryl CH st.), 1650 (C=O st.), 1629 (C=O st.), 1580 (C=C st.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.30-7.14 (6 H, m, ArH,  $H_7$ ), 6.82 (1 H, dd,  $J$  6.8, 1.8,  $H_9$ ), 6.47 (1 H, d,  $J$  9.0,  $H_6$ ), 5.99 (1 H, t,  $J$  6.8,  $H_8$ ), 4.65 (1 H, d,  $J$  14.6,  $CH_2$ ), 4.36 (1 H, d,  $J$  14.6,  $CH_2$ ), 3.79-3.67 (2 H, m,  $H_5$ ), 3.17 (1 H, dd,  $J$  12.3, 4.9,  $H_{4A}$ ), 2.94 (1 H, dd,  $J$  12.3, 9.0,  $H_{4B}$ ), 2.50 (1 H, dt,  $J$  17.8, 5.9,  $H_{1A}$ ), 2.44-2.31 (2 H, m,  $H_{1B}$ ,  $H_3$ ), 1.89 - 1.77 (1 H, m,  $H_{2A}$ ), 1.56 (1 H, dtd,  $J$  13.4, 10.0, 5.9,  $H_{2B}$ );  $\delta_C$  (176 MHz,  $CDCl_3$ ) 169.19 (CO), 162.58 (CO), 139.60 ( $C_9$ ), 137.60 ( $C_7$ ), 136.96 (Ar), 128.69 (Ar), 128.2 (Ar), 127.54 (Ar), 121.30 ( $C_6$ ), 105.97 ( $C_8$ ), 52.21 ( $C_5$ ), 50.19 ( $CH_2Ar$ ), 49.58 ( $C_4$ ), 33.05 ( $C_3$ ), 30.58 ( $C_1$ ), 24.83 ( $C_2$ );  $m/z$  (ESI) 319.2 ( $M^+ + Na$ );  $[\alpha]_D^{25} + 8.8$  ( $c$  0.7 in  $CHCl_3$ ) 20 % ee ( $R$ ) (lit.<sup>68</sup>  $[\alpha]_D^{24} + 31.3$  ( $c$  0.80,  $CHCl_3$ ) 98 % ee ( $R$ )). The ee of **5** could not be determined directly using GC or HPLC. Instead, it was established by chiral HPLC of **235** as described in the next section.

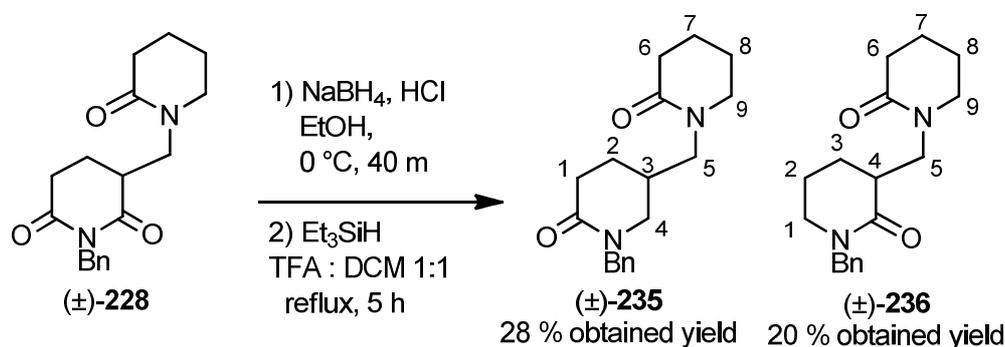
An attempt was made by column chromatography (hexane - ethyl acetate 1:9) to fully purify the minor product **234** (varying yields, commonly a 3:1 ratio of **5** : **234** in the crude product) however this was not possible. Data for **234** obtained from this mixture;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.53 (1 H, dd,  $J$  6.8, 2.0,  $H_9$ ), 7.38-7.20 (6H, m, ArH,  $H_7$ ), 6.55 (1 H, d,  $J$  9.0,  $H_6$ ), 6.16-6.10 (1H, m,  $H_8$ ), 4.60-4.51 (2H, m,  $CH_2$ ), 4.45-4.40 (2H, m,  $H_5$ ), 3.22-3.16 (1H, m,  $H_1$ ), 2.90-2.82 (1H, m,  $H_4$ ), 2.08-2.00 (1H, m,  $H_{3A}$ ), 1.90-1.82 (1H, m,  $H_{3B}$ ), 1.80-1.68 (1H, m,  $H_2$ ), and 1.60-1.50 (1H, m,  $H_2$ ).

*(S)*-1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)piperidin-2-one **235**.



Under nitrogen, a solution of (*R*)-1-((1-benzyl-6-oxopiperidin-3-yl)methyl)piperidin-2-one, (*R*)-**5** (20% ee, 16.0 mg, 0.054 mmol) and palladium on charcoal (6.0 mg,  $2.8 \times 10^{-3}$  mmol, 5 % Pd / w) in dry MeOH (0.90 cm<sup>3</sup>) was hydrogenated at room temperature under 5 bar hydrogen overnight. The catalyst was removed by filtration with celite and the reaction mixture was passed through a short silica gel column (hexane - ethyl acetate 1:9) to yield the product (*S*)-**235** (15 mg, 0.050 mmol, 93 % yield) as a colourless oil; ee was determined by HPLC analysis (Chiracel IA, 25 cm x 4.6 mm column, IPA : hexane 95 : 5, 0.8 mL/min, T = 15 °C, *R* isomer (minor) 15.40 min., *S* isomer (major) 18.56 min.) 20 % ee. Compound (±)-**235** was used as a racemic standard to establish the positions of the required peaks.

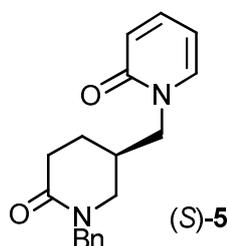
Racemic 1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)piperidin-2-one **235** and regioisomer **236**.



Under nitrogen, a solution of 1-benzyl-3-((2-oxopiperidin-1-yl)methyl)piperidine-2,6-dione, (±)-**228** (56.0 mg, 0.178 mmol) in dry ethanol (1.70 cm<sup>3</sup>) was acidified to approximately pH 7 with HCl (~ 5 μL, 0.8 M) and cooled to 0 °C. To the stirred solution, NaBH<sub>4</sub> (13.5 mg, 0.357 mmol) was added portion-wise at 10 min intervals. Throughout the reaction, HCl (~5 μL, 0.8 M) was added in 10 min intervals to maintain the reaction at approximately pH 7. After 40 min the reaction was neutralised and saturated aqueous sodium hydrocarbonate (1.00 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 1 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the crude intermediate product (52.5 mg) as an oil. No further purification was attempted. Under nitrogen, Et<sub>3</sub>SiH (134 μL, 0.839 mmol) was added to a solution of the crude intermediate product (53.0 mg) in TFA (0.30 cm<sup>3</sup>) and dry DCM (0.30 cm<sup>3</sup>). The mixture was heated to 40 °C and stirred for 5 h before saturated aqueous sodium hydrocarbonate (1 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 1 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the crude product which was purified by column chromatography (95:5 ethyl acetate / methanol) to give the minor amide (±)-**236** (10.5 mg, 0.035 mmol, 20 % yield) as a colourless oil; found (ESI): M<sup>+</sup> + Na, 323.1733. C<sub>18</sub>H<sub>24</sub>N<sub>2</sub>NaO<sub>2</sub> requires M,

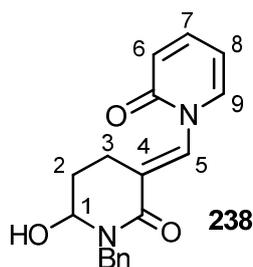
323.1730);  $\nu_{\max}$  3080 (aryl CH st.), 1624 (C=O st.), 1590 (C=C st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (700 MHz,  $\text{CDCl}_3$ ) 7.28-7.14 (5 H, m, ArH), 4.54-4.48 (2H, m,  $\text{CH}_2$ ), 4.09-4.01 (1H, m,  $\text{H}_{5\text{A}}$ ), 3.44 (1H, dd,  $J$  13.6, 5.0,  $\text{H}_{5\text{B}}$ ), 3.39-3.31 (1 H, m,  $\text{H}_{9\text{A}}$ ), 3.21-3.09 (3 H, m,  $\text{H}_{9\text{B}}$ ,  $\text{H}_4$ ), 2.67-2.59 (1H, m,  $\text{H}_3$ ), 2.37-2.28 (2H, m,  $\text{H}_6$ ), 1.90-1.83 (1H, m,  $\text{H}_{2\text{A}}$ ), 1.79 (1H, dtd,  $J$  13.2, 6.5, 2.7,  $\text{H}_{2\text{B}}$ ), 1.76-1.69 (2H, m,  $\text{H}_1$ ), 1.66-1.46 (4H, m,  $\text{H}_7$ ,  $\text{H}_8$ );  $\delta_{\text{C}}$  (176 MHz,  $\text{CDCl}_3$ ) 170.84 (CO), 170.42 (CO), 137.15 (Ar), 128.60 (Ar), 127.99 (Ar), 127.36 (Ar), 50.37 ( $\text{CH}_2\text{Ar}$ ), 48.15, 48.01, 47.45, 40.42 ( $\text{C}_4$ ), 32.38 ( $\text{C}_6$ ), 24.62, 23.28, 21.30, 21.20;  $m/z$  (ESI) 301.2 ( $\text{M}^+ + 1$ ), 323.2 ( $\text{M}^+ + 23$ ) and the major amide ( $\pm$ )-**235** (15.0 mg, 0.050 mmol, 28 % yield) as a colourless oil; found (ESI):  $\text{M}^+ + \text{H}$ , 301.1922.  $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_2$  requires  $\text{M}$ , 301.1911);  $\nu_{\max}$  1631 br. (C=O st., C=C st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.36-7.21 (5 H, m), 4.72 (1 H, d,  $J$  14.7), 4.44 (1 H, d,  $J$  14.7), 3.78-3.71 (1 H, m), 3.38-3.30 (1 H, m), 3.22 (1 H, dd,  $J$  13.6, 7.3), 3.19-3.11 (2 H, m), 3.00-2.95 (1 H, m), 2.64-2.54 (1 H, m), 2.49-2.38 (1 H, m), 2.37-2.31 (1 H, m), 2.25-2.12 (1 H, m), 1.89 - 1.80 (2 H, m), 1.79 - 1.69 (4 H, m), 1.62 - 1.50 (1 H, m);  $\delta_{\text{C}}$  (176 MHz,  $\text{CDCl}_3$ ) 170.18 (CO), 169.51 (CO), 137.06 (Ar), 128.59 (Ar), 128.15 (Ar), 127.39 (Ar), 50.36, 50.14, 49.78, 48.98, 32.67 ( $\text{C}_3$ ), 32.23 ( $\text{C}_6$ ), 31.19 ( $\text{C}_1$ ), 25.33 ( $\text{C}_2$ ), 23.26 ( $\text{C}_8$ ), 21.22 ( $\text{C}_7$ );  $m/z$  (ESI) 301.2 ( $\text{M}^+ + 1$ ), 323.2 ( $\text{M}^+ + 23$ ). This sample was used in chiral HPLC to confirm the retention times of the enantiomers. The HPLC data is given in the following section.

Procedure for the formation of (*R*)-1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)pyridin-2(1*H*)-one with  $\text{LiAlH}_4$ .



Alternatively,  $\text{LiAlH}_4$  was used to reduce imide **218** to the intermediate  $\alpha$ -lactam. The same procedure of intermediate  $\alpha$ -lactam reduction with  $\text{Et}_3\text{SiH}$  and TFA (as detailed in the previous section) was used to form lactam **5**. Under nitrogen,  $\text{LiAlH}_4$  (2M in THF, 0.05  $\text{cm}^3$ , 0.100 mmol) was added to a solution of (*S*)-1-benzyl-3-((2-oxopiperidin-1-yl)methyl)piperidine-2,6-dione, **218** (95 % ee, 30 mg, 0.097 mmol) in dry THF (1.0  $\text{cm}^3$ ) and the solution was stirred at  $-78^\circ\text{C}$  for 2 h before water (2  $\text{cm}^3$ ) was added. Following extraction with DCM (3 x 5  $\text{cm}^3$ ) the organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to give the intermediate product (30 mg). This intermediate was further reduced to yield product (*S*)-**5** via the procedure shown in the previous section, using a solution of  $\text{Et}_3\text{SiH}$  (77  $\mu\text{L}$ , 0.482 mmol) in TFA (1  $\text{cm}^3$ ) and dry DCM (1  $\text{cm}^3$ ). Following concentration under reduced pressure, the product (*S*)-**5** (10 mg, 0.034 mmol, 35 % yield from imide (*S*)-**218**) was obtained as a colourless oil, as determined by  $^1\text{H}$  NMR, following purified by column chromatography (ethyl acetate – methanol 95:5). The ee of this sample was found to be 13 % ee via indirect reduction to product **235**. Full characterisation data and HPLC separations were listed in the previous section.

*(Z)*-1-((1-Benzyl-6-hydroxy-2-oxopiperidin-3-ylidene)methyl)pyridin-2(1H)-one, **238**

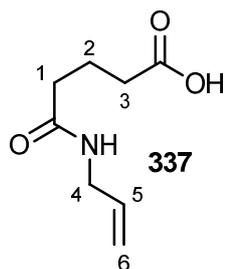


Under nitrogen, cerium(III) chloride heptahydrate (363 mg, 0.97 mmol) was added to (*E*)-1-benzyl-3-((2-oxopyridin-1(2H)-yl)methylene)-piperidine-2,6-dione **1** (300 mg, 0.974 mmol) in methanol (2.4 cm<sup>3</sup>) and stirred at room temperature for 5 min. Sodium borohydride (165 mg, 4.362 mmol) was added portionwise at room temperature and the mixture was left stirring for 3 hours before aqueous sodium hydrocarbonate (10 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 5 cm<sup>3</sup>), the organic extracts were washed with aqueous sodium hydrocarbonate (10 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the crude product which was purified by column chromatography (ethyl acetate – heptane 9:1) and preparative HPLC (Waters XBridge Prep C<sub>18</sub> OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH<sub>3</sub>) and MeCN as eluents to give compound **238** (60 mg, 0.193 mmol, 20 % yield) as a white powder; Mp 175-178 °C; (found (ESI): M<sup>+</sup> - H<sub>2</sub>O, 293.12836. C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub> requires M, 293.34526); ν<sub>max</sub> 3423 (OH st.), 1656 br. (C=O st., C=C st.) cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.91 (1 H, s, H<sub>4</sub>), 7.22 – 7.42 (6 H, m, ArH, H<sub>7</sub>), 7.19 (1 H, dd, *J* 7.0, 1.6, H<sub>9</sub>), 6.61 (1 H, d, *J* 9.2, H<sub>6</sub>), 6.23 (1 H, td, *J* 7.0, 1.3, H<sub>8</sub>), 5.10 (1 H, d, *J* 15.0, CH<sub>2</sub>), 5.02 (1 H, t, *J* 3.0, H<sub>1</sub>), 4.50 (1 H, d, *J* 15.0, CH<sub>2</sub>), 3.48 (1H, bs, OH), 2.79 – 2.9 (1 H, m, H<sub>2A</sub>), 2.42 (1 H, m, H<sub>2B</sub>), 1.95-1.82 (2 H, m, H<sub>4</sub>); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 162.95 (CO), 162.10 (CO), 140.42 (C<sub>7</sub>), 137.15 (Ar), 136.54 (C<sub>9</sub>), 133.66 (C<sub>5</sub>), 128.53 (Ar), 128.04 (Ar), 127.80 (C<sub>4</sub>), 127.33 (Ar), 121.21 (C<sub>6</sub>), 106.44

(C<sub>8</sub>), 78.05 (C<sub>1</sub>), 47.85 (CH<sub>2</sub>Ph), 29.28 (C<sub>2</sub>), 19.28 (C<sub>3</sub>); *m/z* (ESI) 293.04 (M<sup>+</sup> - H<sub>2</sub>O), 333.07 (M<sup>+</sup> + 23).

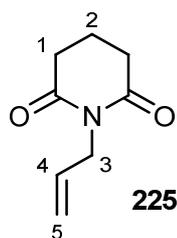
*Section 3.1.3: The Attempted Synthesis of (-)-Sparteine.*

*5-Oxo-5-(prop-2-en-1-ylamino)pentanoic acid, 337*



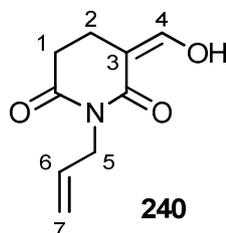
This compound has been reported but not fully characterised.<sup>181</sup> Glutaric anhydride (2.00 g, 17.53 mmol) was added to NEt<sub>3</sub> (2.44 cm<sup>3</sup>, 17.51 mmol) in THF (38 cm<sup>3</sup>) and stirred for 5 min at 0 °C. Allylamine (1.32 cm<sup>3</sup>, 17.60 mmol) in THF (30 cm<sup>3</sup>) was added dropwise over one hour at 0 °C. The mixture was heated to 75 °C and left stirring for 24 h before hydrochloric acid (1 M, 40 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 40 cm<sup>3</sup>), the organic extracts were washed with brine (30 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the product **337** (1.25 g, 7.31 mmol, 42 % yield) as an oil; (found (ESI): M<sup>+</sup> + Na, 194.0787. C<sub>8</sub>H<sub>13</sub>NNaO<sub>3</sub> requires M, 194.0788);  $\nu_{\max}$  3314 br. (OH st.), 1706 (C=O st.), 1620 (C=O st.), 1547 (NH st.), 1230 (C-O st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 9.69 (1H, br s, NH), 5.83 (1H, ddt, *J* 16.4, 9.6, 5.5, H<sub>4</sub>), 5.19 (1H, d, *J* 16.4, H<sub>6A</sub>), 5.14 (1H, d, *J* 9.6, H<sub>6B</sub>), 3.89 (2H, t, *J* 5.5, H<sub>4</sub>), 2.43 (2H, t, *J* 6.5, H<sub>3</sub>), 2.31 (2H, t, *J* 6.5, H<sub>1</sub>), 1.99 (2H, quin, *J* 6.5, H<sub>2</sub>);  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>) 177.85 (CO), 171.85 (CO), 132.44 (C<sub>5</sub>), 116.61 (C<sub>6</sub>), 42.02 (C<sub>4</sub>), 35.22 (C<sub>3</sub>), 32.13 (C<sub>1</sub>), 20.35 (C<sub>2</sub>); *m/z* (ESI) 193.8 (M<sup>+</sup> + Na). No further purification was carried out.

*1-Allylpiperidine-2,6-dione, 225.*



This compound has been reported but not fully characterised.<sup>182</sup> 5-Oxo-5-(prop-2-en-1-ylamino)pentanoic acid **337** (2.34 g, 13.68 mmol) was added to acetyl chloride (33 cm<sup>3</sup>) and the solution was left stirring 65 °C for 8 h. Following concentration under reduced pressure, product **225** (0.675 g, 4.41 mmol, 32 %) was obtained as a colourless oil, following purification by column chromatography (hexane - ethyl acetate 1:1); (found (ESI): M<sup>+</sup> + Na, 176.0683 C<sub>8</sub>H<sub>11</sub>NaNO<sub>2</sub> requires M, 176.0682);  $\nu_{\max}$  3090 (alkene CH st.), 1760 (C=O st.), 1722 (C=O st.), 1667 (C=C st.), 1172 (amide III), 1022 (=CH b.), 925 (=CH b.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 5.65 (1H, ddt, *J* 16.7, 9.7, 5.7, H<sub>4</sub>), 5.01 (1H, d, *J* 16.7, H<sub>5A</sub>), 4.98 (1H, d, *J* 9.7, H<sub>5B</sub>), 4.19 (2H, d, *J* 5.7, H<sub>3</sub>), 2.52 (4H, t, *J* 6.5, H<sub>1</sub>), 1.84 (2H, q, *J* 6.5, H<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 171.90 (CO), 131.87 (C<sub>4</sub>), 116.54 (C<sub>5</sub>), 41.00 (C<sub>3</sub>), 32.27 (C<sub>1</sub>), 16.67 (C<sub>2</sub>); *m/z* (ESI) 154.2 (M<sup>+</sup> + 1).

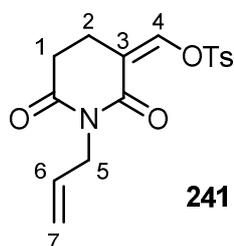
*(Z)-1-Allyl-3-(hydroxymethylene)piperidine-2,6-dione, 240.*



Dry ethanol (2.33 cm<sup>3</sup>, 39.90 mmol) was added dropwise to a suspension of NaH (60% in oil, 1.60 g, 40.00 mmol) in Et<sub>2</sub>O (46.5 cm<sup>3</sup>) at 0 °C and left stirring for 20 min. A solution of 1-allylpiperidine-2,6-dione **225** (2.14 g, 13.98 mmol) and ethyl

formate (1.96 cm<sup>3</sup>, 24.24 mmol) in Et<sub>2</sub>O (46.5 cm<sup>3</sup>) was added dropwise over 1 h at 0 °C, then left to warm to room temperature and stirred for 16 h before extraction with water (2 x 40 cm<sup>3</sup>). The aqueous extracts were acidified with HCl (30 cm<sup>3</sup>, 2M), followed by extraction with Et<sub>2</sub>O (3 x 50 cm<sup>3</sup>). The organic extract was washed with saturated aqueous sodium hydrocarbonate, dried (MgSO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (hexane - ethyl acetate 1 : 1), to give product **240** (1.63 g, 9.00 mmol, 64 % yield) as an oil; (found (ESI): M<sup>+</sup> + Na, 204.0640. C<sub>9</sub>H<sub>11</sub>NNaO<sub>3</sub> requires M, 204.0631);  $\nu_{\max}$  3250 (OH st.), 3090 (alkene CH st.), 1715 (C=O st.), 1678 (C=O st.), 1642 (C=C st.), 1600 (C=C st.), 1153 (Amide III), 990 (alkene CH b.), 926 (alkene CH b.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 12.24 (1H, d, *J* 12.2, OH), 7.18 (1H, d, *J* 12.2, H<sub>4</sub>), 5.83 (1H, ddt, *J* 13.6, 7.5, 5.8, H<sub>6</sub>), 5.19 (1H, d, *J* 13.6, H<sub>7A</sub>), 5.16 (1H, d, *J* 7.5, H<sub>7B</sub>), 4.40 (2H, d, *J* 5.8, H<sub>5</sub>), 2.66 (2H, t, *J* 7.0, H<sub>1</sub>), and 2.47 (2H, t, *J* 7.0, H<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 171.37 (CO), 170.87 (CO), 160.64 (C<sub>4</sub>), 131.87 (C<sub>6</sub>), 117.10 (C<sub>7</sub>), 99.95 (C<sub>3</sub>), 41.13 (C<sub>5</sub>), 32.29 (C<sub>1</sub>), 19.61 (C<sub>2</sub>); *m/z* (ESI) 204.1 (M<sup>+</sup>+1).

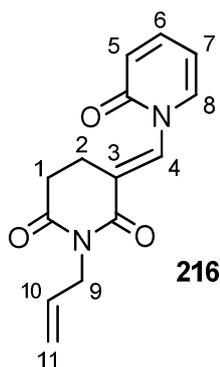
*(Z)*-(1-Allyl-2,6-dioxopiperidin-3-ylidene)methyl 4-methylbenzenesulfonate, **241**.



*(Z)*-1-Allyl-3-(hydroxymethylene)piperidine-2,6-dione, **240** (1.40 g, 7.73 mmol) was added to NEt<sub>3</sub> (1.29 cm<sup>3</sup>, 9.26 mmol) in dry DCM (25.0 cm<sup>3</sup>) and cooled to 0 °C. A solution of *p*-toluenesulfonyl chloride (1.77 g, 9.28 mmol) in dry DCM (25.0 cm<sup>3</sup>) was added and the mixture was allowed to warm to room temperature and stir for 1 h

before saturated ammonium chloride (40 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 40 cm<sup>3</sup>), the organic extracts were washed with saturated hydrogen carbonate (3 x 40 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give product **241** (2.38 g, 7.10 mmol, 92 % yield) as a dark purple solid; (found (ESI): M<sup>+</sup> + Na, 358.0725. C<sub>16</sub>H<sub>17</sub>NNaO<sub>5</sub>S requires M, 358.0720);  $\nu_{\max}$  3090 (alkene CH st.), 1718 (C=O st.), 1678 (C=O st.), 1643 (C=C st.), 1593 (C=C st.), 1372 (SO st.), 1343 (SO st.), 1197 (SO st.), 1173 (Amide III), 1114 (SO st.), 957 (alkene CH b.), 934 (alkene CH b.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.84-7.82 (2H, m, ArH), 7.72 (1H, s, H<sub>4</sub>), 7.41-7.38 (2H, m, ArH), 5.77 (1H, ddt, *J* 16.3, 9.5, 5.8, H<sub>6</sub>), 5.16 (1H, d, *J* 16.3, H<sub>7A</sub>), 5.14 (1H, d, *J* 9.5, H<sub>7B</sub>), 4.38 (2H, d, *J* 5.8, H<sub>5</sub>), 2.59 (4H, m, H<sub>1,2</sub>), and 2.47 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 170.76 (CO), 164.66 (CO), 146.23 (Ar), 144.42 (C<sub>4</sub>), 131.66 (C<sub>6</sub>), 131.59 (Ar), 130.13 (Ar), 127.91 (Ar), 117.42 (C<sub>7</sub>), 115.48 (C<sub>3</sub>), 41.87 (C<sub>5</sub>), 30.87 (C<sub>1</sub>), 21.54 (CH<sub>3</sub>), 17.54 (C<sub>2</sub>); *m/z* (ESI) 358.0 (M<sup>+</sup> + Na).

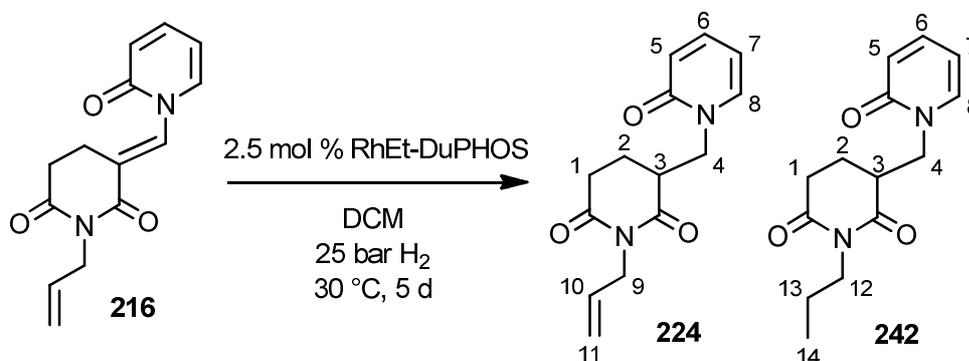
*(Z)*-1-Allyl-3-((2-oxopyridin-1(2H)-yl)methylene)piperidine-2,6-dione, **216**.



*(Z)*-(1-Allyl-2,6-dioxopiperidin-3-ylidene)methyl 4-methylbenzenesulfonate **241** (2.35 g, 7.01 mmol) was added to 2-hydroxypridine (1.33 g, 13.99 mmol) and NEt<sub>3</sub> (2.44 cm<sup>3</sup>, 17.51 mmol) in dry toluene (70.0 cm<sup>3</sup>) at room temperature. The mixture was heated to 110 °C and stirred for 20 h before concentration under reduced pressure and purification by column chromatography (ethyl acetate – hexane 9 : 1),

to give the product **216** (1.29 g, 5.00 mmol, 71 % yield) as an oil; (found (ESI):  $M^+ + Na$ , 281.0902.  $C_{14}H_{14}N_2NaO_3$  requires  $M$ , 281.0897);  $\nu_{max}$  3020 (alkene CH st.), 1721 (C=O st.), 1661 (C=O st.), 1640 (C=C st.), 1586 (C=C st.), 1533 (C=C st.), 1268 (Amide III), 992 (alkene CH b.), 916 (alkene CH b.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.96 (1H, s,  $H_4$ ), 7.40 (1H, ddd,  $J$  9.3, 6.8, 1.7,  $H_6$ ), 7.13 (1H, dd,  $J$  6.8, 1.7,  $H_8$ ), 6.64 (1H, d,  $J$  9.3,  $H_5$ ), 6.26 (1H, t,  $J$  6.8,  $H_7$ ), 5.82 (1H, ddt,  $J$  17.1, 9.5, 5.8,  $H_4$ ), 5.24 (1H, d,  $J$  17.1,  $H_{11A}$ ), 5.18 (1H, d,  $J$  9.5,  $H_{11B}$ ), 4.47 (2H, d,  $J$  5.8,  $H_9$ ), 2.75-2.67 (4H, m,  $H_{1,2}$ );  $\delta_C$  (100 MHz,  $CDCl_3$ ) 170.57 (CO), 164.91 (CO), 161.54 (CO), 140.26 ( $C_6$ ), 136.27 ( $C_4$ ), 135.54 ( $C_8$ ), 131.70 ( $C_{10}$ ), 124.58 ( $C_3$ ), 121.95 ( $C_5$ ), 117.83 ( $C_{11}$ ), 106.42 ( $C_7$ ), 42.31 ( $C_9$ ), 31.38 ( $C_1$ ), 21.01 ( $C_2$ );  $m/z$  (ESI) 259.1 ( $M^+ + H$ ), 281.1 ( $M^+ + Na$ ). The *O*-substituted isomer was not observed.

*Asymmetric hydrogenation of (Z)-1-Allyl-3-((2-oxopyridin-1(2H)-yl)methylene)piperidine-2,6-dione 216.*



A solution of thoroughly dried (*Z*)-1-Allyl-3-((2-oxopyridin-1(2*H*)-yl)methylene)-piperidine-2,6-dione **216** (143.0 mg, 0.554 mmol) and  $[Rh(COD)((R,R)\text{-Et-DuPHOS})]BF_4$  (9.3 mg,  $1.41 \times 10^{-2}$  mmol) in dry DCM (1.86  $cm^3$ ) was degassed three times. To the stirred solution, the hydrogenation was performed at 30 °C under 25 bar hydrogen for 5 days. The reaction mixture was passed through a short silica gel column to remove the catalyst to give an unseparable mixture of what was

characterised to be the desired allyl imide **224** and the over reduced propyl derivative **242** (36 % and 63 % respectively as determined by comparison of the allyl and propyl group integrals by  $^1\text{H}$  NMR):  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.45-7.40 (1H, m,  $\text{H}_8$ ), 7.30-7.25 (1H, m,  $\text{H}_6$ ), 6.50-6.44 (1H, m,  $\text{H}_5$ ), 6.14-6.10 (1H, m,  $\text{H}_7$ ), 5.70-5.65 (1H, m,  $\text{H}_{10}$ ), 5.10-5.02 (2H, m,  $\text{H}_{11}$ ), 4.35-4.25 (2H, m,  $\text{H}_{4\text{A}}$ ,  $\text{H}_9$ ), 4.12-4.05 (1H, m,  $\text{H}_{4\text{B}}$ ), 3.68-3.58 (1H, m,  $\text{H}_{12}$ ), 3.10-2.98 (1H, m,  $\text{H}_3$ ), 2.80-2.70 (1H, m,  $\text{H}_{1\text{A}}$ ), 2.60-2.48 (1H, m,  $\text{H}_{1\text{B}}$ ), 2.08-1.96 (1H, m,  $\text{H}_{2\text{A}}$ ), 1.75-1.60 (1H, m,  $\text{H}_{2\text{B}}$ ), 1.50-1.38 (2H, q,  $J$  7.0,  $\text{H}_{13}$ ), 0.88-0.78 (3H, t,  $J$  7.0,  $\text{H}_{14}$ ).

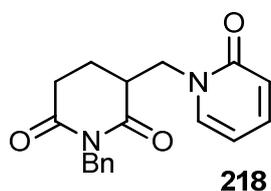
### **Section 3.2: Procedures from Section 2.2.**

#### *Section 3.2.1: ATH of Enamides.*

##### *General procedure for the transfer hydrogenation of $\alpha,\beta$ -unsaturated imides.*

Under nitrogen, a solution of  $\alpha,\beta$ -unsaturated imide (1 mmol) and  $[\text{Ru}(\text{teth-TsDPEN})]$  in dry methanol (1.6  $\text{cm}^3$ ) was stirred at 28  $^\circ\text{C}$  for 5 min before FA/TEA (5:2, 0.5  $\text{cm}^3$ ) was added. The solution was left stirring at 28  $^\circ\text{C}$  for the specified time before saturated aqueous hydrogen carbonate was added. Following extraction with DCM (3 x 5  $\text{cm}^3$ ), the organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to give the crude product which was analysed by  $^1\text{H}$  NMR. Where applicable the crude material was purified by column chromatography and analysed by chiral HPLC to determine the ee. The synthesis of all subsequently listed compounds was carried out by this procedure at equivalent stoichiometric ratios.

The formation of 1-benzyl-3-((2-oxopyridin-1(2H)-yl)methyl)piperidine-2,6-dione, ( $\pm$ )-**218** via ATH.



This compound was prepared following the general procedure for transfer hydrogenation of  $\alpha,\beta$ -unsaturated imides, using (*E*)-1-benzyl-3-((2-oxopyridin-1(2*H*)-yl)methylene)piperidine-2,6-dione, **1** (10 mg,  $3.2 \times 10^{-2}$  mmol) and (*S,S*)-Ruteth-TsDPEN, (*S,S*)-**248** (0.6 mg,  $9.7 \times 10^{-4}$  mmol), following a reaction time of 5 d. Following solvent removal and column chromatography, the product **218** (8 mg,  $2.6 \times 10^{-2}$  mmol, 81 % yield) was obtained as colourless oil. The product was found to be racemic. Full characterisation data for **218** was stated in the previous section.

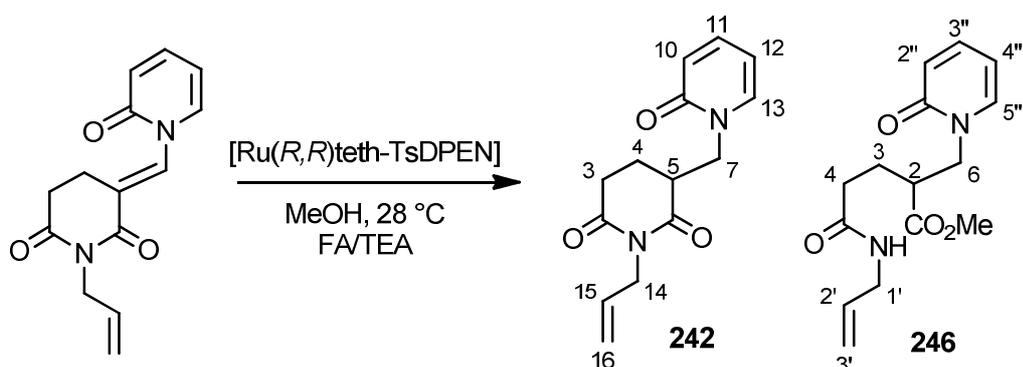
*Procedure for the transfer hydrogenation of (*E*)-1-benzyl-3-((2-oxopyridin-1(2*H*)-yl)methylene)piperidine-2,6-dione **218** with RuTsEN, **249**.*

This method conveniently used the racemic TH catalyst, Ru(TsEN) to carry out the TH. The material was otherwise formed by ATH in racemic form by using the chiral catalyst, RutethTsDPEN. The catalyst was formed *in situ* by combination of the precatalyst and diamine ligand by a known procedure.

Under nitrogen, a solution of [Ru(cymene)Cl<sub>2</sub>]<sub>2</sub> (0.4 mg,  $6.5 \times 10^{-4}$  mmol) and TsEN (0.8 mg,  $2.2 \times 10^{-3}$  mmol) in dry ethanol (1.0 cm<sup>3</sup>) and FA/TEA (5:2) (78  $\mu$ L) were stirred for 20 min at 28 °C. (*E*)-1-benzyl-3-((2-oxopyridin-1(2*H*)-yl)methylene)-piperidine-2,6-dione **1** (20 mg,  $6.5 \times 10^{-2}$  mmol) was added and the solution was

stirred at 28 °C for 5 days before saturated aqueous hydrogen carbonate (1 cm<sup>3</sup>) was added. Following extraction with DCM (3 × 2 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the product **218** (18 mg, 5.8 × 10<sup>-2</sup> mmol, 89 % yield) as determined by <sup>1</sup>H NMR. Full characterisation data for **218** was stated in Section 1.

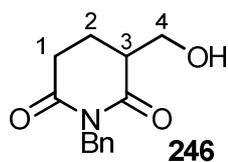
*The formation of 1-benzyl-3-((2-oxopyridin-1(2H)-yl)methyl)piperidine-2,6-dione and methyl 5-oxo-2-[(2-oxopyridin-1(2H)-yl)methyl]-5-(prop-2-en-1-ylamino)pentanoate.*



(*Z*)-1-Allyl-3-((2-oxopyridin-1(2H)-yl)methylene)piperidine-2,6-dione, **216** (566 mg, 2.19 mmol) was added to [Ru(*R,R*)teth-TsDPEN] (27.2 mg, 4.4 × 10<sup>-2</sup> mmol) in dry MeOH (3.50 cm<sup>3</sup>) at 28 °C before FA/TEA (5:2) (1.10 cm<sup>3</sup>) was added. The solution was stirred at 28 °C for 3 days before saturated aqueous hydrogen carbonate (5 cm<sup>3</sup>) was added. Following extraction with DCM (3 × 5 cm<sup>3</sup>), the organic extracts dried (Mg<sub>2</sub>SO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (ethyl acetate – methanol 95:5) to give product **247** (100 mg, 0.34 mmol, 16 % yield), as an oil, following; (found (ESI): M<sup>+</sup> + Na, 315.1314. C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>NaO<sub>4</sub> requires M, 315.1315); ν<sub>max</sub> 3078 (alkene CH st.), 1732 (C=O st.), 1655 (C=O st.), 1580 (C=C st.), 1540 (C=C st.), 993 (alkene CH b.), 924 (alkene CH

b.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (600 MHz,  $\text{CDCl}_3$ ) 7.32 - 7.37 (2 H, m,  $\text{H}_{5''}$ ,  $\text{H}_{3''}$ ), 6.54 (1 H, d,  $J$  9.0,  $\text{H}_{2''}$ ), 6.39 (1 H, bs, NH), 6.14 - 6.18 (1 H, td,  $J$  7.0, 1.0,  $\text{H}_{4''}$ ), 5.80 - 5.87 (1 H, ddt,  $J$  17.0, 10.0, 4.5,  $\text{H}_2$ ), 5.19 (1 H, dd,  $J$  17.0, 1.5,  $\text{H}_{3'A}$ ), 5.12 (1 H, dd,  $J$  10.0, 1.5,  $\text{H}_{3'B}$ ), 4.35 (1 H, dd,  $J$  13.0, 4.5,  $\text{H}_{1'A}$ ), 3.85 - 3.91 (3 H, m,  $\text{H}_{1'B}$ ,  $\text{H}_6$ ), 3.66 (3 H, s, Me), 2.93 - 2.99 (1 H, m,  $\text{H}_2$ ), 2.49 - 2.42 (1 H, m,  $\text{H}_{4A}$ ), 2.38 - 2.30 (1 H, m,  $\text{H}_{4B}$ ), 2.12 - 2.04 (1 H, m,  $\text{H}_{3A}$ ), 1.90 - 1.83 (1 H, m,  $\text{H}_{3B}$ );  $\delta_{\text{C}}$  (151 MHz,  $\text{CDCl}_3$ ) 174.16 (CO), 171.69 (CO), 162.68 (CO), 140.04 ( $\text{C}_{5''}$ ), 138.52 ( $\text{C}_{3''}$ ), 134.21 ( $\text{C}_{2''}$ ), 120.81 ( $\text{C}_{2''}$ ), 116.27 ( $\text{C}_{3'}$ ), 106.10 ( $\text{C}_{4''}$ ), 52.10 ( $\text{CH}_3$ ), 50.44 ( $\text{C}_{1'}$ ), 43.82 ( $\text{C}_2$ ), 41.98 ( $\text{C}_6$ ), 33.92 ( $\text{C}_4$ ), 26.31 ( $\text{C}_3$ );  $m/z$  (ESI) 293.2 ( $\text{M}^+ + \text{H}$ ), 315.1 ( $\text{M}^+ + \text{Na}$ ); followed by an impure sample containing what was characterised to be product **242** (400 mg); (found (EI):  $\text{M}^+ + \text{Na}$ , 283.1058.  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{NaO}_3$  requires M, 283.1053);  $\nu_{\text{max}}$  3084 (aryl CH st.), 1715 (C=O st.), 1662 (C=O st.), 1647 (C=O st.), 1581 (C=C st.), 1538 (C=C st.), 1157 (amide III)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.48 (1 H, dd,  $J$  7.0, 2.5,  $\text{H}_{13}$ ), 7.38 - 7.32 (1 H, m,  $\text{H}_{11}$ ), 6.56 (1 H, d,  $J$  9.0,  $\text{H}_{10}$ ), 6.21 - 6.16 (1 H, m,  $\text{H}_{12}$ ), 5.83 - 5.71 (1 H, m,  $\text{H}_{15}$ ), 5.16 (1 H, dd,  $J$  8.0, 1.5,  $\text{H}_{16A}$ ), 5.14 - 5.11 (1 H, m,  $\text{H}_{16B}$ ), 4.40 - 4.34 (1 H, m,  $\text{H}_{7A}$ ), 4.19 (1 H, dd,  $J$  13.5, 5.5,  $\text{H}_{7B}$ ), 3.12 (1 H, ddd,  $J$  18.0, 10.5, 5.5,  $\text{H}_5$ ), 2.87 (1 H, dt,  $J$  16.0, 7.0,  $\text{H}_{3A}$ ), 2.63 (1 H, m,  $\text{H}_{3B}$ ), 2.18 - 2.08 (1 H, m,  $\text{H}_{4A}$ ), 1.82 - 1.69 (1 H, m,  $\text{H}_{4B}$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 173.15 (CO), 171.41 (CO), 162.89 (CO), 139.84 ( $\text{C}_{13}$ ), 138.81 ( $\text{C}_{11}$ ), 133.73 ( $\text{C}_{15}$ ), 131.89, 120.72 ( $\text{C}_{10}$ ), 117.38 ( $\text{C}_{16}$ ), 105.92 ( $\text{C}_{12}$ ), 50.35 ( $\text{C}_7$ ), 41.91 ( $\text{C}_{14}$ ), 41.68 ( $\text{C}_5$ ), 32.26 ( $\text{C}_3$ ), 21.30 ( $\text{C}_4$ );  $m/z$  (ESI) 283.1 ( $\text{M}^+ + \text{Na}$ ).

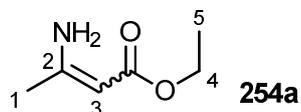
*1-Benzyl-3-(hydroxymethyl)piperidine-2,6-dione, 246*



This compound was prepared following the general procedure (A) for transfer hydrogenation of  $\alpha,\beta$ -unsaturated imides using (*Z*)-1-benzyl-5-(hydroxylmethylene)piperidine-2,6-dione **220** (32 mg, 0.139 mmol) and Ru(*S,S*)-*teth*-TsDPEN (1.7 mg,  $2.7 \times 10^{-3}$  mmol), for 16 h. Following column chromatography (ethyl acetate – hexane 1:1), the product **246** (25 mg, 0.107 mmol, 77 % yield) was obtained as an oil;  $[\alpha]_D^{24} + 19$  ( $c$ 0.09 in  $\text{CHCl}_3$ ) 31 % ee; (found (ESI):  $M^+ + \text{Na}$ , 256.0942.  $\text{C}_{13}\text{H}_{15}\text{NNaO}_3$  requires  $M$ , 256.0944);  $\nu_{\text{max}}$  3387 (OH st.), 3033 (aryl CH st.) 1722 (C=O st.), 1667 (C=O st.), 1165 (amide III)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.33 - 7.13 (5 H, m, ArH), 4.88 (2 H, s,  $\text{CH}_2\text{Ph}$ ), 3.90 - 3.73 (2 H, m,  $\text{H}_4$ ), 2.98 - 2.73 (2 H, m,  $\text{H}_1$ ), 2.68 - 2.49 (1 H, m,  $\text{H}_3$ ), 1.93 - 1.71 (2 H, m,  $\text{H}_2$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 175.00 (CO), 171.99 (CO), 137.03 (Ar), 128.59 (Ar), 128.48 (Ar), 127.52 (Ar), 63.03 ( $\text{C}_4$ ), 44.62 ( $\text{CH}_2\text{Ar}$ ), 42.94 ( $\text{C}_3$ ), 32.41 ( $\text{C}_1$ ), 20.22, ( $\text{C}_2$ );  $m/z$  (ESI) 256.1 ( $M^+ + \text{Na}$ ). The ee was determined by HPLC analysis (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 95:1, 1 mL/min, T = 30 °C, minor isomer 57.34 min, major isomer 62.04 min.) 31 % ee. For HPLC analysis, a racemic standard was used to establish the position of the two enantiomers. This standard was obtained from the combination of an equal amount of two samples of the alcohol product which were both opposite enantiomers. These had been formed by ATH through the (*R,R*) and (*S,S*) forms of the catalyst respectively.

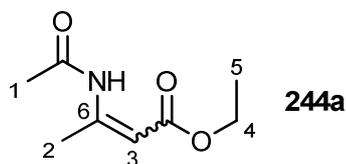
Section 3.2.2: Synthesis and ATH of  $\beta$ -(Acylamino)acrylates.

Ethyl-3-(amino)but-2-enoate, **254a**.



This compound has been reported and characterised.<sup>183</sup> A solution of ammonium acetate (1.59 g, 20.62 mmol) and ethyl acetoacetate (0.50 g, 3.84 mmol) in ethanol (5.3 cm<sup>3</sup>) were stirred at room temperature for 60 h, before the solution was concentrated under reduced pressure and chloroform (10 cm<sup>3</sup>) was added. The resulting salt precipitate was removed by filtration and the filtrate was washed with water (15 cm<sup>3</sup>), and brine (15 cm<sup>3</sup>); dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the product, **254a** (0.300 g, 2.32 mmol, 61 %) as an oil;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 4.52 (1 H, s, H<sub>3</sub>), 4.11 (2 H, q,  $J$  7.0, H<sub>4</sub>), 1.91 (3 H, s, H<sub>1</sub>), 1.25 (1 H, t,  $J$  7.0, H<sub>5</sub>) *A resonance attributable to NH<sub>2</sub> was not observed*;  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>) 170.18 (CO), 159.67 (C<sub>2</sub>), 83.96 (C<sub>3</sub>), 58.41 (C<sub>4</sub>), 22.21 (C<sub>1</sub>), 14.48 (C<sub>5</sub>). This data was in agreement with the literature.

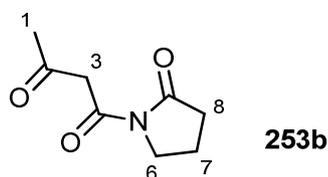
Ethyl-3-[acetylamino]but-2-enoate, **244a**.



This compound is been reported and characterised.<sup>184</sup> Under nitrogen, acetic anhydride (6.00 cm<sup>3</sup>, 6.48 g, 63.47 mmol) and pyridine (2.00 cm<sup>3</sup>, 1.96 g, 24.73 mmol) were added to a solution of ethyl-3-(amino)but-2-enoate **254a** (1.55 g, 12.01 mmol) in THF (15.0 cm<sup>3</sup>) at room temperature. The solution was left stirring at 65 °C for 15 h before being concentrated under reduced pressure. The residue was re-dissolved in ethyl acetate (10 cm<sup>3</sup>), washed with water (5 cm<sup>3</sup>), HCl (1M, 5 cm<sup>3</sup>),

saturated aqueous sodium hydrocarbonate (5 cm<sup>3</sup>) and saturated aqueous brine (5 cm<sup>3</sup>). The organic extracts were dried (MgSO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (ethyl acetate – hexane 1 : 9) to give the products (*Z/E* = 2.2:1, as determined by <sup>1</sup>H NMR) (*Z*)-**244a** (0.40 g, 2.34 mmol, 19 %) and (*E*)-**244a** (0.18 g, 1.05 mmol, 9 %) as colourless solids; (*Z*)-**244a**: δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 11.13 (1 H, bs, NH), 4.90 (1 H, s, H<sub>3</sub>), 4.15 (2 H, q, *J* 7.0, H<sub>4</sub>), 2.38 (3 H, s, H<sub>1</sub>), 2.14 (3 H, s, H<sub>2</sub>), 1.28 (3 H, t, *J* 7.0, H<sub>5</sub>); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 169.16 (CO), 168.95 (CO), 110.15 (C<sub>6</sub>), 96.40 (C<sub>3</sub>), 59.60 (C<sub>4</sub>), 25.41 (CH<sub>3</sub>), 21.88 (CH<sub>3</sub>), 14.98 (C<sub>5</sub>). (*E*)-**244a**: δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 6.75 (1 H, s, H<sub>3</sub>), 6.70 (1 H, bs, NH), 4.14 (2 H, q, *J* 7.0, H<sub>4</sub>), 2.35 (3 H, s, H<sub>1</sub>), 2.13 (3 H, s, H<sub>2</sub>), 1.27 (1 H, t, *J* 7.0, H<sub>5</sub>); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 169.77 (CO), 168.41 (CO), 149.16 (C<sub>6</sub>), 102.34 (C<sub>3</sub>), 59.39 (C<sub>4</sub>), 24.66 (CH<sub>3</sub>), 18.10 (CH<sub>3</sub>), 14.11 (C<sub>5</sub>). This data was in agreement with the literature.

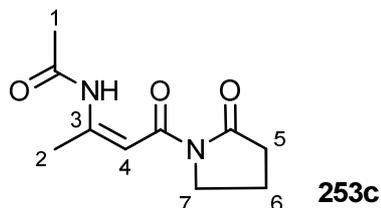
*1-(2-Oxopyrrolidin-1-yl)butane-1,3-dione*, **253b**.



This compound has been reported but not fully characterised.<sup>185</sup> A solution of pyrrolidin-2-one (0.90 cm<sup>3</sup>, 1.01 g, 11.84 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (1.87 cm<sup>3</sup>, 2.00 g, 14.08 mmol) in xylene (9.0 cm<sup>3</sup>) stirred at 140 °C for 90 min. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – heptanes 1:1), the product **253b** (1.61 g, 9.52 mmol, 80 %) was obtained as a pale yellow liquid; (found (ESI): M<sup>+</sup> + H, 169.0728. C<sub>8</sub>H<sub>11</sub>NO<sub>3</sub> requires M, 169.0739); ν<sub>max</sub> 1728 (C=O st.), 1693 (C=O st.), 1630 (C=O st.), 1192 (amide III) cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 3.98 (2 H, s, H<sub>3</sub>), 3.90 – 3.77 (2 H, m, H<sub>6</sub>), 2.56 (2 H, t, *J* 8.0, H<sub>8</sub>), 2.25 (3 H, s, H<sub>1</sub>), 2.11 – 1.98 (2 H, m, H<sub>7</sub>); δ<sub>C</sub> (101

MHz, CDCl<sub>3</sub>) 201.37 (C<sub>2</sub>), 175.79 (C<sub>4</sub>), 167.12 (C<sub>9</sub>), 52.46 (C<sub>3</sub>), 45.33 (C<sub>6</sub>), 33.37 (C<sub>8</sub>), 30.30 (C<sub>1</sub>), 17.16 (C<sub>7</sub>); *m/z* (ESI) 169 (M<sup>+</sup>+1).

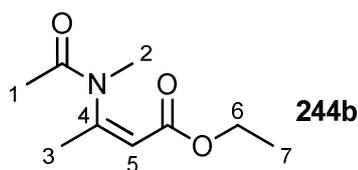
*(Z)*-*N*-(4-Oxo-4-(2-oxopyrrolidin-1-yl)but-2-en-2-yl)acetamide, **253c**.



Under nitrogen, a solution of ammonium acetate (3.28 g, 42.55 mmol) and 1-(2-oxopyrrolidin-1-yl)butane-1,3-dione **253b** (1.44 g, 8.52 mmol) in methanol (10.64 cm<sup>3</sup>) were left stirring at room temperature for 24 h before solution was concentrated under reduced pressure and chloroform (30 cm<sup>3</sup>) was added. The resulting precipitate of salt was removed by filtration and the resulting filtrate was washed with water (30 cm<sup>3</sup>) and brine (30 cm<sup>3</sup>), then dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the intermediate product (1.95 g) as a solid;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 6.12 (1 H, s, CH), 4.91 (2 H, bs, NH<sub>2</sub>), 4.14 – 4.07 (2 H, m, CH<sub>2</sub>), 3.09 (2 H, t, *J* 8.0, CH<sub>2</sub>), 2.27 (3 H, s, CH<sub>3</sub>), 2.02 – 1.93 (2 H, m, CH<sub>2</sub>);  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>) 174.88 (CO), 168.42 (CO), 162.83 (CO), 110.08 (=CH), 46.88 (NCH<sub>2</sub>), 32.76 (CH<sub>2</sub>), 23.78 (CH<sub>3</sub>), 19.12 (CH<sub>2</sub>). A solution of the intermediate product (1.95 g), acetic anhydride (5.61 cm<sup>3</sup>, 6.06 g, 59.35 mmol) and pyridine (1.92 cm<sup>3</sup>, 23.74 mmol) in THF (14.9 cm<sup>3</sup>) was stirred at 70 °C for 15 h before the solution was concentrated under reduced pressure. The residue was re-dissolved in EtOAc (30 cm<sup>3</sup>) and washed with H<sub>2</sub>O (10 cm<sup>3</sup>), 1 M HCl (10 cm<sup>3</sup>), saturated aqueous sodium hydrocarbonate (10 cm<sup>3</sup>) and saturated aqueous brine (10 cm<sup>3</sup>). The organic extracts were dried (MgSO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (ethyl acetate – hexane 3 : 7) to give the product **253c** (0.50 g, 2.38

mmol, 28 % over two steps) as a colourless solid; Mp 118-120 °C; (Found (ESI):  $M^+ + H$ , 211.10762.  $C_{10}H_{15}N_2O_3$  requires  $M$ , 211.10772);  $\nu_{\max}$  1727 (C=O st.), 1614 br. (C=O st., C=C st.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 11.86 (1 H, s, NH), 6.54 (1 H, d,  $J$  1.0,  $H_4$ ), 3.91 – 3.80 (2 H, m,  $H_7$ ), 2.61 (2 H, t,  $J$  8.0,  $H_5$ ), 2.46 (3 H, d,  $J$  1.0,  $H_1$ ), 2.16 (3 H, s,  $H_2$ ), 2.09 – 1.97 (2 H, m,  $H_6$ );  $\delta_C$  (101 MHz,  $CDCl_3$ ) 175.08 (CO), 169.37 (CO), 169.15 (CO), 157.68 ( $C_3$ ), 97.13 ( $C_4$ ), 45.58 ( $C_7$ ), 34.17 ( $C_5$ ), 25.62 ( $C_1$ ), 22.74 ( $C_2$ ), 17.10 ( $C_6$ );  $m/z$  (ESI) 211 ( $M^+ + H$ ), 233 ( $M^+ + Na$ ). The assignment of *E* alkene geometry was supported by an  $^1H$  NMR nOe experiment. Irradiation of  $H_3$  resulted in the excitation of protons  $H_2$ .

*Ethyl-3-[acetyl(methyl)amino]but-2-enoate, 244b.*

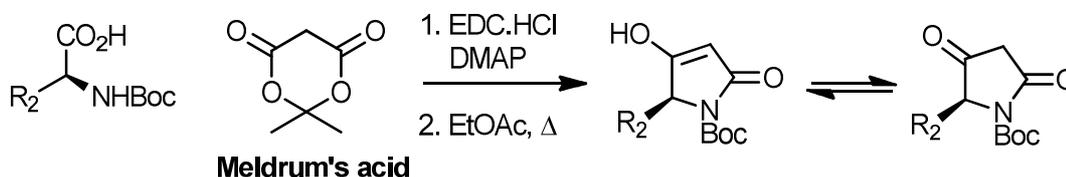


Acetic acid (1.23  $cm^3$ , 1.29 g, 21.49 mmol) and methylamine (33 % w/w ethanol solution, 2.12  $cm^3$ , 0.70 g, 22.52 mmol) were added to a solution of ethyl acetoacetate (0.5 g, 3.84 mmol) in ethanol (5.4  $cm^3$ ) and stirred at room temperature for 24 h, before the solution was concentrated under reduced pressure to give the intermediate product (2.10 g) as an oil;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 4.47 (1 H, s, CH), 4.08 (2 H, d,  $J$  7.0 Hz,  $CH_2$ ), 2.90 (3 H, s,  $CH_3$ ), 2.92 (3 H, s,  $CH_3$ ), 1.92 (3 H, s,  $CH_3$ ), 1.25 (3 H, t,  $J$  7.0 Hz,  $CH_3$ );  $\delta_C$  (75 MHz,  $CDCl_3$ ) 177.56 (CO), 170.55 (NC=), 81.65(=CH), 58.12 ( $OCH_2$ ), 29.41 ( $CH_3$ ), 24.38 ( $CH_3$ ), 14.47 ( $CH_3$ ). A solution of acetic anhydride (2.04  $cm^3$ , 2.20 g, 21.58 mmol), pyridine (0.70  $cm^3$ , 0.68 g, 8.65 mmol) and the intermediate product (2.10 g) in THF (5.4  $cm^3$ ) were stirred at 40 °C for 8 h before the solution was concentrated under reduced pressure. The residue was re-dissolved in EtOAc (10  $cm^3$ ) and washed with water (5  $cm^3$ ), 1 M HCl (5  $cm^3$ ),

saturated aqueous sodium hydrocarbonate (5 cm<sup>3</sup>) and saturated aqueous brine (5 cm<sup>3</sup>). The organic extracts were dried (MgSO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (ethyl acetate – hexane 3:7) to give the product **244b** (205 mg, 1.11 mmol, 29 %) as a colourless solid; Mp 140-144 °C; Found (ESI): M<sup>+</sup> + Na, 208.0944. C<sub>9</sub>H<sub>15</sub>NNaO<sub>3</sub> requires M, 208.0944);  $\nu_{\max}$  1678 (C=O st.), 1569 (C=O st.), 766 (alkene CH b.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 12.36 (1 H, bs, H<sub>5</sub>), 4.23 (2 H, q, *J* 7.0, H<sub>6</sub>), 3.01 (s, H<sub>2</sub>), 2.25 (3 H, s, H<sub>1</sub>), 2.18 (3 H, s, H<sub>3</sub>), 1.33 (3 H, t, *J* 7.0, H<sub>7</sub>);  $\delta_{\text{C}}$  (126 MHz, CDCl<sub>3</sub>) 170.00 (CO), 168.19 (CO), 117.13 (C<sub>4</sub>), 103.89 (C<sub>5</sub>), 59.81 (C<sub>6</sub>), 29.36 (CH<sub>3</sub>), 28.29 (CH<sub>3</sub>), 16.02 (CH<sub>3</sub>), 13.48 (C<sub>7</sub>); *m/z* (ESI) 208.1 (M<sup>+</sup> + Na).

### Section 3.2.3: Synthesis and ATH of *N*-Boc Tetramic Acids.

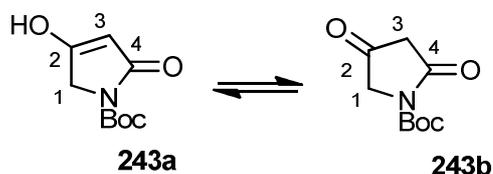
General procedure for the synthesis of tetramic acids.



These tetramic acids were observed as both keto and enol tautomer forms, by <sup>1</sup>H and <sup>13</sup>C NMR depending upon the solvent used. It was found that in d<sub>6</sub>-DMSO, the enolic tautomer was exclusively observed; and in chloroform the keto tautomer was exclusively observed. This was consistent for each tetramic acid synthesised. The reported NMR spectra for each tetramic acid synthesised have been reported in both CDCl<sub>3</sub> and d<sub>6</sub> DMSO. The tetramic acids included in the following experimental section were synthesised according to the following general procedure stated by Størgaard *et al.*<sup>186</sup>

Under nitrogen, a solution of the Boc-protected amino acid (6.25 mmol), Meldrum's acid (9.20 mmol) and DMAP (9.20 mmol) in dry DCM (82 cm<sup>3</sup>) was cooled to 0 °C. EDC.HCl (9.20 mmol) was added and the mixture was stirred at 0 °C for 15 m. The mixture was allowed to warm to room temperature and stirred for 4 h before ethyl acetate (245 cm<sup>3</sup>) was added. This solution was washed with brine (2 x cm<sup>3</sup>), 5 % citric acid (2 x 125 cm<sup>3</sup>), and by brine (125 cm<sup>3</sup>), then dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the intermediate adduct. Ethyl acetate (50 cm<sup>3</sup>) was added and the mixture was stirred at 75 °C for 30 min before the solvent was removed by reduced pressure to give the crude product which was purified as stated.

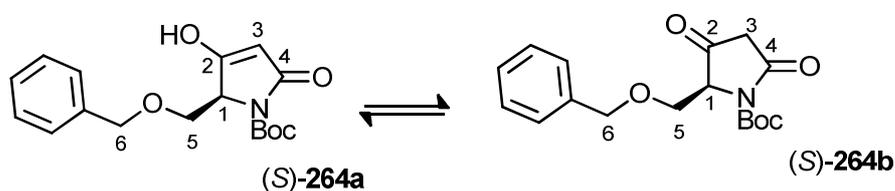
*Tert-butyl 4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate, 243.*



This compound has been reported but not fully characterised.<sup>188</sup> This compound was prepared following the general procedure for the synthesis of tetramic acids using Boc-glycine (1.10 g, 6.28 mmol), Meldrum's acid (1.35 g, 9.37 mmol), DMAP (1.15 g, 9.41 mmol) and EDC.HCl (1.80 g, 9.39 mmol). Following concentration under reduced pressure, the product **243** (1.27 g, 6.38 mmol) was obtained as a solid; Mp 120-124 °C (lit Mp 123-127°C); (Found (ESI): M<sup>+</sup> + Na, 222.0743. C<sub>9</sub>H<sub>13</sub>NNaO<sub>4</sub> requires M, 222.0737);  $\nu_{\max}$  1751 (C=O st.), 1597 (C=C st.) cm<sup>-1</sup>; *enol form, 243a*:  $\delta_{\text{H}}$  (300 MHz, DMSO-d<sub>6</sub>) 12.16 (1H, bs, OH), 4.89 (1H, s, H<sub>3</sub>), 4.14 (2H, s, H<sub>1</sub>), 1.44 (9H, s, <sup>t</sup>Bu);  $\delta_{\text{C}}$  (75 MHz, DMSO-d<sub>6</sub>) 174.38 (CO), 169.20 (CO), 148.88 (C<sub>2</sub>), 94.27 (C<sub>3</sub>), 80.76 (C(CH<sub>3</sub>)<sub>3</sub>), 49.33 (C<sub>1</sub>), 27.72 (C(CH<sub>3</sub>)<sub>3</sub>); *keto form, 243b*:  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 4.25 (2 H, s, H<sub>1</sub>), 3.25 (2 H, s, H<sub>3</sub>), 1.57 (9 H, s, <sup>t</sup>Bu);  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>)

200.59 (C<sub>2</sub>), 167.33 (CO), 148.93 (CO), 84.44 (C(CH<sub>3</sub>)<sub>3</sub>), 57.08 (C<sub>1</sub>), 43.59 (C<sub>3</sub>), 27.95(C(CH<sub>3</sub>)<sub>3</sub>); m/z (ESI) 222.1 (M<sup>+</sup> + Na), 421.0 (M<sub>2</sub><sup>+</sup> + Na). The compound was used in its crude form as prescribed.<sup>186</sup> This data was in agreement with the literature.

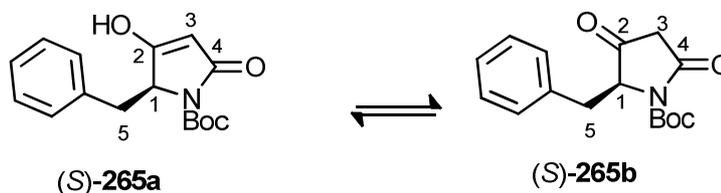
*Tert-butyl (2S)-2-[(benzyloxy)methyl]-3-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate, 264.*



This compound has been reported but not fully characterised.<sup>187</sup> This compound was prepared following the general procedure for the synthesis of tetramic acids using *O*-benzyl Boc-L-serine (1.00 g, 3.39 mmol), Meldrum's acid (0.747 g, 5.18 mmol), DMAP (0.635 g, 5.20 mmol) and EDC.HCl (0.996 g, 5.20 mmol). Following concentration under reduced pressure the product **264** (1.07 g, 3.35 mmol, 99 % yield) was obtained as an oil;  $[\alpha]_D^{25} + 73.25$  (c0.40 in MeOH) (*S*) > 99 % ee (lit.<sup>187</sup>  $[\alpha]_D^{20} + 55$  (c1.00, MeOH) (*S*), > 99 % ee); (Found (ESI): M<sup>+</sup> + Na, 342.1309. C<sub>17</sub>H<sub>21</sub>NNaO<sub>5</sub> requires M, 342.1312);  $\nu_{\max}$  1753 (C=O st.), 1712 (C=O st.), 1618 (C=C st.) cm<sup>-1</sup>; *enol form, 264a*:  $\delta_H$  (400 MHz, DMSO-*d*<sub>6</sub>) 12.29 (1 H, br. s, OH), 7.36 - 7.22 (5 H, m, ArH), 4.90 (1 H, s, H<sub>3</sub>), 4.53 - 4.40 (3 H, m, H<sub>6</sub>, H<sub>1</sub>), 3.96 (1 H, dd, *J* 10.3, 2.9, H<sub>5A</sub>), 3.76 (1 H, dd, *J* 10.3, 1.8, H<sub>5B</sub>), 1.41 (9 H, s, <sup>t</sup>Bu);  $\delta_C$  (101 MHz, DMSO-*d*<sub>6</sub>) 174.95 (CO), 169.29 (CO), 148.79 (C<sub>2</sub>), 138.05 (Ar), 128.24 (Ar), 127.48 (Ar), 127.28 (Ar), 94.74 (C<sub>3</sub>), 80.96 (C(CH<sub>3</sub>)<sub>3</sub>), 72.33 (C<sub>6</sub>), 65.53 (C<sub>5</sub>), 60.31 (C<sub>1</sub>), 27.74 (C(CH<sub>3</sub>)<sub>3</sub>); *keto form, 264b*:  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.37 - 7.18 (5 H, m,

ArH), 4.52 (1 H, d,  $J$  12.4, H<sub>6A</sub>), 4.45 (1 H, d,  $J$  12.4, H<sub>6B</sub>), 4.40 - 4.36 (1 H, m, H<sub>1</sub>), 3.93 (1 H, dd,  $J$  9.8, 2.3, H<sub>5A</sub>), 3.83 (1 H, dd,  $J$  9.8, 2.0, H<sub>5B</sub>), 3.27 (1 H, dd,  $J$  22.1, 1.5, H<sub>3</sub>), 3.10 (1 H, d,  $J$  22.1, H<sub>3</sub>), 1.50 (9 H, s, <sup>t</sup>Bu);  $\delta_C$  (101 MHz, CDCl<sub>3</sub>) 202.92 (C<sub>2</sub>), 167.99 (CO), 148.72 (CO), 136.87 (Ar), 128.43 (Ar), 127.84 (Ar), 127.38 (Ar), 84.02 (C(CH<sub>3</sub>)<sub>3</sub>), 73.28 (C<sub>6</sub>), 67.85 (C<sub>5</sub>), 67.75 (C<sub>1</sub>), 43.66 (C<sub>3</sub>), 27.82 (C(CH<sub>3</sub>)<sub>3</sub>); m/z (ESI) 342.1 (M<sup>+</sup> + Na), 660.9 (M<sub>2</sub><sup>+</sup> + Na).

*Tert-butyl (2S)-2-benzyl-3-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate*,  
(*S*)-**265**.

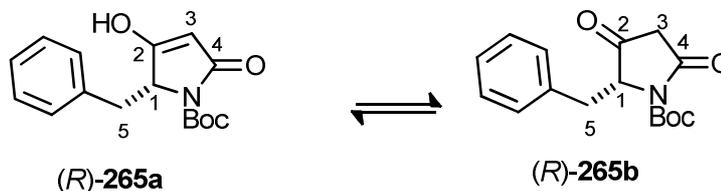


Both enantiomers of tetramic acid **265** were synthesised to enable comparison of their ATH products, to establish whether a DKR may have occurred. This compound has been reported with full characterisation.<sup>188</sup>

This compound was prepared following the general procedure for the synthesis of tetramic acids using Boc-L-phenyl alanine (4.33 g, 16.32 mmol), Meldrum's acid (0.655 g, 4.54 mmol), DMAP (0.350 g, 2.86 mmol) and EDC.HCl (0.549 g, 2.86 mmol). Following concentration under reduced pressure, the product (*S*)-**265** (2.53 g, 8.75 mmol, 54 %) was obtained as a fine white powder, following recrystallisation (ethyl acetate – hexane);  $[\alpha]_D^{25} + 227.3$  ( $c$ 1.00 in MeOH) (*S*) > 99 % ee (lit.<sup>188</sup>  $[\alpha]_D^{25} + 230$  ( $c$ 1.00, MeOH) (*S*), > 99 % ee); *enol form*, (*S*)-**265a**:  $\delta_H$  (400 MHz, DMSO) 12.34 (1 H, s, OH), 7.29 – 7.17 (3 H, m, ArH), 7.01 – 6.98 (2 H, m, ArH), 4.65 (1 H, s, H<sub>3</sub>), 4.62 (1 H, m, H<sub>1</sub>), 3.36 (1 H, dd,  $J$  13.5, 5.5, H<sub>5A</sub>), 3.08 (1 H, dd,  $J$  13.5, 2.5,

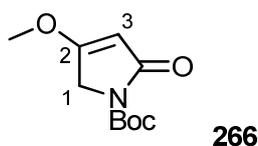
H<sub>5B</sub>), 1.52 (9 H, s, <sup>t</sup>Bu); δ<sub>C</sub> (101 MHz, DMSO-*d*<sub>6</sub>) 175.51 (CO), 168.74 (CO), 149.02 (C<sub>2</sub>), 134.54 (Ar), 129.55 (Ar), 127.94 (Ar), 126.69 (Ar), 94.87 (C<sub>3</sub>), 81.00 (C(CH<sub>3</sub>)<sub>3</sub>), 59.74 (C<sub>1</sub>), 34.21 (C<sub>5</sub>), 27.87 (C(CH<sub>3</sub>)<sub>3</sub>); *keto form*, (*S*)-**265b**: δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.35 - 7.23 (3 H, m, ArH), 7.08 – 6.98 (2 H, m, ArH), 4.70 – 4.63 (1 H, m, H<sub>1</sub>), 3.38 (1 H, dd, *J* 14.0, 5.3, H<sub>5A</sub>), 3.24 (1 H, dd, *J* 14.0, 3.0, H<sub>5B</sub>), 2.87 (1 H, d, *J* 22.4, H<sub>3A</sub>), 2.27 (1 H, dd, *J* 22.4, 1.9, H<sub>3B</sub>), 1.63 (9 H, s, <sup>t</sup>Bu); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 204.22 (C<sub>2</sub>), 167.32 (CO), 149.09 (CO), 133.82 (Ar), 129.79 (Ar), 128.94 (Ar), 127.83 (Ar), 84.33 (C(CH<sub>3</sub>)<sub>3</sub>), 68.12 (C<sub>1</sub>), 43.31 (C<sub>3</sub>), 36.52 (C<sub>5</sub>), 27.98(C(CH<sub>3</sub>)<sub>3</sub>).

*Tert-butyl (2R)-2-benzyl-3-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate*, (*R*)-**265**.



The enantiomer (*R*)-**265** was obtained using the unnatural amino acid, Boc-D-phenyl alanine as starting material. This compound was prepared following the general procedure for the synthesis of tetramic acids using Boc-D-phenyl alanine (1.00 g, 3.77 mmol), Meldrum's acid (0.815, 5.65 mmol), DMAP (0.691 g, 5.66 mmol) and EDC.HCl (1.08 g, 5.65 mmol). Following concentration under reduced pressure, the product (*R*)-**265** (0.15 g, 0.52 mmol, 14 %) was obtained as a fine white powder, following recrystallisation (ethyl acetate – hexane); [α]<sub>D</sub><sup>20</sup> – 253.8 (*c*1.00 in MeOH) (*R*) > 99 % ee (lit.<sup>188</sup> [α]<sub>D</sub><sup>25</sup> - 230 (*c*1.00, MeOH) (*R*) > 99 % ee). Full characterisation was stated in the previous section.

*Tert-butyl 4-methoxy-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate*, **266**.



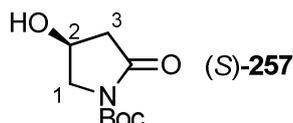
This compound has been reported but not fully characterised.<sup>189</sup> Methyl iodide (18  $\mu\text{L}$ , 41.0 mg, 0.289 mmol) was added to a solution of *tert*-butyl 4-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate **243** (50 mg, 0.251 mmol) and silver carbonate (69 mg, 0.250 mmol) in dry acetonitrile (0.50  $\text{cm}^3$ ) at room temperature and left stirring for 24 h before saturated aqueous sodium hydrocarbonate (5  $\text{cm}^3$ ) was added. Following extraction with DCM (3 x 10  $\text{cm}^3$ ) the organic extracts were dried ( $\text{MgSO}_4$ ), concentrated under reduced pressure and purified by column chromatography (ethyl acetate – hexane 8:2) to give product **266** (18 mg, 0.084 mmol, 34 % yield) as a colourless oil; (Found (ESI):  $\text{M}^+ + \text{Na}$ , 236.0893.  $\text{C}_{10}\text{H}_{15}\text{NNaO}_4$  requires  $\text{M}$ , 236.0893);  $\nu_{\text{max}}$  1775 (C=O st.), 1624 (C=C st.), 1325 (C-O-C st.), 1157 (amide III)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 5.11 (1 H, s,  $\text{H}_3$ ), 4.18 (2 H, s,  $\text{H}_1$ ), 3.84 (3 H, s,  $\text{CH}_3$ ), 1.55 (9 H, s,  $^t\text{Bu}$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 174.60 (CO), 169.20 (CO), 149.34 ( $\text{C}_2$ ), 94.92 ( $\text{C}_3$ ), 82.60 ( $\text{C}(\text{CH}_3)_3$ ), 58.48 ( $\text{CH}_3$ ), 49.16 ( $\text{C}_1$ ), 28.05 ( $\text{C}(\text{CH}_3)_3$ );  $m/z$  (ESI) 236.1 ( $\text{M}^+ + 23$ ), 449.0 ( $\text{M}_2^+ + 23$ ). The C-alkylation product was not obtained from the reaction.

*General procedure for the transfer hydrogenation of tetramic acids.*

The following compounds were prepared using the following general procedure: A solution of the tetramic acid (1 mmol) and Ru(*teth*-TsDPEN) (2 mol %) in dry methanol (0.625 M w/r to the tetramic acid) was stirred at room temperature for 5 min. before FA/TEA (5:2, 0.5  $\text{cm}^3$  / mmol substrate) was added. The solution was left stirring at room temperature for 18 h before saturated aqueous hydrogen

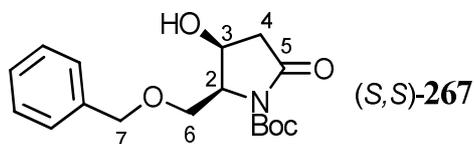
carbonate was added. Following extraction with DCM (3 x 5 cm<sup>3</sup>) the organic extracts were dried (MgSO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (where applicable) to give the product.

*(S)*-Tert-butyl 4-hydroxy-2-oxopyrrolidine-1-carboxylate, **257**.



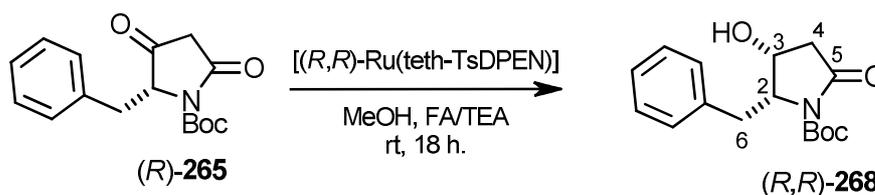
This compound has been reported but not fully characterised.<sup>190</sup> This compound was prepared following the general procedure for the ATH of tetramic acids using *tert*-butyl 4-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate **243** (70 mg, 0.352 mmol) and Ru(*R,R*)*teth*-TsDPEN (4.4 mg, 7.11 x 10<sup>-3</sup> mmol). Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – hexane 9:1), the product (*S*)-**257** (43 mg, 0.214 mmol, 61 % yield) was obtained as a colourless solid;  $[\alpha]_D^{23} + 2.15$  (*c*0.77 in CHCl<sub>3</sub>) 41 % ee (*S*) (lit.<sup>190</sup>  $[\alpha]_D^{25} + 2.1$  (*c*1.86, CHCl<sub>3</sub>) 99.9 % ee (*S*)); (Found (ESI): M<sup>+</sup> + Na, 224.0899. C<sub>9</sub>H<sub>15</sub>NNaO<sub>4</sub> requires M, 224.0893);  $\nu_{\max}$  3454 (OH st.), 1773 (C=O st.) cm<sup>-1</sup>;  $\delta_H$  (500 MHz, DMSO-*d*<sub>6</sub>) 5.27 (1 H, d, *J* 3.6, OH), 4.24 - 4.16 (1 H, m, H<sub>2</sub>), 3.76 (1 H, dd, *J* 11.3, 4.7, H<sub>1A</sub>), 3.51 (1 H, d, *J* 11.3, H<sub>1B</sub>), 2.74 (1 H, dd, *J* 17.2, 5.8, H<sub>3A</sub>), 2.18 (1 H, d, *J* 17.2, H<sub>3B</sub>), 1.45 (9 H, s, <sup>t</sup>Bu);  $\delta_C$  NMR (126 MHz, DMSO-*d*<sub>6</sub>) 173.27 (CO), 149.16 (CO), 81.46 (C(CH<sub>3</sub>)<sub>3</sub>), 61.83 (C<sub>2</sub>), 55.05 (C<sub>1</sub>), 42.41 (C<sub>3</sub>), 27.64 (C(CH<sub>3</sub>)<sub>3</sub>); *m/z* (ESI) 224.1 (M<sup>+</sup> + Na), 425.0 (M<sub>2</sub>Na<sup>+</sup>). The ee was determined by HPLC analysis (Chiralpak OB, 4.6 mm x 250 mm, heptane : IPA 9:1, 1 mL/min, T = 25 °C, *R* (minor) isomer 12.1 min, *S* (major) isomer 15.3 min.) 41 % ee.

*Tert-butyl (2S)-2-[(benzyloxy)methyl]-3-hydroxy-5-oxocyclopentanecarboxylate, (S,S)-267.*



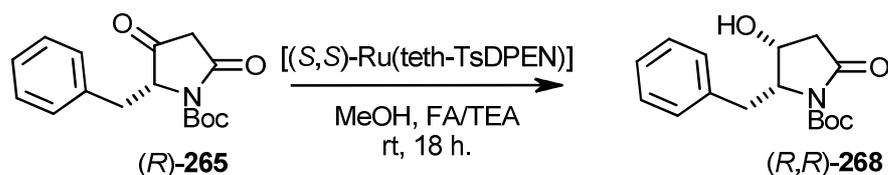
This compound has been reported but not fully characterised.<sup>153</sup> This compound was prepared following the general procedure for the ATH of tetramic acids using *tert*-butyl (2*S*)-2-[(benzyloxy)methyl]-3-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate, (*R*)-**264** (52 mg, 0.163 mmol) and Ru(*R,R*)*teth*-TsDPEN (2.0 mg, 3.22 x 10<sup>-3</sup> mmol). Following concentration under reduced pressure and purification by column chromatography (methanol - ethyl acetate 5:95), the product (*S,S*)-**267** (40 mg, 0.125 mmol, 76 % yield) was obtained as an oil;  $[\alpha]_{\text{D}}^{30} + 27$  (*c*0.10 in MeOH) (lit.<sup>153</sup>  $[\alpha]_{\text{D}}^{20} + 59$  (*c*1.00, MeOH)); Found (ESI):  $\text{M}^+ + \text{Na}$ , 344.1465.  $\text{C}_{17}\text{H}_{23}\text{NNaO}_5$  requires  $\text{M}$ , 344.1468);  $\nu_{\text{max}}$  3459 (OH st.), 1772 (C=O st.), 1713 (C=O st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*<sub>6</sub>) 7.36 - 7.24 (5 H, m, Ar*H*), 5.45 (1 H, d, *J* 4.5, OH), 4.53 (1 H, d, *J* 12.5, H<sub>7A</sub>), 4.54 - 4.44 (2 H, m, H<sub>7B</sub>, H<sub>3</sub>), 4.08 (1 H, dt, *J* 7.5, 3.5, H<sub>2</sub>), 3.77 (1 H, dd, *J* 9.7, 3.5, H<sub>6A</sub>), 3.72 (1 H, dd, *J* 9.7, 3.5, H<sub>6B</sub>), 1.38 (9 H, s, <sup>t</sup>Bu);  $\delta_{\text{C}}$  (75 MHz, DMSO-*d*<sub>6</sub>) 171.53 (CO), 149.25 (CO), 138.42 (Ar), 128.21 (Ar), 127.33 (Ar), 127.08 (Ar), 81.58 (C(CH<sub>3</sub>)<sub>3</sub>), 72.38 (C<sub>7</sub>), 66.09 (C<sub>6</sub>), 63.51 (C<sub>2</sub>), 60.43 (C<sub>3</sub>), 40.63 (C<sub>4</sub>), 27.57 (C(CH<sub>3</sub>)<sub>3</sub>); *m/z* (ESI) 344.1 (M + Na), 665.1 (M<sub>2</sub><sup>+</sup> + Na). The ee of this sample was not determined.

ATH of (*R*)-**265** with (*R,R*)-Ru(*teth*-TsDPEN).



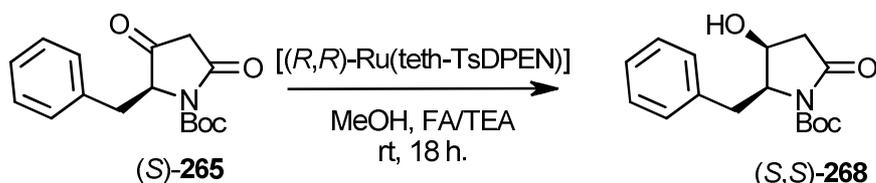
This compound has been reported and fully characterised.<sup>188</sup> This compound was prepared following the general procedure for the ATH of tetramic acids using tert-butyl (2*R*)-2-benzyl-3-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (*R*)-**265** (60 mg, 0.208 mmol) and Ru(*R,R*)*teth*-TsDPEN (2.6 mg, 4.19 × 10<sup>-3</sup> mmol). Following concentration under reduced pressure the product (*R,R*)-**268** (40 mg, 0.137 mmol, 66 % yield) was obtained as colourless solid, following column chromatography (ethyl acetate – hexane 9:1); [ $\alpha$ ]<sub>D</sub><sup>28</sup> – 44.5 (*c*1.00 in MeOH) > 99 % ee (lit.<sup>188</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> – 43.5 (*c*1.00, MeOH));  $\delta_{\text{H}}$  (500 MHz, DMSO-*d*<sub>6</sub>) 7.36 - 7.24 (5 H, m, Ar*H*), 5.50 (1 H, d, *J* 4.5 Hz, OH), 4.32 - 4.22 (2 H, m, H<sub>2,3</sub>), 3.06 (1 H, dd, *J* 13.5, 7.0, H<sub>6A</sub>), 2.93 (1 H, dd, *J* 13.5, 5.0, H<sub>6B</sub>), 2.43 - 2.49 (1 H, m, H<sub>4A</sub>), 2.23 (1 H, dd, *J* 17.0, 8.0, H<sub>4B</sub>), 1.34 (9 H, s, <sup>t</sup>Bu);  $\delta_{\text{C}}$  (126 MHz, DMSO-*d*<sub>6</sub>) 171.36 (CO), 149.26 (CO), 138.34 (Ar), 129.80 (Ar), 128.05 (Ar), 126.02 (Ar), 81.53 (C(CH<sub>3</sub>)<sub>3</sub>), 63.91 (C<sub>2</sub>), 62.43 (C<sub>3</sub>), 33.15 (C<sub>6</sub>), 27.46 (C(CH<sub>3</sub>)<sub>3</sub>). The ee was determined by HPLC analysis (Chiralpak IC, 4.6 mm x 250 mm, heptane : IPA 1:1, 1 mL/min, T = 25 °C, (*S,S*) (minor) isomer 5.18 min, (*R,R*) (major) isomer 5.97 min.) > 99 % ee.

ATH of (*R*)-**265** with (*S,S*)-Ru(*teth*-TsDPEN).



This compound was prepared following the general procedure for the ATH of tetramic acids using tert-butyl (2*R*)-2-benzyl-3-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (*R*)-**265** (100 mg, 0.346 mmol) and Ru(*S,S*)*teth*-TsDPEN (4.4 mg,  $7.09 \times 10^{-3}$  mmol). Following concentration under reduced pressure and column chromatography (ethyl acetate – hexane 9:1), the product (*R,R*)-**268** (70 mg, 0.240 mmol, 69 % yield) was obtained as colourless solid;  $[\alpha]_{\text{D}}^{25} - 59.3$  (*c*0.34 in MeOH) > 99 % ee (lit.<sup>188</sup>  $[\alpha]_{\text{D}}^{25} - 43.5$  (*c*1.00, MeOH)); ee determined by HPLC analysis (Chiralpak IC, 4.6 mm x 250 mm, heptane : IPA 1:1, 1 mL/min, T = 25 °C, (*S,S*) (minor) isomer 5.18 min, (*R,R*) (major) isomer 5.98 min) > 99 % ee.

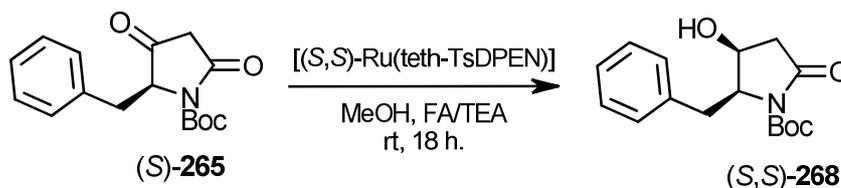
ATH of (*S*)-**265** with (*R,R*)-Ru(*teth*-TsDPEN).



This compound was prepared following the general procedure for the ATH of tetramic acids using tert-butyl (2*S*)-2-benzyl-3-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (*S*)-**265** (50 mg, 0.172 mmol) and Ru(*R,R*)*teth*-TsDPEN (2.1 mg,  $3.39 \times 10^{-3}$  mmol). Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – hexane 9:1), the product (*S,S*)-**268** (25 mg, 0.086 mmol, 50 % yield) was obtained as colourless solid;  $[\alpha]_{\text{D}}^{25} + 56$  (*c*0.10 in MeOH) 99 % ee (lit.<sup>188</sup>  $[\alpha]_{\text{D}}^{25} + 43$  (*c*1.00, MeOH)); ee determined by

HPLC analysis (Chiralpak IC, 4.6 mm x 250 mm, heptane : IPA 1:1, 1 mL/min, T = 25 °C, (*S,S*) (major) isomer 5.57 min, (*R,R*) (minor) isomer 6.56 min.) 99 % ee.

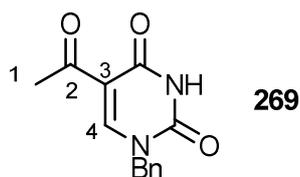
*ATH of (S)-265 with (S,S)-Ru(teth-TsDPEN).*



This compound was prepared following the general procedure for the ATH of tetramic acids using tert-butyl (2*S*)-2-benzyl-3-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (*S*)-**265** (55 mg, 0.19 mmol) and Ru(*S,S*)*teth*-TsDPEN (2.4 mg, 3.87 x 10<sup>-3</sup> mmol). Following concentration under reduced pressure, and purification by column chromatography (ethyl acetate – hexane 9:1), the product (*R,R*)-**268** (49 mg, 0.168 mmol, 89 % yield) was obtained as colourless solid;  $[\alpha]_D^{26} + 43.5$  (*c*1.00 in MeOH) > 99 % ee (lit.<sup>188</sup>  $[\alpha]_D^{25} + 43$  (*c*1.00, MeOH)); Ee determined by HPLC analysis (Chiralpak IC, 4.6 mm x 250 mm, heptane : IPA 1:1, 1 mL/min, T = 25 °C, (*S,S*) (major) isomer 5.17 min, (*R,R*) (minor) isomer 5.95 min.) > 99 % ee.

*Section 3.2.4: ATH of 5-Acetyluracil.*

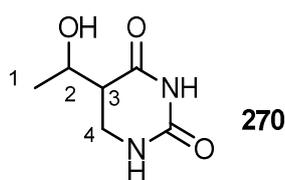
*5-Acetyl-1-benzylpyrimidine-2,4(1*H*,3*H*)-dione, 269*



This compound has been reported but not fully characterised.<sup>191</sup> Under nitrogen, a suspension of 5-acetyluracil (200 mg, 1.298 mmol) and NaH (60 % in oil, 52 mg,

1.300 mmol) in DMF (6.5 cm<sup>3</sup>) was stirred at room temperature for 90 m. A solution of benzyl bromide (200.6 mg, 1.173 mmol) in DMF (6.5 cm<sup>3</sup>) was added dropwise over 30 min and the mixture was stirred at room temperature for 3 d. Following concentration under reduced pressure, purification by column chromatography (ethyl acetate - petroleum ether 1:1) and recrystallisation (methanol), product **269** (123 mg, 0.504 mmol, 39 % yield) was obtained as colourless needles; Mp 196-198 °C; (found (ESI): M<sup>+</sup> + Na, 267.0740. C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>NaO<sub>3</sub> requires M, 267.0740);  $\nu_{\max}$  3486 (NH st.), 3408 (alkene CH st.), 1724 (C=O st.), 1640 (C=O st.), 1599 (C=O st.), 1554 (NH b.), 1510 (C=C st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.63 (1 H, bs, NH), 8.26 (1 H, s, H<sub>4</sub>), 7.44 - 7.30 (5 H, m, ArH), 4.99 (2 H, s, CH<sub>2</sub>), 2.59 (3 H, s, H<sub>1</sub>);  $\delta_{\text{C}}$  (151 MHz, DMSO-*d*<sub>6</sub>) 193.54 (C<sub>2</sub>), 161.73 (CO), 151.49 (C<sub>4</sub>), 150.36 (CO), 136.24 (Ar), 128.70 (Ar), 127.86 (Ar), 127.66 (Ar), 111.82 (C<sub>3</sub>), 51.04 (CH<sub>2</sub>Ph), 30.26 (CH<sub>3</sub>); *m/z* (ESI) 267.1 (M<sup>+</sup> +Na). The crystals obtained were of sufficient quality for X-diffraction, enabling confirmation of the structure. Full details are shown in Appendix II.

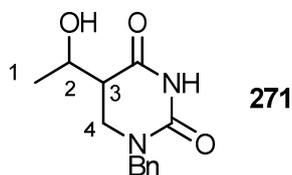
*5-(1-hydroxyethyl) dihydropyrimidine-2,4(1H,3H)-dione, 270.*



This compound was prepared following the general procedure for ketone transfer hydrogenation, using 5-acetyluracil (100 mg, 0.641 mmol) and Ru(*R,R*)*teth*-TsDPEN (8.1 mg, 1.31 x 10<sup>-2</sup> mmol) in neat FA/TEA (700  $\mu$ L, 2M). Following a reaction time of 17 h, DCM (2 cm<sup>3</sup>) was added and the resulting suspension was cooled and filtered. The resulting powder was dried to give an inseparable mixture of the diastereomers (D1/D2 = 3.1:1, as determined by <sup>1</sup>H NMR) (D1)-**270a** and (D2)-**270b** (80 mg, 0.506 mmol, 79 % yield) as a powder; (Found (ESI): M<sup>+</sup> + Na,

181.0588. C<sub>6</sub>H<sub>10</sub>N<sub>2</sub>NaO<sub>3</sub> requires M, 181.0584); Mp 226-230 °C;  $\nu_{\max}$  3400 (OH st.), 3219 (NH st.), 1708 br. (C=O st.), 1674 (NH b.), 1225 (C-O st.) cm<sup>-1</sup>; (D1)-**270a**:  $\delta_{\text{H}}$  (600 MHz, DMSO-*d*<sub>6</sub>) 9.90 (1 H, bs, NH), 7.42 (1 H, bs, NH), 4.82 (1 H, d, *J* 6.0, OH), 4.03 (1 H, sxt, *J* 6.0, H<sub>2</sub>), 3.32 - 3.15 (2 H, m, H<sub>4</sub>), 2.31 (1 H, q, 6.0, H<sub>3</sub>), 1.13 (3 H, d, *J* 6.0, H<sub>1</sub>);  $\delta_{\text{C}}$  (151 MHz, DMSO-*d*<sub>6</sub>) 171.78 (CO), 153.53 (CO), 62.71 (C<sub>2</sub>), 46.80 (C<sub>4</sub>), 36.02 (C<sub>3</sub>), 21.75 (C<sub>1</sub>); (D2)-**270b**:  $\delta_{\text{H}}$  (600 MHz, DMSO-*d*<sub>6</sub>) 9.93 (1 H, bs, NH), 7.43 (1 H, bs, NH), 4.84 - 4.83 (1 H, m, OH), 4.10 - 4.09 (1 H, m, H<sub>2</sub>), 3.32 - 3.15 (2 H, m, H<sub>4</sub>), 2.57 (1 H, dt, *J* 7.2, 6.0, H<sub>3</sub>), 1.06 (3 H, d, *J* 6.4, H<sub>1</sub>);  $\delta_{\text{C}}$  (151 MHz, DMSO-*d*<sub>6</sub>) 171.81 (CO), 153.50 (CO), 64.77 (C<sub>2</sub>), 45.80 (C<sub>4</sub>), 36.08 (C<sub>3</sub>), 19.16 (C<sub>1</sub>); *m/z* (ESI) 159.0 (M<sup>+</sup> - H). No further purification or separation of the diastereomers was carried out.

*1-Benzyl-5-(1-hydroxyethyl)dihydropyrimidine-2,4(1H,3H)-dione*, **271**.



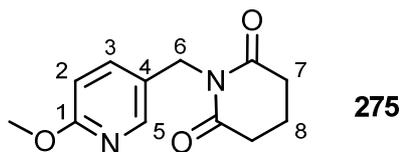
This compound was prepared following the general procedure (C) for ketone transfer hydrogenation, using 5-acetyl-1-benzylpyrimidine-2,4(1H,3H)-dione **269** (30 mg, 0.123 mmol) and Ru(*R,R*)-*teth*-TsDPEN (0.6 mg, 9.67 x 10<sup>-4</sup> mmol) following a reaction time of 20 h. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – petroleum ether 9:1), an inseparable mixture of diastereomers **271a** and **271b** (D1/D2 = 3.48:1, as determined by <sup>1</sup>H NMR) (23 mg, 0.093 mmol, 75 % yield) was obtained as a colourless oil; (found (ESI): M<sup>+</sup> + Na, 271.1049. C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>NaO<sub>3</sub> requires M, 271.1053);  $\nu_{\max}$  3400 (OH st.), 3199 (NH st.), 1670 br. (C=O st.), 1491 cm<sup>-1</sup>; *m/z* (ESI) 270.8 (M<sup>+</sup> +23);

**271a:**  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 8.22 (1 H, bs, NH), 7.41 - 7.25 (5 H, m, ArH), 4.67 (1 H, d,  $J$  14.8,  $\text{CH}_2$ ), 4.58 (1 H, d,  $J$  14.8,  $\text{CH}_2$ ), 4.33 (1 H, sxt,  $J$  6.3,  $\text{H}_2$ ), 3.48 (1 H, dd,  $J$  12.6, 10.8,  $\text{H}_{4\text{A}}$ ), 3.28 (1 H, dd,  $J$  12.6, 6.1,  $\text{H}_{4\text{B}}$ ), 2.66 - 2.59 (1 H, m,  $\text{H}_3$ ), 1.20 (3 H, d,  $J$  6.3,  $\text{H}_1$ ); A resonance attributable to OH was not observed;  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 171.62 (CO), 152.69 (CO), 136.01 (Ar), 128.81 (Ar), 127.90 (Ar), 128.02 (Ar), 63.95 ( $\text{C}_2$ ), 50.64 ( $\text{C}_4$ ), 46.67 ( $\text{CH}_2\text{Ph}$ ), 41.66 ( $\text{C}_3$ ), 19.92 ( $\text{C}_1$ ). Enantiomeric separation was achieved by HPLC analysis (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min, T = 30 °C, minor isomer 72.6 min, major isomer 41.8 min.) 69 % ee; **271b:**  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 8.26 (1 H, bs, NH), 7.40 - 7.27 (5 H, m, ArH), 4.92 (1 H, d,  $J$  1.8, OH), 4.68 (1 H, d,  $J$  14.8,  $\text{CH}_2$ ), 4.57 (1 H, d,  $J$  14.8,  $\text{CH}_2$ ), 4.01 (1 H, quind,  $J$  6.6, 1.8,  $\text{H}_2$ ), 3.25 - 3.15 (2 H, m,  $\text{H}_4$ ), 2.66 - 2.59 (1 H, m,  $\text{H}_3$ ), 1.14 (3 H, d,  $J$  6.6,  $\text{H}_1$ ); A resonance attributable to OH was not observed;  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 172.74 (CO), 152.59 (CO), 135.76 (Ar), 128.85 (Ar), 128.06 (Ar), 127.93 (Ar), 66.21 ( $\text{C}_2$ ), 50.52 ( $\text{CH}_2\text{Ph}$ ), 46.41 ( $\text{C}_4$ ), 43.37 ( $\text{C}_3$ ), 19.99 ( $\text{C}_1$ ); Enantiomeric separation was achieved by HPLC analysis (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min, T = 30 °C, minor isomer 46.0 min, major isomer 51.9 min.) 19 % ee.

### Section 3.3: Procedures from Section 2.3.

#### Section 3.3.1: Synthesis and AH of Pyridone 2.

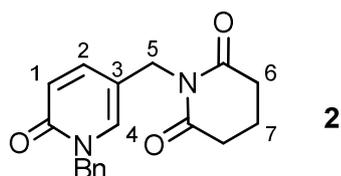
##### 1-((6-Methoxypyridin-3-yl)methyl)piperidine-2,6-dione, **275**.



Under nitrogen, a solution of triphenylphosphine (6.73 g, 25.66 mmol), (6-methoxypyridin-3-yl)methanol **276** (3.50 g, 25.17 mmol) and glutarimide (2.90 g,

25.64 mmol) in THF (75 cm<sup>3</sup>) was stirred at 0 °C for 5 min. A solution of diisopropyl azodicarboxylate (4.99 cm<sup>3</sup>, 5.19 g, 25.66 mmol) in THF (50 cm<sup>3</sup>) was added dropwise over 1 h at 0 °C and the solution was allowed to warm to room temperature and stirred for 18 h. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – hexane 1:1), product **275** (3.03 g, 12.94 mmol, 51 % yield) was obtained as a colourless oil; (found (ESI): M<sup>+</sup> + H, 235.10750. C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub> requires M, 235.10772);  $\nu_{\max}$  3010 (aryl CH st.), 1716 (CO), 1607 (aryl C=C st.), 1491 (aryl C=C st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.22 (1 H, d, *J* 2.5, H<sub>5</sub>), 7.63 (1 H, dd, *J* 8.5, 2.5, H<sub>3</sub>), 6.67 (1 H, d, *J* 8.5, H<sub>2</sub>), 4.87 (2 H, s, H<sub>6</sub>), 3.90 (3 H, s, CH<sub>3</sub>), 2.65 (4 H, t, *J* 6.7, H<sub>7</sub>), 1.92 (2 H, quin, *J* 6.7, H<sub>8</sub>);  $\delta_{\text{C}}$  (101 MHz, DMSO) 172.68 (CO), 162.69 (C<sub>1</sub>), 146.22 (C<sub>5</sub>), 138.98 (C<sub>3</sub>), 126.22 (C<sub>4</sub>), 109.99 (C<sub>2</sub>), 52.99 (CH<sub>3</sub>), 40.18 (C<sub>6</sub>), 32.02 (C<sub>7</sub>), 16.43 (C<sub>8</sub>); *m/z* (ESI) 234.97 (M<sup>+</sup> +1). The synthesis of the starting material, **276** is shown in the next section.

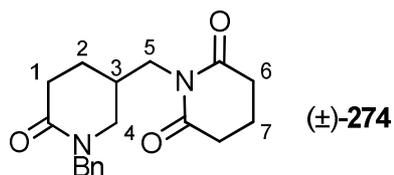
*1-[(1-Benzyl-6-oxo-1,6-dihydropyridin-3-yl)methyl]piperidine-2,6-dione, 2.*



Under nitrogen, a mixture of benzyl bromide (1.02 cm<sup>3</sup>, 1.47 g, 8.59 mmol), 1-((6-methoxypyridin-3-yl)methyl)piperidine-2,6-dione, **275** (1.82 g, 7.77 mmol) and potassium carbonate (2.15 g, 15.56 mmol) in dry acetonitrile (31 cm<sup>3</sup>) was stirred at 80 °C for 24 h before the solution was filtered. The resulting filtrate was concentrated under reduced pressure and recrystallised (ethanol), to give product **2** (1.42 g, 4.58 mmol, 59 % yield) as a white powder; Mp 154-156 °C; (found (ESI): M<sup>+</sup> + Na, 333.1205. C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>3</sub> requires M, 333.1210);  $\nu_{\max}$  1722 (C=O st.), 1666 (C=O st.), 1601 (pyridone C=C st.), 1537 (pyridone C=C st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400

MHz, CDCl<sub>3</sub>) 7.49 - 7.41 (2 H, m, H<sub>2</sub>, H<sub>4</sub>), 7.37 - 7.25 (5 H, m, ArH), 6.52 (1 H, d, *J* 9.3, H<sub>1</sub>), 5.10 (2 H, s, CH<sub>2</sub>), 4.62 (2 H, s, CH<sub>2</sub>), 2.64 (4 H, t, *J* 6.4, H<sub>6</sub>), 1.93 (2 H, quin, *J* 6.4, H<sub>7</sub>); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 172.36 (CO), 161.90 (CO), 141.49 (C<sub>4</sub>), 138.61 (C<sub>2</sub>), 136.23 (Ar), 128.69 (Ar), 128.05 (Ar), 127.85 (Ar), 120.60 (C<sub>1</sub>), 115.36 (C<sub>3</sub>), 52.03 (CH<sub>2</sub>Ph), 39.20 (C<sub>5</sub>), 32.60 (C<sub>6</sub>), 16.85 (C<sub>7</sub>); *m/z* (ESI) 333.1 (M<sup>+</sup> +23). Further recrystallisation (EtOH) provided crystals of sufficient quality for X-diffraction, enabling confirmation of the structure. Full details are shown in Appendix II.

*1-[(1-Benzyl-6-oxopiperidin-3-yl)methyl]piperidine-2,6-dione, (±)-274.*



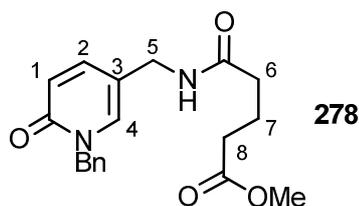
This compound was prepared following the general procedure for alkene hydrogenation, using 1-[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)-methyl]-piperidine-2,6-dione, **2** (1.14 g, 3.68 mmol) and platinum oxide (42 mg, 0.185 mmol) following a reaction time of 20 h, at 30 °C. Following concentration under reduced pressure, product (±)-**274** (1.10 g, 3.50 mmol, 95 % yield) was obtained as colourless oil, following column chromatography (methanol - ethyl acetate 2:8); (found (ESI): M<sup>+</sup> + Na, 337.1522. C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>NaO<sub>3</sub> requires M, 337.1523); ν<sub>max</sub> 1668 (C=O st.), 1634 (C=O st.) cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.36 - 7.19 (5 H, m, ArH), 4.73 (1 H, d, *J* 14.6, CH<sub>2</sub>), 4.42 (1 H, d, *J* 14.6, CH<sub>2</sub>), 3.77 (1 H, dd, *J* 12.4, 7.3, H<sub>5A</sub>), 3.68 (1 H, dd, *J* 12.4, 7.5, H<sub>5B</sub>) 3.11 (1 H, ddd, *J* 11.0, 5.0, 1.3, H<sub>4A</sub>), 2.98 (1 H, t, *J* 11.0, H<sub>4B</sub>), 2.63 (4 H, t, *J* 6.6, H<sub>6</sub>), 2.58 (1 H, ddd, *J* 18.0, 5.8, 3, H<sub>1A</sub>), 2.39 (1 H, ddd, *J* 18.0, 11.5, 6.2, H<sub>1B</sub>), 2.20 - 2.07 (1 H, m, H<sub>3</sub>), 1.89 (2 H, quin, *J* 6.6, H<sub>7</sub>), 1.53 (2 H, dtd, *J* 13.1, 11.5, 6.2, H<sub>2</sub>); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 172.33 (CO), 169.03 (CO),

136.50 (Ar), 128.13 (Ar), 127.53 (Ar), 126.90 (Ar), 50.08 (CH<sub>2</sub>Ph), 49.72 (C<sub>5</sub>), 41.05 (C<sub>4</sub>), 32.84 (C<sub>3</sub>), 32.26 (C<sub>8</sub>), 30.65 (C<sub>1</sub>), 24.77 (C<sub>2</sub>), 16.57 (C<sub>7</sub>); *m/z* (ESI) 337.1 (M<sup>+</sup> +Na). Enantiomeric separation was achieved by HPLC analysis (Chiralpak IB, 4.6 mm x 250 mm, hexane : IPA 80 : 20, 1.0 mL/min, T = 30 °C, 38.1 min, 41.0 min). This sample was used as a racemic standard in chiral HPLC to confirm the retention times of the enantiomers of the AH products prepared in the next section.

*AH screen of 1-[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)-methyl]piperidine-2,6-dione, 2.*

The AH catalyst screen of 1-[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)-methyl]piperidine-2,6-dione **2** was carried out using the general procedure for alkene hydrogenation. Conversions were determined by <sup>1</sup>H NMR. Ees were determined by HPLC analysis using compound (±)-**274** as a racemic standard.

*Methyl 5-oxo-5-[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)methyl]amino}-pentanoate, 278.*

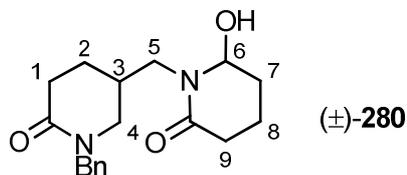


This compound was prepared following the general procedure for alkene hydrogenation, using 1-[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)-methyl]piperidine-2,6-dione **2** (185 mg, 0.587 mmol) and palladium on carbon (10 % Pd w/w, 32 mg, 3.01 x 10<sup>-2</sup> mmol) following a reaction time of 18 h, at room temperature. Following concentration under reduced pressure and purification by column chromatography (methanol - ethyl acetate 5:95), product **278** (115 mg, 0.336

mmol, 57 % yield) was obtained as colourless oil; (found (ESI):  $M^+ + Na$ , 365.1474.  $C_{19}H_{22}N_2NaO_4$  requires  $M$ , 365.1472);  $\nu_{max}$  3281(NH st.), 3062 (aryl CH st.) 1731 (CO), 1661 (CO), 1593 (CO), 1536 (pyridone C=C st.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.38 - 7.21 (7 H, m, ArH, H<sub>2</sub>, H<sub>4</sub>), 6.59 (1 H, d,  $J$  9.3, H<sub>1</sub>), 5.77 (1 H, bs, NH), 5.11 (2 H, s,  $CH_2$ ), 4.12 (2 H, d,  $J$  6.0, H<sub>5</sub>), 3.66 (3 H, s,  $CH_3$ ), 2.35 (2 H, t,  $J$  7.1, H<sub>8</sub>), 2.24 (2 H, t,  $J$  7.1, H<sub>6</sub>), 1.95 (5 H, quin,  $J$  7.1, H<sub>7</sub>);  $\delta_C$  (151 MHz,  $CDCl_3$ ) 173.55 (CO), 172.26 (CO), 162.04 (CO), 140.22 (C<sub>4</sub>), 136.14 (Ar), 135.92 (C<sub>2</sub>), 128.85 (Ar), 128.09 (Ar), 127.95 (Ar), 121.16 (C<sub>1</sub>), 116.83 (C<sub>3</sub>), 51.98 ( $CH_2Ph$ ), 51.55 ( $CH_3$ ), 39.95 (C<sub>5</sub>), 35.14 (C<sub>8</sub>), 32.97 (C<sub>6</sub>), 20.73 (C<sub>7</sub>);  $m/z$  (ESI) 365.1 ( $M^+ + Na$ ).

### Section 3.3.2: Completion of the Synthesis.

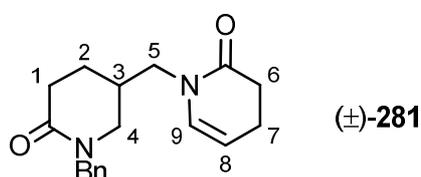
*1-Benzyl-5-[(2-hydroxy-6-oxopiperidin-1-yl)methyl]piperidin-2-one*, ( $\pm$ )-**280**.



Under nitrogen, a solution of cerium chloride heptahydrate (574 mg, 1.54 mmol) and 1-[(1-benzyl-6-oxopiperidin-3-yl)methyl]piperidine-2,6-dione, ( $\pm$ )-**274** (484 mg, 1.54 mmol) in dry methanol (3.85  $cm^3$ ) was stirred at 0 °C for 5 min. Sodium borohydride (118 mg, 3.12 mmol) was added and the mixture was stirred at 0 °C for 4 h before saturated aqueous sodium hydrocarbonate (5  $cm^3$ ) was added. Following extraction with DCM (3 x 10  $cm^3$ ), the organic extracts were dried ( $MgSO_4$ ), concentrated under reduced pressure and purified by column chromatography (methanol - ethyl acetate 5:95), to give an impure sample containing what was characterised to be the inseparable diastereomers ( $\pm$ )-**280** (343 mg, 1.08 mmol, 70 % yield). Data obtained for the mixture of diastereomers is as follows: (found (ESI):  $M^+ + Na$ , 339.1683.  $C_{18}H_{24}N_2NaO_3$  requires  $M$ , 339.1679);  $\nu_{max}$  3303 (OH st.), 1613

(C=O st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.38 - 7.15 (5 H, m, ArH), 4.79 - 4.33 (3 H, m,  $\text{CH}_2$ ,  $\text{H}_6$ ), 3.65 - 3.43 (1 H, m,  $\text{H}_{5\text{A}}$ ), 3.29 - 3.04 (2 H, m,  $\text{H}_{5\text{B}}$ ,  $\text{H}_{4\text{A}}$ ), 3.03 - 2.87 (1 H, m,  $\text{H}_{4\text{B}}$ ), 2.61 - 2.10 (5 H, m,  $\text{H}_1$ ,  $\text{H}_9$ ,  $\text{H}_3$ ), 2.10 - 1.42 (6 H, m,  $\text{H}_2$ ,  $\text{H}_8$ ,  $\text{H}_7$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 171.02 (CO), 169.84 (CO), 137.18 (Ar), 128.58 (Ar), 128.41 (Ar), 128.36 (Ar), 79.92 ( $\text{C}_6$ ), 50.49 ( $\text{CH}_2\text{Ph}$ ), 46.64 ( $\text{C}_5$ ), 41.44 ( $\text{C}_4$ ), 32.79 ( $\text{C}_1$ ), 31.55 ( $\text{C}_9$ ), 30.84 ( $\text{C}_3$ ), 24.99 ( $\text{C}_8$ ), 24.75 ( $\text{C}_7$ ), 15.47 ( $\text{C}_2$ );  $m/z$  (ESI) 339.1 ( $\text{M}^+ + \text{Na}$ ).

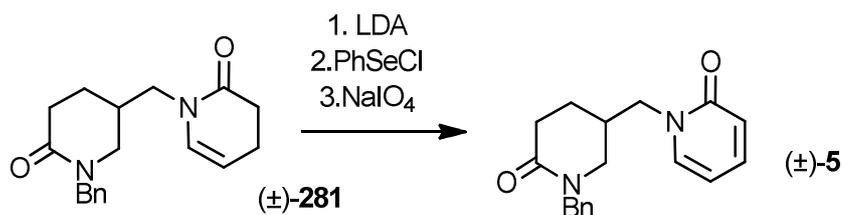
*1-[(1-Benzyl-6-oxopiperidin-3-yl)methyl]-3,4-dihydropyridin-2(1H)-one*, ( $\pm$ )-**281**.



Under nitrogen, a solution of 1-benzyl-5-[(2-hydroxy-6-oxopiperidin-1-yl)methyl]piperidin-2-one, ( $\pm$ )-**280** (240 mg, 0.759 mmol) in dry DCM ( $19 \text{ cm}^3$ ) was stirred at  $-10 \text{ }^\circ\text{C}$  for 10 min. Titanium chloride ( $92 \text{ }\mu\text{L}$ , 159 mg, 0.839 mmol) was added and the solution was stirred at  $-10 \text{ }^\circ\text{C}$  for 10 min before DIPEA ( $147 \text{ }\mu\text{L}$ , 109 mg, 0.844 mmol) was added. The solution was allowed to warm to  $0 \text{ }^\circ\text{C}$  and left stirring for 4 h before saturated aqueous ammonium chloride ( $5 \text{ cm}^3$ ) was added. Following extraction with DCM ( $3 \times 10 \text{ cm}^3$ ), the organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to give product ( $\pm$ )-**281** (203 mg, 0.681 mmol, 90 % yield) as an oil; (found (ESI):  $\text{M}^+ + \text{H}$ , 299.1743.  $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_2$  requires M, 299.1754);  $\nu_{\text{max}}$  1616 br. (C=O st., C=C st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (600 MHz,  $\text{CDCl}_3$ ) 7.21 - 7.36 (5 H, m, ArH), 5.85 (1 H, d,  $J$  7.7,  $\text{H}_9$ ), 5.10 (1 H, dt,  $J$  7.7, 4.1,  $\text{H}_8$ ), 4.67 (1 H, d,  $J$  14.7,  $\text{CH}_2$ ), 4.49 (1 H, d,  $J$  14.7,  $\text{CH}_2$ ), 3.37 (2 H, m,  $\text{H}_4$ ), 3.18 (1 H, ddd,  $J$  12.0, 4.9, 1.5,  $\text{H}_{5\text{A}}$ ), 2.95 (1 H, dd,  $J$  12.0, 9.8,  $\text{H}_{5\text{B}}$ ), 2.58 (1 H, ddd,  $J$  18.0, 6.0, 3.8,  $\text{H}_{1\text{A}}$ ), 2.47 (2 H, t,  $J$  7.9,  $\text{H}_6$ ), 2.43 (1 H, ddd,  $J$  18.0, 11.3, 6.8,  $\text{H}_{1\text{B}}$ ), 2.23 - 2.28 (2 H, m,  $\text{H}_7$ ), 2.13 - 2.21 (1 H, m,  $\text{H}_3$ ), 1.85 - 1.90 (1 H, m,  $\text{H}_{2\text{A}}$ ), 1.50 - 1.58 (1 H, m,  $\text{H}_{2\text{B}}$ );

$\delta_C$  (151 MHz,  $CDCl_3$ ) 169.58 (CO), 169.39 (CO), 136.96 (Ar), 130.04 ( $C_9$ ), 128.60 (Ar), 128.13 (Ar), 127.41 (Ar), 106.45 ( $C_8$ ), 50.18 ( $C_5$ ), 50.10 ( $CH_2Ph$ ), 48.74 ( $C_4$ ), 31.26 ( $C_1$ ), 31.02 ( $C_6$ ), 30.91 ( $C_7$ ), 25.06 ( $C_2$ ), 20.16 ( $C_7$ );  $m/z$  (ESI) 299.2 ( $M^+ + 1$ ).

The selenide oxidation – elimination of enamide ( $\pm$ )-**281**, yielding ( $\pm$ )-1-((1-benzyl-6-oxopiperidin-3-yl)methyl)pyridin-2(1H)-one, ( $\pm$ )-**5**.

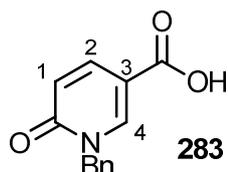


This compound has been reported and fully characterised.<sup>68</sup> Under nitrogen, LDA (1.5M solution in THF, 70  $\mu$ L, 0.105 mmol) was added to a solution of 1-[(1-benzyl-6-oxopiperidin-3-yl)methyl]-3,4-dihydropyridin-2(1H)-one, ( $\pm$ )-**281** (15 mg, 0.050 mmol) in freshly distilled THF (0.7  $cm^3$ ) and the solution was stirred at -78  $^\circ C$  for 1 h. A solution of phenyl selenyl chloride (9.6 mg, 0.050 mmol) in freshly distilled THF (1.0  $cm^3$ ) was added and the solution was stirred at -78  $^\circ C$  for 45 min before saturated ammonium chloride was added and the solution was allowed to warm to room temperature. Following extraction with ethyl acetate (3 x 5  $cm^3$ ), the organic extracts were dried ( $MgSO_4$ ) and concentrated under reduced pressure to give the intermediate product (25 mg). A solution of the intermediate product (25 mg) in THF : methanol :  $H_2O$  18:6:2 (1  $cm^3$ ) and  $NaIO_4$  (37 mg, 0.173 mmol) was stirred at room temperature for 24 h before water was added and the solution was concentrated under reduced pressure. Following extraction with ethyl acetate (3 x 5  $cm^3$ ), the organic extracts were dried ( $MgSO_4$ ) and concentrated under reduced pressure to give a sample containing the product, ( $\pm$ )-**5** (10 mg) as a colourless oil, as determined by  $^1H$  NMR. At this small scale, further purification was not possible.

This data was in accordance the characterisation data for **5** which was given in Section 1.

*Section 3.3.3: Synthesis and AH of 5-Substituted Pyridones.*

*1-Benzyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid, **283**.*

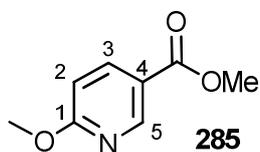


This compound has been reported but not fully characterised.<sup>192</sup> Under nitrogen, a solution of 6-hydroxynicotinic acid (2.10 g, 15.07 mmol) and potassium hydroxide (2.96 g, 52.74 mmol) in water (3.59 cm<sup>3</sup>) and methanol (17.94 cm<sup>3</sup>) was stirred at 70 °C for 5 min before benzyl bromide (3.58 cm<sup>3</sup>, 5.15 g, 30.13 mmol) was added. The mixture was stirred at 70 °C for 90 min before the reaction was cooled to room temperature and concentrated under reduced pressure. The resulting residue was diluted with water (10 cm<sup>3</sup>) and washed diethyl ether (2 x 10 cm<sup>3</sup>). The aqueous phase was acidified to pH 1 with HCl (2M) and the resulting white precipitate was washed with water and dried under reduced pressure to give the crude product (2.68 g) as a white solid. Purification by silica gel chromatography was not possible.

A portion of the crude product (0.290 g) was purified by preparative reverse phase HPLC (Phenomenex Gemini-NX axia Prep C<sub>18</sub> OBD column, 5µ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Following concentration under reduced pressure, product, **283** (0.210 g, 0.916 mmol) was obtained as a white powder; Mp 210-214 °C; (found (ESI): M<sup>+</sup> + H, 230.0807. C<sub>13</sub>H<sub>12</sub>NO<sub>3</sub> requires M, 230.0812); ν<sub>max</sub> 3325 (OH st.), 1708 (C=O st.), 1638 (C=O st.), 1568 (pyridone C=C st.), 1539

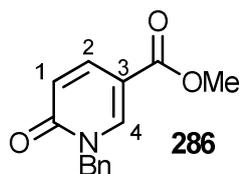
(pyridone C=C st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz, DMSO- $d_6$ ) 12.86 (1 H, bs, OH), 8.56 (1 H, d,  $J$  2.5, H<sub>4</sub>), 7.80 (1 H, dd,  $J$  9.5, 2.5, H<sub>2</sub>), 7.39 - 7.24 (5 H, m, ArH), 6.46 (1 H, d,  $J$  9.5, H<sub>1</sub>), 5.20 (2 H, s, CH<sub>2</sub>);  $\delta_{\text{C}}$  (101 MHz, DMSO) 165.19 (CO), 161.46 (CO), 149.34 (C<sub>4</sub>), 138.88 (C<sub>2</sub>), 136.80 (Ar), 128.61 (Ar), 127.74 (Ar), 127.67 (Ar), 118.91 (C<sub>3</sub>), 109.57 (C<sub>1</sub>), 51.52 (CH<sub>2</sub>Ph);  $m/z$  (ESI) 229.9 ( $\text{M}^+ - 1$ ).

*Methyl 6-methoxynicotinate, 285.*



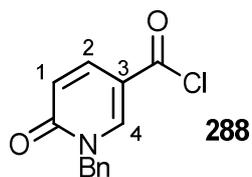
This compound has been reported but not fully characterised.<sup>193</sup> A suspension of 6-methoxynicotinic acid **284** (2.90 g, 18.94 mmol) in methanol (28.0 cm<sup>3</sup>) and sulfuric acid (16 M, 1.1 cm<sup>3</sup>, 20.64 mmol) was stirred at 80 °C for 16 h before the mixture was allowed to cool. The mixture was neutralised by careful addition of sodium bicarbonate. Following concentration under reduced pressure, water (20 cm<sup>3</sup>) and aqueous sodium bicarbonate (10 cm<sup>3</sup>) were added. Following extraction with DCM (3 x 50 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the product **285** (2.480 g, 14.84 mmol, 72 %) as a white powder; (Found: C, 57.11; H, 5.36; N, 8.30. C<sub>8</sub>H<sub>9</sub>NO<sub>3</sub> requires C, 57.48; H, 5.43; N, 8.38 %);  $\nu_{\text{max}}$  1720 (CO), 1603 (C=C st.), 1568 (C=C st.), 1604 (C=C st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.83 (1H, s, H<sub>5</sub>), 8.14 (1H, d,  $J$  8.7, H<sub>3</sub>), 6.76 (1H, d,  $J$  8.7, H<sub>2</sub>), 4.00 (3H, s, CH<sub>3</sub>), 3.91 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>) 167.00 (CO), 150.18 (C<sub>1</sub>), 143.35 (C<sub>5</sub>), 139.90 (C<sub>3</sub>), 119.79 (C<sub>4</sub>), 110.75 (C<sub>2</sub>), 54.09 (CH<sub>3</sub>), 52.17 (CH<sub>3</sub>);  $m/z$  (ESI) 168.1 ( $\text{M}^+ + 1$ ).

*Methyl 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylate, 286.*



This compound has been reported and fully characterised.<sup>194</sup> A mixture of benzyl bromide (4.40 cm<sup>3</sup>, 6.34 g, 37.05 mmol), methyl 6-methoxynicotinate **285** (3.00 g, 17.96 mmol) and potassium carbonate (4.96 g, 35.89 mmol) in dry acetonitrile (72 cm<sup>3</sup>) was stirred at 80 °C for 48 h. The mixture was filtered and concentrated under reduced pressure and purified by column chromatography (ethyl acetate – hexane 1:1) to give product **286** (1.25 g, 5.14 mmol, 29 % yield) as an oil;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 8.18 (1 H, d,  $J$  2.4, H<sub>4</sub>), 7.83 (1 H, dd,  $J$  9.6, 2.4, H<sub>2</sub>), 7.40 - 7.29 (5 H, m, ArH), 6.58 (1 H, d,  $J$  9.6, H<sub>1</sub>), 5.17 (2 H, s, CH<sub>2</sub>), 3.83 (3 H, s, CH<sub>3</sub>);  $^{13}\text{C}$  NMR (101 MHz, CDCl<sub>3</sub>) 164.57 (CO), 162.32 (CO), 142.59 (C<sub>4</sub>), 138.43 (C<sub>2</sub>), 135.46 (Ar), 128.96 (Ar), 128.30 (Ar), 128.11 (Ar), 119.93 (C<sub>3</sub>), 109.87 (C<sub>1</sub>), 52.66 (CH<sub>2</sub>Ph), 51.99 (CH<sub>3</sub>). This data was in agreement with the literature.

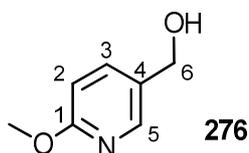
*1-benzyl-6-oxo-1,6-dihydropyridine-3-carbonyl chloride, 288.*



This compound has been reported but not fully characterised.<sup>161</sup> Under nitrogen, potassium carbonate (193 mg, 1.40 mmol) and thionyl chloride (111  $\mu\text{L}$ , 181 mg, 1.52 mmol) were added to a solution of 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid **283** (100 mg, 0.436 mmol) in toluene (4.36 cm<sup>3</sup>) and the mixture was heated to 110 °C for 2.5 h. The mixture was allowed to cool before the mixture was filtered and concentrated under reduced pressure to yield the crude product **288**

(49 mg, 0.198 mmol, 45 %) as a colourless oil; (found (ESI):  $M^+ + H$ , 248.0471.  $C_{13}H_{11}^{35}ClNO_2$  requires  $M$ , 248.0473);  $\nu_{\max}$  1741 (CO), 1656 (CO), 1617 (C=C st.), 1542 (C=C st.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 8.30 (1 H, d,  $J$  2.8,  $H_4$ ), 7.72 (1 H, dd,  $J$  9.5, 2.8,  $H_2$ ), 7.19 - 7.32 (5 H, m,  $ArH$ ), 6.49 (1 H, d,  $J$  9.5,  $H_1$ ), 5.09 (2 H, s,  $CH_2$ );  $\delta_C$  (101 MHz,  $CDCl_3$ ) 163.64 (CO), 161.90 (CO), 146.86 ( $C_4$ ), 138.15 ( $C_2$ ), 134.71 (Ar), 129.26 (Ar), 128.80 (Ar), 128.39 (Ar), 120.19 ( $C_3$ ), 113.42 ( $C_1$ ), 53.22 ( $CH_2Ph$ );  $m/z$  (ESI) 248.0 ( $[^{35}Cl]^+ + 1$ ), 250.0 ( $[^{37}Cl]^+ + 1$ ).

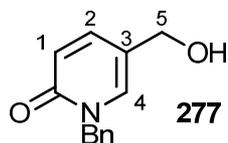
*(6-Methoxypyridin-3-yl)methanol*, **276**.



This compound has been reported but not fully characterised.<sup>195</sup> Under nitrogen, a suspension of lithium aluminum hydride solution in THF (1M, 6.58  $cm^3$ , 6.58 mmol) in THF (3.39  $cm^3$ ) was stirred at 0 °C for 5 min. Methyl 6-methoxynicotinate **285** (1.0 g, 5.98 mmol) was added portionwise and the mixture was stirred for 10 m. The suspension was allowed to warm to room temperature and stirred for 2 h before the solution was cooled to 0 °C. The suspension was carefully quenched with water (0.04  $cm^3$ ), 15 % NaOH (0.04  $cm^3$ ) followed by water (0.12  $cm^3$ ). The resulting precipitate was filtered with celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to give product **276** (0.690 g, 4.96 mmol, 83 % yield) as an oil; (found (ESI):  $M^+ + H$ , 140.0711.  $C_7H_{10}NO_2$  requires  $M$ , 140.0706);  $\nu_{\max}$  3298 (OH st.), 1608 (CO), 1573 (C=C st.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz, DMSO) 8.07 (1H, s,  $H_5$ ), 7.64 (1H, d,  $J$  8.5,  $H_3$ ), 6.77 (1H, d,  $J$  8.5,  $H_2$ ), 5.11 (1H, t,  $J$  5.6, OH), 4.43 (2H, d,  $J$  5.6,  $H_6$ ), 3.83 (3H, s,  $CH_3$ );  $\delta_C$  (101 MHz, DMSO) 162.70 ( $C_1$ ), 144.99

(C<sub>5</sub>), 138.29 (C<sub>3</sub>), 130.63 (C<sub>2</sub>), 109.94 (C<sub>4</sub>), 60.20 (C<sub>6</sub>), 52.94 (CH<sub>3</sub>); *m/z* (ESI) 139.8 (M<sup>+</sup>+1).

*1-Benzyl-5-(hydroxymethyl)pyridin-2(1H)-one*, **277**.



This compound has been reported and fully characterised.<sup>196</sup> A mixture of benzyl bromide (0.56 cm<sup>3</sup>, 0.81 g, 4.71 mmol), 6-methoxypyridin-3-yl)methanol **276** (1.00 g, 7.19 mmol) and potassium carbonate (1.30 g, 9.40 mmol) in dry acetonitrile (17 cm<sup>3</sup>) was stirred at 60 °C for 18 h. The mixture was filtered, concentrated under reduced pressure and purified by column chromatography (methanol - ethyl acetate 5 : 95), to give product **277** (0.500 g, 2.32 mmol, 32 % yield) as an oil;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 7.38 - 7.18 (7 H, m, ArH, H<sub>4</sub>, H<sub>1</sub>), 6.50 (1 H, d, *J* 9.2, H<sub>2</sub>), 5.03 (2 H, s, CH<sub>2</sub>), 4.33 (2 H, d, *J* 5.5, H<sub>5</sub>), 4.00 - 3.94 (1 H, m, OH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 162.33 (CO), 140.10 (C<sub>4</sub>), 136.11 (Ar), 135.12 (C<sub>2</sub>), 128.75 (Ar), 127.95 (Ar), 127.90 (Ar), 120.61 (C<sub>1</sub>), 120.06 (C<sub>3</sub>), 61.26 (C<sub>5</sub>), 52.03 (CH<sub>2</sub>Ph). The *O*-benzylation product was not isolated from the reaction mixture. An nOe <sup>1</sup>H NMR experiment supported the structural assignment: irradiation of the CH<sub>2</sub>Ph protons (5.03 ppm) resulted in the excitation of proton H<sub>3</sub> only. This data was also in agreement with the literature.

*General procedure A - alkene hydrogenation with hydrogen balloons.*

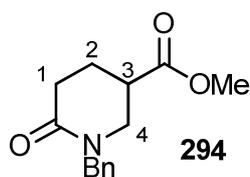
Under nitrogen, the alkene (1.00 mmol) was loaded into a round bottomed flask containing a magnetic stirrer and the specified solvent was added. The heterogeneous catalyst (at the specified catalytic loading) was carefully added before the flask was evacuated with hydrogen and a balloon of hydrogen was attached. The solution was

stirred vigorously for the specified time and temperature before the catalyst was removed by filtration with celite. Following solvent removal under reduced pressure the product was obtained, following purified by column chromatography (where applicable).

*General procedure B - alkene hydrogenation in a hydrogenator.*

The alkene (1 mmol) and catalyst (at the specified catalytic loading) were added to a small glass hydrogenation vial. A suba seal was attached and the contents were flushed with nitrogen for 10 min before the dry solvent (as specified) was added. The suba seal was removed and the vial was quickly placed into the hydrogenation apparatus. The hydrogenator was filled with hydrogen to the appropriate pressure before the pressure was nearly completely released. The hydrogenator was then filled again with hydrogen and the pressure was released. This fill release cycle carried out for a total of 3 times to ensure the vessel was sufficiently charged with hydrogen at the stated pressure. A magnetic stirrer box was placed under the hydrogenator to enable stirring for the specified time before the hydrogen was carefully released and the apparatus was disassembled. Following concentration under reduced pressure, the product was obtained, following purified by column chromatography (where applicable).

*Methyl 1-benzyl-6-oxopiperidine-3-carboxylate, (±)-294.*

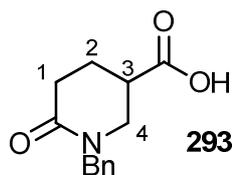


This compound has been reported and fully characterised.<sup>197</sup> This compound was prepared following the general procedure for alkene hydrogenation, using methyl 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylate, **277** (100 mg, 0.411 mmol) and palladium on carbon (5 % w/w, 88 mg,  $4.13 \times 10^{-2}$  mmol) in methanol (1 cm<sup>3</sup>) following a reaction time of 1 d, at 40 °C under a balloon of hydrogen. Following solvent removal and purification by column chromatography (ethyl acetate – hexane 9:1), the product (±)-**294** (30 mg, 0.121 mmol, 30 % yield) was obtained as colourless oil;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.30 - 7.14 (5 H, m, ArH), 4.62 (1 H, d, *J* 14.6, CH<sub>2</sub>), 4.46 (1 H, d, *J* 14.6, CH<sub>2</sub>), 3.59 (3 H, s, CH<sub>3</sub>), 3.42 - 3.28 (2 H, m, H<sub>4</sub>), 2.78 - 2.65 (1 H, m, H<sub>3</sub>), 2.54 (1 H, dt, *J* 17.8, 5.3, H<sub>1A</sub>), 2.47 - 2.35 (1 H, m, H<sub>1B</sub>), 2.13 - 2.02 (1 H, m, H<sub>2A</sub>), 2.00 - 1.89 (1 H, m, H<sub>2B</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 172.51 (CO), 168.79 (CO), 136.68 (Ar), 128.54 (Ar), 128.06 (Ar), 127.41 (Ar), 52.13 (CH<sub>3</sub>), 50.08 (CH<sub>2</sub>Ph), 47.92 (C<sub>4</sub>), 38.99 (C<sub>3</sub>), 30.65 (C<sub>1</sub>), 23.86 (C<sub>2</sub>); Enantiomeric separation was achieved by HPLC analysis (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 85 : 15, 1 mL/min, T = 30 °C, 13.3 min, 14.9 min.). This sample was used as a racemic standard in chiral HPLC to confirm the retention times of the enantiomers of the AH products prepared in the next section.

*AH screen of pyridone 285.*

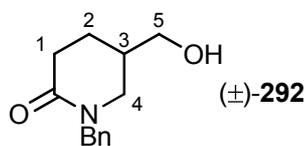
The AH catalyst screen of pyridone **285** was carried out using the general procedure for alkene hydrogenation. Conversions were determined by <sup>1</sup>H NMR. Ees were determined by HPLC analysis using compound (±)-**294** as a racemic standard.

*1-Benzyl-6-oxopiperidine-3-carboxylic acid, (±)-293.*



This compound has been reported and fully characterised.<sup>197</sup> This compound was prepared following the general procedure for alkene hydrogenation, using 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid, **283** (30 mg, 0.131 mmol) and palladium on carbon (10 % w/w, 13 mg,  $1.22 \times 10^{-2}$  mmol) in methanol ( $1 \text{ cm}^3$ ), following a reaction time of 20 h, at room temperature and 25 bar. Following concentration under reduced pressure, (±)-**293** (30 mg, 0.129 mmol, 98 % yield) was obtained as a colourless oil.  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 10.40 (1 H, bs, OH), 7.28 - 7.10 (5 H, m, ArH), 4.68 (1 H, d,  $J$  14.7,  $\text{CH}_2$ ), 4.36 (1 H, d,  $J$  14.7,  $\text{CH}_2$ ), 3.47 - 3.25 (2 H, m,  $\text{H}_4$ ), 2.75 - 2.62 (1 H, m,  $\text{H}_3$ ), 2.56 (1 H, dt,  $J$  17.9, 4.5,  $\text{H}_{1\text{A}}$ ), 2.42 (1 H, dt,  $J$  17.9, 6.5,  $\text{H}_{1\text{B}}$ ), 2.11 - 1.99 (1 H, m,  $\text{H}_{2\text{A}}$ ), 1.98 - 1.82 (1 H, m,  $\text{H}_{2\text{B}}$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 176.85 (CO), 170.43 (CO), 136.11 (Ar), 128.61 (Ar), 128.06 (Ar), 127.58 (Ar), 50.59 ( $\text{CH}_2\text{Ph}$ ), 48.05 ( $\text{C}_4$ ), 38.83 ( $\text{C}_3$ ), 31.48 ( $\text{C}_1$ ), 25.52 ( $\text{C}_2$ ).

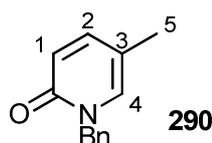
*1-Benzyl-6-oxopiperidine-3-carboxylic acid, (±)-292.*



This compound has been reported and fully characterised.<sup>198</sup> This compound was prepared following the general procedure for alkene hydrogenation, using 1-benzyl-5-(hydroxymethyl)pyridin-2(1H)-one **277** (30 mg, 0.139 mmol) and platinum oxide (3 mg,  $1.32 \times 10^{-2}$  mmol) in methanol ( $1 \text{ cm}^3$ ), following a reaction time of 18 h at room temperature under 5 bar of hydrogen. Following concentration under reduced

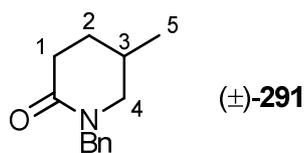
pressure, ( $\pm$ )-**292** (20 mg, 0.091 mmol, 66 % yield) was obtained as an oil;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.37 - 7.19 (5 H, m,  $\text{ArH}$ ), 4.60 (2 H, s,  $\text{CH}_2\text{Ph}$ ), 3.64 - 3.54 (1 H, m,  $\text{H}_{4\text{A}}$ ), 3.53 - 3.45 (1 H, m,  $\text{H}_{4\text{B}}$ ), 3.32 (1 H, ddd,  $J$  12.1, 5.1, 1.8,  $\text{H}_{5\text{A}}$ ), 3.02 (1 H, dd,  $J$  12.1, 10.0,  $\text{H}_{5\text{B}}$ ), 2.57 (1 H, ddd,  $J$  17.8, 6.3, 3.5,  $\text{H}_{1\text{A}}$ ), 2.44 (1 H, ddd,  $J$  17.8, 11.1, 6.5,  $\text{H}_{1\text{B}}$ ), 2.11 - 1.97 (1 H, m,  $\text{H}_3$ ), 1.94 - 1.85 (1 H, m,  $\text{H}_{2\text{A}}$ ), 1.53 (1 H, dtd,  $J$  13.1, 11.1, 6.3,  $\text{H}_{2\text{B}}$ ). A signal attributable to  $\text{OH}$  was not observed;  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 170.00 (CO), 136.93 (Ar), 128.53 (Ar), 127.93 (Ar), 127.33 (Ar), 64.34 ( $\text{C}_5$ ), 50.26 ( $\text{CH}_2\text{Ph}$ ), 49.78 ( $\text{C}_4$ ), 36.34 ( $\text{C}_3$ ), 31.16 ( $\text{C}_1$ ), 23.75 ( $\text{C}_2$ ). This data was in agreement with the literature.

*1-benzyl-5-methylpyridin-2(1H)-one*, **290**.



This compound has been reported and fully characterised.<sup>199</sup> A solution of 1-benzyl-5-(hydroxymethyl)pyridin-2(1H)-one **277** (100 mg, 0.465 mmol) in methanol (1.83  $\text{cm}^3$ ) were hydrogenated in the H-Cube hydrogenation cell using a 30 mm 10% Pd/C cartridge at room temperature, with a hydrogen pressure of 5 bar and a flow rate of 1 ml/minute. Following one circulation of the alkene solution through the H-Cube, the solvent was removed to give 1-benzyl-5-methylpyridin-2(1H)-one **290** (75 mg, 0.377 mmol, 81 % yield) as a white waxy solid;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.21 – 7.38 (5 H, m,  $\text{ArH}$ ), 7.16 (1 H, dd,  $J$  9.3, 2.3,  $\text{H}_4$ ), 7.01 (1 H, d,  $J$  2.3,  $\text{H}_1$ ), 6.56 (1 H, d,  $J$  9.3,  $\text{H}_2$ ), 5.11 (2 H, s,  $\text{CH}_2\text{Ph}$ ), 2.02 (3 H, d,  $J$  0.9,  $\text{H}_5$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 161.70 (CO), 141.80 ( $\text{C}_4$ ), 136.48 (Ar), 134.35 ( $\text{C}_2$ ), 128.57 (Ar), 127.79 (Ar), 127.63 (Ar), 120.58 ( $\text{C}_1$ ), 114.92 ( $\text{C}_3$ ), 51.45 ( $\text{CH}_2\text{Ph}$ ), 16.83 ( $\text{C}_5$ ).

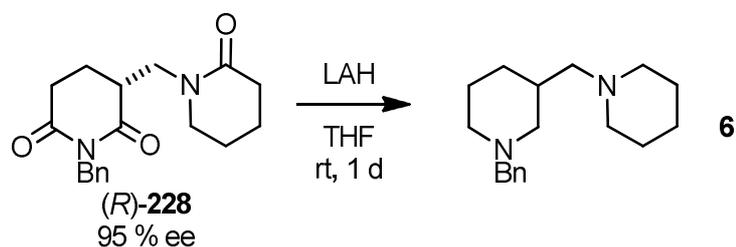
*1-benzyl-5-methylpiperidin-2-one, (±)-291.*



This compound was prepared following the general procedure for alkene hydrogenation, using 1-benzyl-5-(hydroxymethyl)pyridin-2(1H)-one **277** (30 mg, 0.139 mmol) and palladium on barium sulfate (5 % w/w, 30 mg,  $1.41 \times 10^{-2}$  mmol) in methanol (1 cm<sup>3</sup>), following a reaction time of 18 h at room temperature and 5 bar of hydrogen. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – hexane 8:2), (±)-**291** (20 mg, 0.098 mmol, 71 % yield) was obtained as an oil; (found (ESI):  $M^+ + Na$ , 226.1203. C<sub>13</sub>H<sub>17</sub>NNaO requires  $M$ , 226.1202);  $\nu_{\max}$  1619 (C=O st.) cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.22 - 7.36 (5 H, m, ArH), 4.67 (1 H, d,  $J$  14.6, CH<sub>2</sub>), 4.50 (1 H, d,  $J$  14.6, CH<sub>2</sub>), 3.16 (1 H, ddd,  $J$  12.0, 5.1, 2.0, H<sub>4A</sub>), 2.83 (1 H, dd,  $J$  12.0, 10.4, H<sub>4B</sub>), 2.55 (1 H, ddd,  $J$  17.7, 6.0, 3.0, H<sub>1A</sub>), 2.44 (1 H, ddd,  $J$  17.7, 11.5, 6.3, H<sub>1B</sub>), 1.88 - 1.99 (1 H, m, H<sub>3</sub>), 1.84 (1 H, dddd,  $J$  13.2, 6.3, 3.0, 2.0, H<sub>2A</sub>), 1.47 (1 H, dtd,  $J$  13.2, 11.5, 6.0, H<sub>2B</sub>), 0.95 (3 H, d,  $J$  6.5, H<sub>5</sub>)  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 169.78 (CO), 137.27 (Ar), 129.02 (Ar), 128.58 (Ar), 127.33 (Ar), 60.27 (CH<sub>2</sub>Ph), 54.17 (C<sub>4</sub>), 31.72 (C<sub>1</sub>), 29.49 (C<sub>2</sub>), 29.02 (C<sub>3</sub>), 18.55 (C<sub>5</sub>);  $m/z$  (ESI) 203.8 ( $M^+ + 1$ ). The <sup>1</sup>H NMR spectrum of this sample is shown in Appendix I.

### Section 3.4: Procedures from Section 2.4.

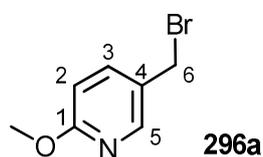
#### Section 3.4.1: Reduction of Imide **228**.



This method was used to form the product **6** from an optically pure sample of imide **228**. Under nitrogen, LDA (1M solution in THF, 0.72 cm<sup>3</sup>, 0.720 mmol) was added to a solution of 1-benzyl-3-((2-oxopiperidin-1-yl)methyl)piperidine-2,6-dione (*R*)-**228** (95 % ee, 15 mg, 4.84 x 10<sup>-2</sup> mmol) in THF (0.17 cm<sup>3</sup>) and the solution was stirred at room temperature for 24 h before water (14 μL) was added, followed by 15 % aqueous NaOH (14 μL), and water (42 μL). The resulting precipitate was filtered and the resulting filtrate was concentrated under reduced pressure to give a sample containing product **6** (10 mg, 3.67 x 10<sup>-2</sup> mmol, 76 %), as determined by <sup>1</sup>H NMR. Full characterisation data for **6** is given in the next section. The ee of this sample could not be determined by chiral GC or HPLC.

#### Section 3.4.2: Synthesis and AH of Pyridone **3**.

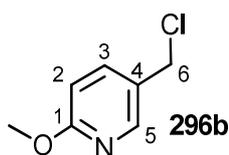
##### 5-Bromomethyl-2-methoxypyridine, **296a**.



This compound has been reported but not fully characterised.<sup>200</sup> Under nitrogen, phosphorus tribromide (68 μL, 196 mg, 0.723 mmol) was added to a solution of (6-methoxy-pyridin-3-yl)methanol **276** (50 mg, 0.360 mmol) in dry toluene (0.83 cm<sup>3</sup>) and the solution was stirred at room temperature for 1 h before water (5 cm<sup>3</sup>) was

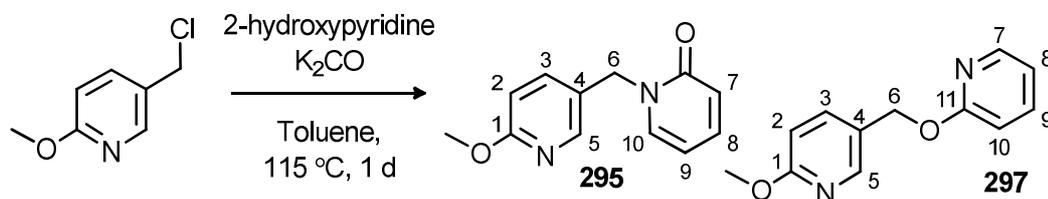
added. Following extraction with toluene (2 x 5 cm<sup>3</sup>) the organic extracts were concentrated under reduced pressure to give the product **296a** (50 mg, 0.248 mmol, 69 % yield) as an oil; (found (ESI): M<sup>+</sup> + H, 201.9865. C<sub>7</sub>H<sub>9</sub><sup>79</sup>BrNO requires M, 201.9862);  $\nu_{\max}$  3019 (aryl CH st.), 1658 (C=C st.), 1585 (C=C st.), 1537 (C=C st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, DMSO) 8.25 (1 H, d, *J* 2.4, H<sub>5</sub>), 7.78 (1 H, dd, *J* 8.6, 2.4, H<sub>3</sub>), 6.83 (1 H, d, *J* 8.6, H<sub>2</sub>), 4.71 (2 H, s, H<sub>6</sub>), 3.85 (3 H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 162.05 (C<sub>1</sub>), 145.41 (C<sub>5</sub>), 140.96 (C<sub>3</sub>), 126.98 (C<sub>2</sub>), 111.68 (C<sub>4</sub>), 54.69 (CH<sub>3</sub>), 29.74 (C<sub>6</sub>); *m/z* (ESI) 202.0 (M[<sup>79</sup>Br]<sup>+</sup>+1), 204.0 (M[<sup>81</sup>Br]<sup>+</sup>+1).

*5-Chloromethyl-2-methoxypyridine, 296b.*



This compound has been reported and fully characterised.<sup>201</sup> Under nitrogen, thionyl chloride (2.05 cm<sup>3</sup>, 3.34 g, 28.09 mmol) was added to a solution of (6-methoxypyridin-3-yl)methanol **276** (3.56 g, 25.60 mmol) in dry toluene (10.6 cm<sup>3</sup>) and the solution was stirred at room temperature for 1 h before NaOH (2M, 10 cm<sup>3</sup>) was added. The solution was stirred for 10 min before extraction with toluene (2 x 20 cm<sup>3</sup>). The organic extracts were washed (water) and concentrated under reduced pressure to give the product **296b** (3.85 g, 24.52 mmol, 96 % yield) as an oil;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.15 (1 H, d, *J* 2.7, H<sub>5</sub>), 7.62 (1 H, dd, *J* 8.5, 2.7, H<sub>2</sub>), 6.75 (1 H, d, *J* 8.5, H<sub>1</sub>), 4.55 (2 H, s, H<sub>6</sub>), 3.94 (3 H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>) 163.56 (C<sub>1</sub>), 146.66 (C<sub>5</sub>), 139.16 (C<sub>3</sub>), 126.12 (C<sub>2</sub>), 111.25 (C<sub>4</sub>), 53.57 (CH<sub>3</sub>), 43.34 (C<sub>6</sub>). This data is in agreement with the literature.

1-((6-methoxypyridin-3-yl)methyl)pyridin-2(1H)-one **295** and 2-methoxy-5-((pyridin-2-yl)oxy)methyl)pyridine, **297**.

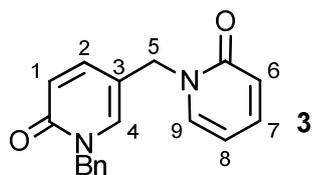


Under nitrogen, a mixture of 5-chloromethyl-2-methoxypyridine **296b** (0.342 g, 2.18 mmol), 2-hydroxypyridine (0.413 g, 4.34 mmol) and potassium carbonate (0.601 g, 4.35 mmol) in toluene (22 cm<sup>3</sup>) was stirred at 115 °C for 1 d, before the solution was allowed to cool. Following filtration, the filtrate was concentrated under reduced pressure and purified by column chromatography (ethyl acetate), to give the *O*-substituted product **297** (58 mg, 0.268 mmol, 12 % yield) as a colourless oil; (found (ESI): M<sup>+</sup> + H, 216.0891. C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> requires M, 216.0899);  $\nu_{\max}$  1610 (C=O st.), 1596 (C=C st.), 1571 (C=C st.), 1495 (C=C st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.27 (1 H, d, *J* 2.3, H<sub>7</sub>), 8.17 (1 H, d, *J* 7.8, H<sub>5</sub>), 7.70 (1 H, dd, *J* 8.5, 2.5, H<sub>3</sub>), 7.55 – 7.60 (1 H, m, H<sub>9</sub>), 6.88 (1 H, t, *J* 6.0, H<sub>8</sub>), 6.76 (2 H, m, H<sub>2</sub>, H<sub>10</sub>), 5.31 (2 H, s, H<sub>6</sub>), 3.94 (3 H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (176 MHz, CDCl<sub>3</sub>) 164.00 (C<sub>11</sub>), 163.36 (C<sub>1</sub>), 147.04 (C<sub>5</sub>), 146.56 (C<sub>7</sub>), 139.20 (C<sub>10</sub>), 138.56 (C<sub>2</sub>), 125.60 (C<sub>3</sub>), 117.28 (C<sub>9</sub>), 111.36 (C<sub>4</sub>), 111.04 (C<sub>8</sub>), 64.96 (C<sub>6</sub>), 53.60 (CH<sub>3</sub>); *m/z* (ESI) 215.97 (M<sup>+</sup> + 1).

Increasing the polarity of the eluent (methanol – ethyl acetate 5:95) gave the *N*-substituted product, **295** (0.299 g, 1.384 mmol, 63 % yield) as a colourless oil; (found (ESI): M<sup>+</sup>, 216.0887. C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> requires M, 216.0899);  $\nu_{\max}$  3018 (aryl CH st.), 1657 (C=O st.), 1587 (C=C st.), 1568 (C=C st.), 1490 (C=C st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.14 (1 H, d, *J* 2.5, H<sub>5</sub>), 7.63 (1 H, dd, *J* 8.7, 2.5, H<sub>2</sub>), 7.34 - 7.25 (2 H, m, H<sub>8</sub>, H<sub>10</sub>), 6.72 (1 H, d, *J* 8.7, H<sub>3</sub>), 6.60 (1 H, dd, *J* 9.2, 1.2, H<sub>7</sub>), 6.15 (1 H, td, *J*

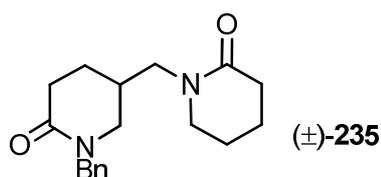
6.8, 1.5, H<sub>9</sub>), 5.06 (2 H, s, H<sub>6</sub>), 3.92 (3 H, s, CH<sub>3</sub>);  $\delta_C$  (101 MHz, DMSO-*d*<sub>6</sub>) 163.09 (CO), 161.38 (C<sub>1</sub>), 146.65 (C<sub>5</sub>), 140.09 (C<sub>3</sub>), 139.24 (C<sub>10</sub>), 138.80 (C<sub>8</sub>), 126.10 (C<sub>4</sub>), 119.83 (C<sub>7</sub>), 110.44 (C<sub>2</sub>), 105.62 (C<sub>9</sub>), 53.14 (C<sub>6</sub>), 48.36 (CH<sub>3</sub>); *m/z* (ESI) 215.97 (M<sup>+</sup> + 1).

*1-Benzyl-5-[(2-oxopyridin-1(2H)-yl)methyl]pyridin-2(1H)-one, 3.*



Under nitrogen, a mixture of benzyl bromide (1.60 cm<sup>3</sup>, 2.30 cm<sup>3</sup>, 13.53 mmol), 1-((6-methoxypyridin-3-yl)methyl)pyridin-2(1H)-one, **295** (1.45 g, 6.71 mmol) and potassium carbonate (1.85 g, 13.39 mmol) in dry acetonitrile (27 cm<sup>3</sup>) was stirred at 80 °C for 24 h before the solution was allowed to cool. Following filtration, the resulting filtrate was concentrated under reduced pressure and recrystallised (ethanol), to give product **3** (1.00 g, 3.42 mmol, 51 % yield) as a white powder; 140-142 °C; (found (ESI): M<sup>+</sup> + Na, 315.1102. C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>NaO<sub>2</sub> requires M, 315.1104);  $\nu_{\max}$  3034 (aryl CH st.), 1714 (C=O st.), 1666 (C=O st.), 1649 (C=C st.), 1595 (C=C st.), 1568 (C=C st.), 1493 (C=C st.) cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.45 (1 H, d, *J* 2.5, H<sub>3</sub>), 7.37 - 7.27 (7 H, m, ArH, H<sub>6</sub>, H<sub>2</sub>), 7.23 (1 H, dd, *J* 6.8, 2.0, H<sub>8</sub>), 6.58 (2 H, d, *J* 9.3, H<sub>1</sub>, H<sub>5</sub>), 6.16 (1 H, td, *J* 6.8, 1.4, H<sub>7</sub>), 5.12 (2 H, s, CH<sub>2</sub>), 4.78 (2 H, s, CH<sub>2</sub>);  $\delta_C$  (101 MHz, CDCl<sub>3</sub>) 162.41 (CO), 161.83 (CO), 139.93 (C<sub>9</sub>), 139.70 (C<sub>4</sub>), 137.53 (C<sub>7</sub>), 136.57 (C<sub>2</sub>), 135.93 (Ar), 128.72 (Ar), 127.91 (Ar), 127.85 (Ar), 121.16 (C<sub>6</sub>), 121.07 (C<sub>1</sub>), 114.51 (C<sub>3</sub>), 106.58 (C<sub>8</sub>), 52.02 (C<sub>5</sub>), 49.17 (CH<sub>2</sub>Ph); *m/z* (ESI) 293.1 (M<sup>+</sup> + 1), 315.1 (M<sup>+</sup> + 23). Further recrystallisation (EtOH) provided crystals of sufficient quality for X-diffraction, enabling confirmation of the structure. Full details are shown in Appendix II.

*1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)piperidin-2-one*, ( $\pm$ )-**235**.



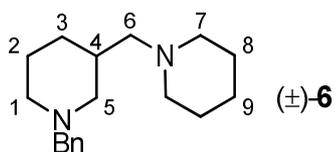
This compound was prepared following the general procedure for alkene hydrogenation, using 1-benzyl-5-[(2-oxopyridin-1(2*H*)-yl)methyl]pyridin-2(1*H*)-one, **3** (0.644 g, 2.20 mmol) and platinum oxide (25 mg, 0.110 mmol) following a reaction time of 20 h, at 30 °C. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – methanol 95:5), product ( $\pm$ )-**235** (497 mg, 1.66 mmol, 75 % yield) was obtained as an oil, Full characterisation data was listed in Section 1.

*AH screen of 1-benzyl-5-[(2-oxopyridin-1(2*H*)-yl)methyl]-pyridin-2(1*H*)-one*, **6**.

The AH catalyst screen of 1-benzyl-5-[(2-oxopyridin-1(2*H*)-yl)methyl]pyridin-2(1*H*)-one **3** was carried out using the general procedure (B) for alkene hydrogenation. Conversions were determined by <sup>1</sup>H NMR. Ees were determined by HPLC analysis using compound ( $\pm$ )-**235** as a racemic standard.

*Section 3.4.3: Synthesis of (1-Benzyl-3-(piperidin-1-ylmethyl)piperidine)* **6**.

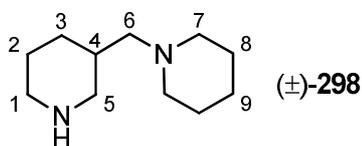
*1-Benzyl-3-(piperidin-1-ylmethyl)piperidine*, ( $\pm$ )-**6**.



Under nitrogen, triethyl-silane (1.41 cm<sup>3</sup>, 8.79 mmol) was added to a solution of 1-((1-benzyl-6-oxopiperidin-3-yl)methyl)piperidin-2-one, ( $\pm$ )-**235** (377 mg, 1.256 mmol) and triruthenium dodecacarbonyl (16 mg, 2.50 x 10<sup>-2</sup> mmol) in dry toluene

(2.5 cm<sup>3</sup>) and the mixture was stirred at 100 °C for 18 h. The solution was concentrated under reduced pressure and purified by column chromatography (ethyl acetate – hexane – triethylamine 10:90:1) to give product (±)-**6** (194 mg, 0.713 mmol, 57 % yield) as a colourless oil; (found (ESI): M<sup>+</sup> + H, 273.2323. C<sub>18</sub>H<sub>29</sub>N<sub>2</sub> requires M, 273.2325);  $\nu_{\max}$  2928 (alkyl CH st.), 2849 (alkyl CH st.), 2793 (alkyl CH st.), 2754 (alkyl CH st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (700 MHz, CDCl<sub>3</sub>) 7.33 - 7.20 (5 H, m, ArH), 3.57 (1 H, d, *J* 13.2, CH<sub>2</sub>), 3.40 (1 H, d, *J* 13.2, CH<sub>2</sub>), 2.90 (1 H, d, *J* 10.1, H<sub>5A</sub>), 2.76 (1 H, d, *J* 10.5, H<sub>1A</sub>), 2.37 - 2.21 (4 H, m, H<sub>7</sub>), 2.13 - 2.06 (2 H, m, H<sub>6</sub>), 1.89 (1 H, m, H<sub>1B</sub>), 1.87 - 1.81 (1 H, m, H<sub>4</sub>), 1.74 (1 H, dq, *J* 13.0, 3.4, H<sub>3A</sub>), 1.71 - 1.65 (1 H, m, H<sub>5B</sub>), 1.62 (1 H, dquin, *J* 13.0, 3.4, H<sub>2A</sub>), 1.58 - 1.48 (5 H, m, H<sub>8</sub>, H<sub>2B</sub>), 1.43 - 1.36 (2 H, m, H<sub>9</sub>), 0.89 (1 H, qd, *J* 13.0, 3.4, H<sub>3B</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 136.62 (Ar), 129.20 (Ar), 128.06 (Ar), 126.80 (Ar), 63.76 (CH<sub>2</sub>Ph), 63.60 (C<sub>6</sub>), 59.36 (C<sub>5</sub>), 55.08 (C<sub>1</sub>), 54.10 (C<sub>7</sub>), 33.63 (C<sub>4</sub>), 29.77 (C<sub>3</sub>), 25.89 (C<sub>8</sub>), 25.14 (C<sub>2</sub>), 24.50 (C<sub>9</sub>); *m/z* (ESI) 273.0 (M<sup>+</sup> + 1). The assignments of these proton signals were supported by <sup>13</sup>C HMQC and COSY correlation NMR experiments. These can be found in Appendix I.

*1-(Piperidin-3-ylmethyl)piperidine, (±)-298.*

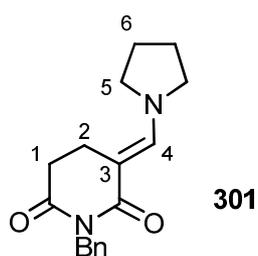


This compound was prepared following the general procedure for alkene hydrogenation, using 1-benzyl-3-(piperidin-1-ylmethyl)piperidine (±)-**6** (22 mg, 0.081 mmol) and palladium hydroxide on carbon (20 % w/w, 6 mg, 8.55 x 10<sup>-3</sup> mmol) following a reaction time of 18 h, at room temperature. Following filtration with celite, the resulting filtrate was passed through an Isolute-XL SCX amine

scavenger resin and the resin was washed with DCM (3 x 1 cm<sup>3</sup>). The free amine was liberated by passing a solution of approx. 2 % NH<sub>4</sub>OH in methanol through the resin, followed by washing with DCM (3 x 1 cm<sup>3</sup>). Following concentration under reduced pressure, product (±)-**298** (20 mg, 0.110 mmol) was obtained as a colourless oil; (found (ESI): M<sup>+</sup> + H, 183.1857. C<sub>11</sub>H<sub>23</sub>N<sub>2</sub> requires M, 183.1856);  $\nu_{\max}$  3400 (NH st.), 2927 (alkyl CH st.), 2848 (alkyl CH st.), 2795 (alkyl CH st.), 2758 (alkyl CH st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (700 MHz, CDCl<sub>3</sub>) 3.14 (1 H, dd, *J* 11.9, 1.5, H<sub>1A</sub>), 3.01 (1 H, d, *J* 11.9, H<sub>5A</sub>), 2.54 (1 H, td, *J* 11.8, 2.8, H<sub>5B</sub>), 2.19 - 2.43 (5 H, m, H<sub>7</sub>, H<sub>1B</sub>), 2.09 (1 H, dd, *J* 12.3, 8.1, H<sub>6A</sub>), 2.05 (1 H, dd, *J* 12.3, 6.2, H<sub>6B</sub>), 1.81 (1 H, dq, *J* 12.7, 3.5, H<sub>3A</sub>), 1.67 - 1.73 (1 H, m, H<sub>4</sub>), 1.64 (1 H, dquin, *J* 12.8, 3.5, H<sub>2A</sub>), 1.54 (4 H, quin, *J* 6.4, H<sub>8</sub>), 1.46 (1 H, qt, *J* 12.8, 3.5, H<sub>2B</sub>), 1.42 - 1.37 (2 H, m, H<sub>9</sub>), 1.01 (1 H, qd, *J* 12.8, 3.5, H<sub>3B</sub>);  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>) 63.88 (C<sub>6</sub>), 55.17 (C<sub>7</sub>), 51.96 (C<sub>1</sub>), 47.21 (C<sub>5</sub>), 34.61 (C<sub>4</sub>), 30.34 (C<sub>3</sub>), 26.39 (C<sub>8</sub>), 26.03 (C<sub>2</sub>), 24.55 (C<sub>9</sub>); *m/z* (ESI) 182.9 (M<sup>+</sup>+1).

#### Section 3.4.4: Synthesis and Hydrogenation of Enamide **301**.

##### (3E)-1-Benzyl-3-(pyrrolidin-1-ylmethylidene)piperidine-2,6-dione **301**.



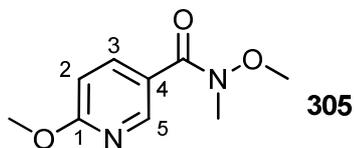
Under nitrogen, (1-benzyl-2,6-dioxopiperidin-3-ylidene)methyl-4-methyl-benzene sulfonate **219** (0.46 g, 1.19 mmol) was added to a solution of pyrrolidine (0.20 cm<sup>3</sup>, 0.170 g, 2.40 mmol) and NEt<sub>3</sub> (0.41 cm<sup>3</sup>, 0.298 g, 2.94 mmol) in dry toluene (14.0 cm<sup>3</sup>) and the mixture stirred at 125 °C for 8 h. The mixture was concentrated under reduced pressure and purified by column chromatography (hexane - ethyl acetate

1:9), to give the product **301** (0.119 g, 0.419 mmol, 35 %) as an oil; (found (ESI):  $M^+ + Na$ , 307.1410.  $C_{17}H_{20}N_2NaO_2$  requires  $M$ , 307.1417);  $\nu_{max}$  3020 (aryl CH st.), 1716 (C=O st.), 1668 (C=O st.), 1608(C=C st.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.64 (1 H, s,  $H_3$ ), 7.33-7.08 (5 H, m,  $ArH$ ), 4.94 (2 H, s,  $CH_2$ ), 3.50-3.40 (4 H, m,  $H_4$ ), 2.72 (2 H, t,  $J$  7.2,  $H_1$ ), 2.52 (2 H, t,  $J$  7.2,  $H_2$ ), 1.88-1.77 (4 H, m,  $H_5$ );  $\delta_C$  (101 MHz,  $CDCl_3$ ) 172.68 (CO), 168.92 (CO), 146.75 ( $C_4$ ), 138.55 (Ar), 128.37 (Ar), 128.20 (Ar), 126.82 (Ar), 92.99 ( $C_3$ ), 51.70 ( $CH_2Ph$ ), 42.93 ( $C_5$ ), 33.03 ( $C_1$ ), 25.37 ( $C_2$ ), 19.25 ( $C_6$ );  $m/z$  (ESI) 307.1 ( $M^+ + 23$ ).

### Section 3.5: Procedures from Section 5.

#### Section 3.5.1: Synthesis of Ketones.

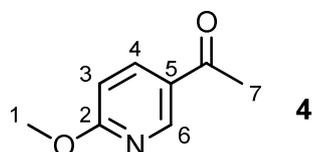
##### *N*,6-Dimethoxy-*N*-methylpyridine-3-carboxamide, **305**



Under nitrogen, a solution of methyl 6-methoxynicotinate **285** (3.00 g, 17.96 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (5.36 g, 54.95 mmol) in THF (40  $cm^3$ ) was stirred at  $-40$  °C for 10 min. Isopropyl magnesium chloride (2 M solution in THF, 26  $cm^3$ , 52.00 mmol) was added dropwise over 15 min and the reaction was stirred at  $-40$  °C for 90 min before aqueous acetic acid (20 %, 20  $cm^3$ ) was added. This solution was extracted with diethyl ether (3 x 20  $cm^3$ ) and the organic extracts were set aside. The remaining aqueous phase was then basified with saturated aqueous sodium hydrocarbonate and extracted with DCM (2 x 10  $cm^3$ ). The combined organic extracts were dried ( $MgSO_4$ ), concentrated under reduced pressure and purified by column chromatography (petroleum ether – ethyl acetate 9:1), to give the product **305** (2.38 g, 12.14 mmol, 68 % yield) as a colourless oil; (found

(ESI):  $M + Na$ , 219.0740.  $C_9H_{12}N_2NaO_3$  requires  $M$ , 219.0740);  $\nu_{max}$  1635 (C=O st.), 1600 (C=C st.), 1566 (C=C st.), 1495 (C=C st.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 8.65 (1 H, d,  $J$  2.5,  $H_5$ ), 7.99 (1 H, dd,  $J$  8.7, 2.5,  $H_3$ ), 6.76 (1 H, d,  $J$  8.7,  $H_2$ ), 3.99 (3 H, s,  $CH_3$ ), 3.58 (3 H, s,  $CH_3$ ), 3.38 (3 H, s,  $CH_3$ );  $\delta_C$  (75 MHz,  $CDCl_3$ ) 167.29 (CO), 165.28 ( $C_1$ ), 148.24 ( $C_5$ ), 139.32 ( $C_3$ ), 122.73 ( $C_4$ ), 110.14 ( $C_2$ ), 61.00 ( $CH_3$ ), 53.71 ( $CH_3$ ), 33.29 ( $CH_3$ );  $m/z$  (ESI) 196.8 ( $M^+ + 1$ ).

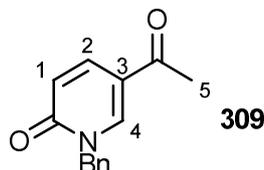
*1-(6-Methoxypyridin-3-yl)ethanone, 4.*



This compound has been reported but not fully characterised.<sup>202</sup> Under nitrogen, a solution of *N*,6-dimethoxy-*N*-methylpyridine-3-carboxamide **305** (3.66 g, 18.67 mmol) in THF (64  $cm^3$ ) was stirred at 0 °C for 15 m. Methyl magnesium bromide (3M solution in THF, 6.42  $cm^3$ , 19.26 mmol) was added dropwise over 5 min and the solution was stirred at 0 °C for 1 h. The solution was allowed to warm to room temperature and stirred for 1 d before the solution was concentrated under reduced pressure and HCl (2 M, 10  $cm^3$ ) was added. Following extraction with diethyl ether (3 x 30  $cm^3$ ), the organic extracts were washed with brine, dried ( $MgSO_4$ ), concentrated under reduced pressure and purified by column chromatography (petroleum ether – ethyl acetate 2:8), to give product **4** (1.73 g, 11.48 mmol, 61 % yield) as a colourless solid; Mp 60 – 64 °C; (found (ESI):  $M^+ + Na$ , 174.0525.  $C_8H_9NNaO_2$  requires  $M$ , 174.0525);  $\nu_{max}$  1671 (C=O st.), 1597 (C=C st.), 1562 (C=C st.), 1494 (C=C st.)  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 8.78 (1 H, dd,  $J$  2.5, 0.6,  $H_6$ ), 8.14 (1 H, dd,  $J$  8.8, 2.5,  $H_4$ ), 6.79 (1 H, dd,  $J$  8.8, 0.6,  $H_3$ ), 4.01 (3 H, s,  $H_1$ ), 2.71 - 2.55 (3

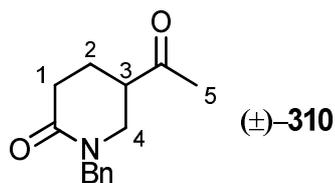
H, s, H<sub>7</sub>);  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>) 195.64 (CO), 166.76 (C<sub>2</sub>), 149.39 (C<sub>6</sub>), 138.13 (C<sub>4</sub>), 126.96 (C<sub>5</sub>), 111.12 (C<sub>3</sub>), 54.03 (C<sub>1</sub>), 26.32 (C<sub>7</sub>);  $m/z$  (ESI) 152.1 (M<sup>+</sup>+1).

*5-Acetyl-1-benzylpyridin-2(1H)-one*, **309**.



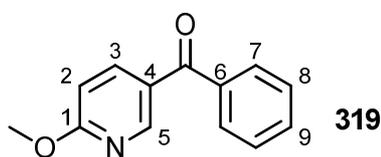
This compound has been reported but not fully characterised.<sup>203</sup> A mixture of benzyl bromide (0.43 cm<sup>3</sup>, 0.62 g, 3.62 mmol), 1-(6-methoxypyridin-3-yl)ethanone **4** (0.500 g, 3.31 mmol) and potassium carbonate (0.914 g, 6.61 mmol) in dry acetonitrile (17 cm<sup>3</sup>) was stirred at 80 °C for 2 d before the mixture was allowed to cool to room temperature. Following filtration, concentration under reduced pressure and purification by column chromatography (ethyl acetate - hexane 8:2), the product **309** (0.395 g, 1.74 mmol, 48 % yield) was obtained as a colourless oil; (found (ESI): M<sup>+</sup> + Na, 250.0837. C<sub>14</sub>H<sub>13</sub>NNaO<sub>2</sub> requires M, 250.0838);  $\nu_{\text{max}}$  3063 (aryl CH st.), 1640 (C=O st.), 1542 (C=C st.), 1496 (C=C st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 8.10 (1 H, d,  $J$  2.5, H<sub>4</sub>), 7.85 (1 H, dd,  $J$  9.6, 2.5, H<sub>3</sub>), 7.42 - 7.25 (5 H, m, ArH), 6.60 (1 H, d,  $J$  9.6, H<sub>1</sub>), 5.19 (2 H, s, CH<sub>2</sub>), 2.39 (3 H, s, H<sub>5</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 193.01 (CO), 162.25 (CO), 142.05 (C<sub>4</sub>), 137.56 (C<sub>2</sub>), 135.31 (Ar), 129.07 (Ar), 128.45 (Ar), 128.14 (Ar), 120.11 (C<sub>3</sub>), 117.98 (C<sub>1</sub>), 52.71 (CH<sub>2</sub>Ph), 25.69 (C<sub>5</sub>);  $m/z$  (ESI) 227.8 (M<sup>+</sup>+1), 249.8 (M<sup>+</sup>+23). Insufficient literature characterisation data was reported for comparison.

5-Acetyl-1-benzylpiperidin-2-one, ( $\pm$ )-**310**.



This compound has been reported and fully characterised.<sup>197</sup> This compound was prepared following the general procedure for alkene hydrogenation, using 5-acetyl-1-benzylpyridin-2(1*H*)-one, **309** (260 mg, 1.14 mmol) and palladium on carbon (10 % w/w, 61 mg,  $5.73 \times 10^{-2}$  mmol) following a reaction time of 36 h, at room temperature. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – hexane 9:1), product ( $\pm$ )-**310** (23 mg, 0.010 mmol, 9 % yield) was obtained as a colourless oil;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.23 - 7.35 (5 H, m, ArH), 4.74 (1 H, d,  $J$  14.6,  $\text{CH}_2$ ), 4.47 (1 H, d,  $J$  14.6,  $\text{CH}_2$ ), 3.43 (1 H, dd,  $J$  12.4, 9.5,  $\text{H}_{4\text{A}}$ ), 3.30 (1 H, ddd,  $J$  12.4, 5.6, 1.5,  $\text{H}_{4\text{B}}$ ), 2.80 (1 H, tdd,  $J$  9.5, 5.6, 3.5,  $\text{H}_3$ ), 2.59 (1 H, ddd,  $J$  17.8, 5.8, 4.5,  $\text{H}_{1\text{A}}$ ), 2.50 (1 H, ddd,  $J$  17.8, 10.0, 6.0,  $\text{H}_{1\text{B}}$ ), 2.16 (3 H, s,  $\text{H}_5$ ), 1.82 - 1.94 (2 H, m,  $\text{H}_2$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 206.79 (CO), 168.19 (CO), 136.16 (Ar), 127.95 (Ar), 127.56 (Ar), 126.93 (Ar), 49.59 ( $\text{CH}_2\text{Ph}$ ), 46.66 ( $\text{C}_4$ ), 46.08 ( $\text{C}_3$ ), 34.17 ( $\text{C}_5$ ), 30.47 ( $\text{C}_1$ ), 23.30 ( $\text{C}_2$ ).

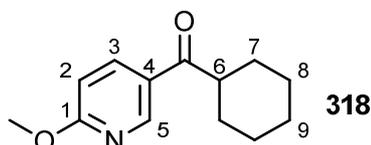
(6-Methoxypyridin-3-yl)(phenyl)methanone, **319**.



This compound has been reported but not fully characterised.<sup>204</sup> Under nitrogen, a solution of *N*,6-dimethoxy-*N*-methylpyridine-3-carboxamide, **305** (100 mg, 0.510 mmol) in THF (0.96  $\text{cm}^3$ ) was cooled to 0 °C and left stirring for 5 min. Phenyl magnesium bromide (1M solution in THF, 0.79  $\text{cm}^3$ , 0.79 mmol) was added

dropwise over 5 min and the solution was stirred at 0 °C for the 3 h before the solution was concentrated under reduced pressure and HCl (2 M, 5 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 5 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (petroleum ether – ethyl acetate 9:1), to give product **319** (60 mg, 0.282 mmol, 55 % yield) as an oil; (found (ESI): M<sup>+</sup> + H, 214.0860. C<sub>13</sub>H<sub>12</sub>NO<sub>2</sub> requires M, 214.0863);  $\nu_{\max}$  1651 (CO), 1592 (C=C st.), 1492 (C=C st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.62 (1 H, d, *J* 2.4, H<sub>5</sub>), 8.10 (1 H, dd, *J* 8.9, 2.4, H<sub>3</sub>), 7.83 - 7.73 (2 H, m, H<sub>7</sub>), 7.63 - 7.56 (1 H, m, H<sub>9</sub>), 7.54 - 7.43 (2 H, m, H<sub>8</sub>), 6.85 (1 H, d, *J* 8.9, H<sub>2</sub>), 4.03 (3 H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>) 193.63 (CO), 166.50 (C<sub>1</sub>), 150.79 (C<sub>5</sub>), 140.00 (C<sub>3</sub>), 137.50 (C<sub>6</sub>), 129.68 (C<sub>7</sub>), 128.41 (C<sub>8</sub>), 126.90 (C<sub>9</sub>), 126.50 (C<sub>4</sub>), 111.01 (C<sub>2</sub>), 54.04 (CH<sub>3</sub>); *m/z* (ESI) 214.1 (M<sup>+</sup> + 1).

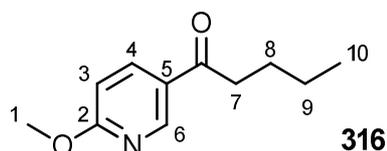
*Cyclohexyl(6-methoxypyridin-3-yl)methanone, 318.*



Under nitrogen, cyclohexyl magnesium bromide (1 M solution in Et<sub>2</sub>O, 1.5 cm<sup>3</sup>, 1.5 mmol) was added to a solution of *N*,6-dimethoxy-*N*-methylpyridine-3-carboxamide, **305** (200 mg, 1.02 mmol) in THF (1.9 cm<sup>3</sup>) and the solution was stirred at room temperature for 5 min. The solution was stirred at 70 °C for 2.5 h, before the solution was concentrated under reduced pressure and HCl (2 M, 5 cm<sup>3</sup>) was added. Following extraction with DCM (5 x 10 cm<sup>3</sup>), the organic extracts were washed with brine (10 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure and purified by column chromatography (petroleum ether – ethyl acetate 1:9), to give product **318** (51 mg, 0.233 mmol, 23 % yield) as an oil; (found (ESI): M<sup>+</sup> + H, 220.1331.

$C_{13}H_{18}NO_2$  requires M, 220.1332);  $\nu_{\max}$  2926 (alkyl CH st.), 2853 (alkyl CH st.), 1677 (C=O st.), 1600 (C=C st.), 1565 (C=C st.), 1494 (C=C st.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 8.79 (1 H, d,  $J$  2.2, H<sub>5</sub>), 8.14 (1 H, dd,  $J$  8.8, 2.2, H<sub>3</sub>), 6.79 (1 H, d,  $J$  8.8, H<sub>2</sub>), 4.01 (3 H, s,  $CH_3$ ), 3.16 (1 H, tt,  $J$  11.3, 3.3, H<sub>6</sub>), 1.94 - 1.79 (4 H, m, H<sub>7</sub>), 1.60 - 1.18 (6 H, m, H<sub>8,9</sub>);  $\delta_C$  (101 MHz,  $CDCl_3$ ) 201.46 (CO), 166.51 (C<sub>1</sub>), 148.90 (C<sub>5</sub>), 138.52 (C<sub>3</sub>), 125.72 (C<sub>4</sub>), 111.13 (C<sub>2</sub>), 53.94 (CH<sub>3</sub>), 45.71 (C<sub>6</sub>), 33.32 (C<sub>7</sub>), 29.33 (C<sub>8</sub>), 25.85 (C<sub>9</sub>);  $m/z$  (ESI) 219.9 ( $M^+ + 1$ ).

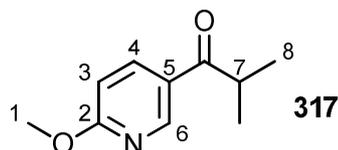
*1-(4-Methoxyphenyl)pentan-1-one, 316.*



Under nitrogen, *n*-butyl magnesium bromide (2 M solution in THF, 0.77  $cm^3$ , 1.54 mmol) was added to a solution of *N*,6-dimethoxy-*N*-methylpyridine-3-carboxamide, **305** (200 mg, 1.02 mmol) in THF (1.15  $cm^3$ ) and the solution was stirred at room temperature for 18 h before HCl (2 M, 3  $cm^3$ ) was added. Following extraction with DCM (3 x 5  $cm^3$ ), the organic extracts were washed with brine (5  $cm^3$ ), dried ( $MgSO_4$ ), concentrated under reduced pressure and purified by column chromatography (petroleum ether – ethyl acetate 1:9), to give product **316** (107 mg, 0.554 mmol, 54 % yield) as a colourless oil; (found (ESI):  $M^+ + H$ , 194.1172.  $C_{11}H_{16}NO_2$  requires M, 194.1176);  $\nu_{\max}$  2955 (alkyl CH st.), 2872 (alkyl CH st.), 1678 (C=O st.), 1593 (C=C st.), 1562 (C=C st.), 1493 (C=C st.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 8.79 (1 H, d,  $J$  2.4, H<sub>3</sub>), 8.14 (1 H, dd,  $J$  8.7, 2.4, H<sub>1</sub>), 6.79 (1 H, d,  $J$  8.7, H<sub>2</sub>), 4.00 (3 H, s, H<sub>8</sub>), 2.91 (2 H, t,  $J$  7.7, H<sub>4</sub>), 1.72 (2 H, quin,  $J$  7.7, H<sub>5</sub>), 1.40 (2 H, sxt,  $J$  7.7, H<sub>6</sub>), 0.96 (3 H, t,  $J$  7.7, H<sub>7</sub>);  $\delta_C$  (101 MHz,  $CDCl_3$ ) 198.22 (CO), 166.59

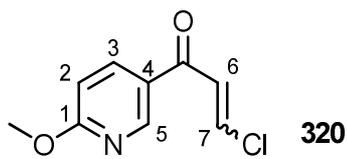
(C<sub>2</sub>), 148.90 (C<sub>6</sub>), 138.12 (C<sub>4</sub>), 126.73 (C<sub>5</sub>), 111.06 (C<sub>3</sub>), 53.96 (C<sub>1</sub>), 38.15 (C<sub>7</sub>), 26.45 (C<sub>8</sub>), 22.43 (C<sub>9</sub>), 13.85 (C<sub>10</sub>); *m/z* (ESI) 193.9 (M<sup>+</sup> + 1).

*1-(6-Methoxypyridin-3-yl)-2-methylpropan-1-one, 317.*



Under nitrogen, isopropyl magnesium bromide (2 M solution in THF, 0.77 cm<sup>3</sup>, 1.54 mmol) was added to a solution of *N*,6-dimethoxy-*N*-methylpyridine-3-carboxamide, **305** (200 mg, 1.02 mmol) in THF (1.53 cm<sup>3</sup>) and the solution was stirred at room temperature for 18 h before the solution was concentrated under reduced pressure and HCl (2 M, 5 cm<sup>3</sup>) was added. Following extraction with DCM (5 x 10 cm<sup>3</sup>), the organic extracts were washed with brine (5 cm<sup>3</sup>), dried (MgSO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (petroleum ether – ethyl acetate 15:85), to give ketone **317** (30 mg, 0.168 mmol, 16 % yield) as an oil; (found (ESI): M<sup>+</sup> + H, 180.1017. C<sub>10</sub>H<sub>14</sub>NO<sub>2</sub> requires M, 180.1019);  $\nu_{\max}$  2973 (alkyl CH st.), 2944 (alkyl CH st.), 1679 (C=O st.), 1601 (C=C st.), 1562 (C=C st.), 1493 (C=C st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.80 (1 H, d, *J* 2.5, H<sub>6</sub>), 8.15 (1 H, dd, *J* 8.8, 2.5, H<sub>3</sub>), 6.80 (1 H, d, *J* 8.8, H<sub>4</sub>), 4.02 (3 H, s, H<sub>1</sub>), 3.46 (1 H, spt, *J* 7.0, H<sub>7</sub>), 1.22 (6 H, d, *J* 7.0, H<sub>8</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 202.18 (CO), 166.59 (C<sub>2</sub>), 148.98 (C<sub>6</sub>), 138.60 (C<sub>4</sub>), 125.66 (C<sub>5</sub>), 111.21 (C<sub>3</sub>), 54.00 (C<sub>1</sub>), 35.43 (C<sub>7</sub>), 19.06 (C<sub>8</sub>); *m/z* (ESI) 180.1 (M<sup>+</sup> + 1).

*3-Chloro-1-(6-methoxypyridin-3-yl)prop-2-en-1-one, 320.*



Under nitrogen, ethynyl magnesium bromide (0.5 M solution in THF, 1.53 cm<sup>3</sup>, 0.765 mmol) was added to *N*,6-dimethoxy-*N*-methylpyridine-3-carboxamide, **305** (100 mg, 0.510 mmol) and the solution was stirred at room temperature for 5 min. The solution was stirred at 70 °C for 1 h before the solution was concentrated under reduced pressure and HCl (2 M, 5 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 5 cm<sup>3</sup>), the organic extracts were washed with brine (10 cm<sup>3</sup>), dried (MgSO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (petroleum ether – ethyl acetate 9:1), to give the isomers (*Z/E* = 2.7:1, as determined by <sup>1</sup>H NMR of the crude reaction mixture) (*E*)-**320** (21 mg, 0.107 mmol, 21 %) and (*Z*)-**320** (32 mg, 0.162 mmol, 32 %) as a colourless solids; (*E*)-**320**: Mp 82-84 °C; (found (ESI): M<sup>+</sup> + Na, 220.0136. C<sub>9</sub>H<sub>8</sub><sup>35</sup>ClNNaO<sub>2</sub> requires M, 220.0136); ν<sub>max</sub> 3075 (alkene CH st.), 1652 (C=O st.), 1608 (C=C st.), 1581 (C=C st.), 1504 (C=C st.), 1497 (C=C st.) cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 8.69 (1 H, d, *J* 2.5, H<sub>5</sub>), 8.07 (1 H, dd, *J* 8.6, 2.5, H<sub>3</sub>), 7.41 (1 H, d, *J* 13.3, H<sub>7</sub>), 7.19 (1 H, d, *J* 13.3, H<sub>6</sub>), 6.75 (1 H, d, *J* 8.6, H<sub>2</sub>), 3.95 (3 H, s, CH<sub>3</sub>); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 185.57 (CO), 167.04 (C<sub>1</sub>), 149.43 (C<sub>5</sub>), 138.52 (C<sub>3</sub>), 138.24 (C<sub>7</sub>), 127.81 (C<sub>6</sub>), 126.47 (C<sub>4</sub>), 111.54 (C<sub>2</sub>), 54.16 (CH<sub>3</sub>); *m/z* (ESI) 197.8 (M[<sup>35</sup>Cl]<sup>+</sup> + 1), 199.8 (M[<sup>37</sup>Cl]<sup>+</sup> + 1). (*Z*)-**320**: Mp 120-122 °C; (found (ESI): M<sup>+</sup> + Na, 220.0144. C<sub>9</sub>H<sub>8</sub><sup>35</sup>ClNNaO<sub>2</sub> requires M, 220.0136); ν<sub>max</sub> 3069 (alkene CH st.), 1658 (C=O st.), 1603 (C=C st.), 1580 (C=C st.), 1564 (C=C st.), 1498 (C=C st.) cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 8.75 (1 H, d, *J* 2.5, H<sub>5</sub>), 8.16 (1 H, dd, *J* 8.8, 2.5, H<sub>2</sub>), 6.93 (1 H, d, *J* 8.3, H<sub>5</sub>), 6.82 (1 H, d, *J* 8.8, H<sub>1</sub>), 6.77 (1 H, d, *J* 8.3, H<sub>4</sub>), 4.02 (3 H, s, CH<sub>3</sub>); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 187.25 (CO), 166.98 (C<sub>1</sub>), 149.92 (C<sub>5</sub>),

138.46 (C<sub>3</sub>), 129.21 (C<sub>7</sub>), 126.73 (C<sub>4</sub>), 125.84 (C<sub>6</sub>), 111.47 (C<sub>2</sub>), 54.20 (CH<sub>3</sub>); *m/z* (ESI) 197.7 (M[<sup>35</sup>Cl]<sup>+</sup> +1), 199.8 (M[<sup>35</sup>Cl]<sup>+</sup> + 1).

*Section 3.5.2: ATH of Ketones.*

*General procedure for the ATH of ketones.*

All ketones in the following section were asymmetrically reduced using the following general procedure: Under nitrogen, FA/TEA (5:2, concentration w/r to ketone as specified) was added to a mixture of the ketone (1 mmol) and [Ru(*teth*-TsDPEN)Cl] (1 mol %). The solution was left stirring at 45 °C for the specified time before the product was obtained, following removal of the catalyst (the reaction mixture directly through a plug of silica gel using ethyl acetate - petroleum ether (1:1) as eluent). Conversion was primarily determined by <sup>1</sup>H NMR. Ee was determined by chiral GC or HPLC via direct analysis, or alternatively indirectly via acetate derivatisation of the product.

*General procedure for the preparation of acetate derivatives.*

All acetate derivatives of alcohols obtained from asymmetric ketone reduction, and of alcohols used as racemic standards were prepared using the following general procedure, for subsequent chiral analysis by GC or HPLC. A solution of acetic anhydride (1 drop), the alcohol (10 mg) and DMAP (1 mg) in DCM (1 cm<sup>3</sup>) was stirred at room temperature for 18 h. Following concentration under reduced pressure and purification by column chromatography, the product was obtained. The product was used directly in subsequent GC or HPLC analysis.

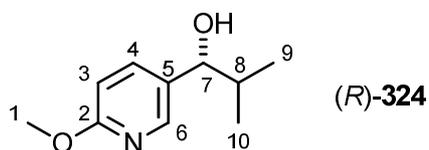
*General procedure for the formation of racemic standards: reduction of ketones with NaBH<sub>4</sub>.*

Racemic standards for the determination of the ee of asymmetrically reduced ketones were prepared (unless otherwise specified) via reduction with NaBH<sub>4</sub>, using the following procedure: Under nitrogen, NaBH<sub>4</sub> (1.1 mmol) was added to a solution of the ketone (1 mmol) in methanol and the solution was stirred at room temperature until the reaction reached completion. Saturated aqueous hydrogen carbonate was then added. Following extraction with DCM (3 x 5 cm<sup>3</sup>) the organic extracts were dried (MgSO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (ethyl acetate – petroleum ether 1:1), to give the product. The sample was directly used as a racemic standard for chiral GC or HPLC analysis.

In some cases this was not appropriate. Instead, two samples of the alcohol formed from opposite isomers of the catalyst respectively were equally combined. This approximately racemic sample was then used as a racemic standard for subsequent chiral GC or HPLC analysis of asymmetrically formed alcohols.

*ATH of ketones.*

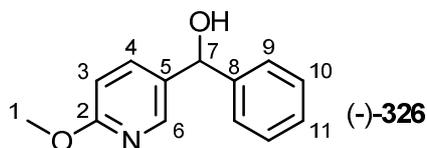
*(R)*-1-(6-Methoxypyridin-3-yl)-2-methylpropan-1-ol, **(R)**-324.



This compound was prepared following the general procedure for ketone transfer hydrogenation, using 1-(6-methoxypyridin-3-yl)-2-methylpropan-1-one, **317** (11.3 mg, 6.31 x 10<sup>-2</sup> mmol), Ru(*R,R*)*teth*-TsDPEN (0.4 mg, 6.45 x 10<sup>-4</sup> mmol) in FA/TEA

(32  $\mu$ L, 2M), following a reaction time of 22 h. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – hexane 1:1), product (*R*)-**324** (6.9 mg, 0.038 mmol, 60 % yield) was obtained as colourless oil;  $[\alpha]_D^{21} + 23.2$  ( $c$ 0.35 in  $\text{CHCl}_3$ ) 53 % ee; (found (ESI):  $\text{M}^+ + \text{H}$ , 182.1176.  $\text{C}_{10}\text{H}_{16}\text{NO}_2$  requires  $\text{M}$ , 182.1176);  $\nu_{\text{max}}$  3398 (OH st.), 1609 (C=C st.), 1575 (C=C st.), 1493 (C=C st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 8.05 (1 H, d,  $J$  2.4,  $\text{H}_6$ ), 7.57 (1 H, dd,  $J$  8.6, 2.4,  $\text{H}_4$ ), 6.74 (1 H, d,  $J$  8.6,  $\text{H}_3$ ), 4.34 (1 H, d,  $J$  6.9,  $\text{H}_7$ ), 3.93 (3 H, s,  $\text{H}_1$ ), 1.94 (1 H, oct,  $J$  6.9,  $\text{H}_8$ ), 1.02 (3 H, d,  $J$  6.9,  $\text{H}_9$ ), 0.79 (3 H, d,  $J$  6.9,  $\text{H}_{10}$ );  $\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 163.85 ( $\text{C}_2$ ), 150.22 ( $\text{C}_6$ ), 145.18 ( $\text{C}_4$ ), 137.00 ( $\text{C}_5$ ), 110.53 ( $\text{C}_3$ ), 77.65 ( $\text{C}_1$ ), 53.42 ( $\text{C}_7$ ), 35.15 ( $\text{C}_8$ ), 18.72 ( $\text{C}_9$ ), 18.37 ( $\text{C}_{10}$ );  $m/z$  (ESI) 181.9 ( $\text{M}^+ + 1$ ); Enantiomeric separation was determined by GC analysis (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25  $\mu\text{m}$ , gas: He,  $T = 140$   $^\circ\text{C}$ ,  $P = 18$  psi He, det = 220  $^\circ\text{C}$ , inj = 220  $^\circ\text{C}$ , major isomer 21.54 min., minor isomer 22.56 min.) 53 % ee (*R*). The absolute configuration was assigned analogy with the expected outcome of the theoretical model.

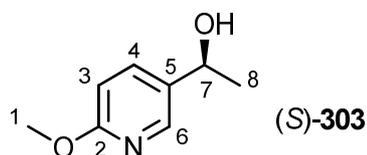
(6-Methoxypyridin-3-yl)(phenyl)methanol, (-)-**326**.



This compound has been reported but not fully characterised.<sup>205</sup> This compound was prepared following the general procedure for ketone transfer hydrogenation, using (6-methoxypyridin-3-yl)(phenyl)methanone, **319** (15 mg, 0.070 mmol) and  $\text{Ru}(\text{R,R})\text{teth-TsDPEN}$  (0.4 mg,  $6.45 \times 10^{-4}$  mmol) in FA/TEA (58  $\mu\text{L}$ , 2M), following a reaction time of 24 h. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – petroleum ether 1:1),

product (-)-**326** (10 mg, 0.046 mmol, 66 % yield) was obtained as colourless oil;  $[\alpha]_D^{20} - 9.8$  ( $c$ 0.365 in  $\text{CHCl}_3$ ) 48 % ee (lit.<sup>205</sup>  $[\alpha]_D^{22} - 26.2$  ( $c$ 0.26,  $\text{CHCl}_3$ ) 96.0 % ee); (found (ESI):  $\text{M}^+ + \text{H}$ , 216.1019.  $\text{C}_{13}\text{H}_{14}\text{NO}_2$  requires  $\text{M}$ , 216.1019);  $\nu_{\text{max}}$  3340 (OH st.) 1607 (C=C st.), 1573 (C=C st.), 1491 (C=C st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 8.13 (1 H, d,  $J$  2.5,  $\text{H}_6$ ), 7.54 (1 H, dd,  $J$  8.3, 2.5,  $\text{H}_4$ ), 7.32 - 7.38 (3 H, m,  $\text{ArH}$ ), 7.26 - 7.30 (2 H, m,  $\text{ArH}$ ), 6.70 (1 H, d,  $J$  8.3,  $\text{H}_3$ ), 5.81 (1 H, d,  $J$  3.3,  $\text{H}_7$ ), 3.91 (3 H, s,  $\text{H}_1$ ), 2.47 (1 H, d,  $J$  3.5,  $\text{OH}$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 158.57 ( $\text{C}_2$ ), 145.13 ( $\text{C}_6$ ), 143.21 ( $\text{C}_5$ ), 137.38 ( $\text{C}_4$ ), 132.11 ( $\text{C}_8$ ), 128.62 ( $\text{C}_9$ ), 127.77 ( $\text{C}_{10}$ ), 126.26 ( $\text{C}_{11}$ ), 110.94 ( $\text{C}_3$ ), 73.81 ( $\text{C}_7$ ), 53.47 ( $\text{C}_1$ );  $m/z$  (ESI) 216.1 ( $\text{M}^+ + 1$ ), 238.1 ( $\text{M}^+ + 23$ ). Enantiomeric separation was achieved by HPLC analysis (Chiralpak IC, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min,  $T = 30$  °C, minor isomer 12.2 min, major isomer 14.9 min.) 48 % ee.

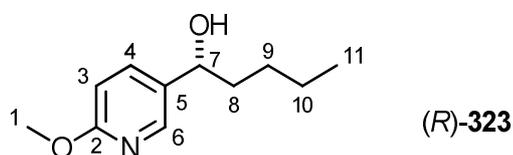
(*S*)-1-(6-Methoxypyridin-3-yl)ethanol, (*S*)-**303**.



This compound has been reported but not fully characterised.<sup>206</sup> This compound was prepared following the general procedure for ketone transfer hydrogenation, using 1-(6-methoxypyridin-3-yl)ethanone, **4** (30 mg, 0.199 mmol) and  $\text{Ru}(\text{S,S})\text{teth-TsDPEN}$  (1.2 mg,  $1.93 \times 10^{-3}$  mmol) in FA/TEA (199  $\mu\text{L}$ , 1 M), following a reaction time of 22 h. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – hexane 1:1), product (*S*)-**303** (21 mg, 0.137 mmol, 69 % yield) was obtained as colourless oil;  $[\alpha]_D^{15} - 42.4$  ( $c$ 1.05 in  $\text{CHCl}_3$ ) 82 % ee (lit.<sup>206</sup>  $[\alpha]_D^{23} + 33.7$  ( $c$ 2.70,  $\text{CHCl}_3$ ) 98.0 % ee (*R*)); (found (ESI):  $\text{M}^+ + \text{H}$ , 154.0861.  $\text{C}_8\text{H}_{12}\text{NO}_2$  requires  $\text{M}$ , 154.0863);  $\nu_{\text{max}}$  3300 (OH st.), 1607 (C=C st.), 1574 (C=C

st.), 1492 (C=C st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz, DMSO) 8.09 (1 H, d,  $J$  2.5, H<sub>6</sub>), 7.66 (1 H, dd,  $J$  8.5, 2.5, H<sub>4</sub>), 6.76 (1 H, d,  $J$  8.5, H<sub>3</sub>), 5.12 (1 H, d,  $J$  4.5, OH), 4.76 – 4.65 (1 H, qd,  $J$  6.5, 4.5, H<sub>7</sub>), 3.82 (3 H, s, H<sub>1</sub>), 1.32 (3 H, d,  $J$  6.5, H<sub>8</sub>);  $\delta_{\text{C}}$  (101 MHz, DMSO) 162.55 (C<sub>2</sub>), 143.74 (C<sub>6</sub>), 136.62 (C<sub>4</sub>), 135.32 (C<sub>5</sub>), 109.84 (C<sub>3</sub>), 65.60 (C<sub>1</sub>), 52.91 (C<sub>7</sub>), 25.41 (C<sub>8</sub>);  $m/z$  (ESI) 154.0 ( $\text{M}^+ + 1$ ), 176.0 ( $\text{M}^+ + 23$ ). Enantiomeric separation was determined by GC analysis of the acetate derivative: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25  $\mu\text{m}$ , gas: He, T = 170 °C, P = 18 psi He, det = 250 °C, inj = 220 °C, *S* (major) isomer 3.82 min., *R* (minor) isomer 3.95 min.) 82 % ee (*S*). The configuration was primarily assigned by comparison the reported optical rotation. This was also in agreement with that expected from the theoretical model. This characterisation data was in agreement with the literature.

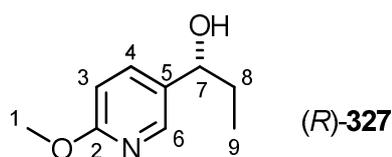
(*R*)-1-(6-Methoxypyridin-3-yl)pentan-1-ol, (*R*)-**323**.



This compound was prepared following the general procedure for ketone transfer hydrogenation, using 1-(4-methoxyphenyl)pentan-1-one, **316** (30 mg, 0.155 mmol) and Ru(*R,R*)-*teth*-TsDPEN (1.0 mg,  $1.61 \times 10^{-3}$  mmol) in FA/TEA (78  $\mu\text{L}$ , 2M), following a reaction time of 20 h. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – hexane 1:1), product (*R*)-**323** (15 mg, 0.077 mmol, 50 % yield) was obtained as colourless oil;  $[\alpha]_{\text{D}}^{22} + 28.5$  ( $c$  0.61 in  $\text{CHCl}_3$ ) 76 % ee; (found (ESI):  $\text{M}^+ + \text{H}$ , 196.1329.  $\text{C}_{11}\text{H}_{18}\text{NO}_2$  requires M, 196.1332);  $\nu_{\text{max}}$  3339 (OH st.), 2931 (alkyl CH st.), 2859 (alkyl CH st.), 1607 (C=C st.), 1573 (C=C st.), 1491 (C=C st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 8.09 (1 H, d,  $J$  2.3, H<sub>3</sub>), 7.61 (1 H, dd,  $J$  8.7, 2.3, H<sub>2</sub>), 6.75 (1 H, d,  $J$  8.7, H<sub>1</sub>), 4.64 (1 H, td,  $J$

6.7, 3.2, H<sub>4</sub>), 3.93 (3 H, s, CH<sub>3</sub>), 1.90 - 1.76 (2 H, m, H<sub>5A</sub>, OH), 1.78 - 1.63 (2 H, m, H<sub>5B</sub>), 1.47 - 1.17 (4 H, m, H<sub>6-7</sub>), 0.93 - 0.85 (3 H, m, H<sub>8</sub>);  $\delta_C$  (101 MHz, CDCl<sub>3</sub>) 163.81 (C<sub>2</sub>), 144.69 (C<sub>6</sub>), 136.62 (C<sub>4</sub>), 132.77 (C<sub>5</sub>), 110.89 (C<sub>3</sub>), 72.07 (C<sub>1</sub>), 53.43 (C<sub>7</sub>), 38.44 (C<sub>8</sub>), 27.85 (C<sub>9</sub>), 22.51 (C<sub>10</sub>), 13.96 (C<sub>11</sub>);  $m/z$  (ESI) 195.9 (M<sup>+</sup> + 1). Enantiomeric separation was determined by GC analysis for the acetate derivative: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25  $\mu$ m, gas: He, T = 140 °C, P = 18 psi He, det = 220 °C, inj = 220 °C, major isomer 21.30 min., minor isomer 22.33 min.) 76 % ee (*R*). The absolute configuration was assigned analogy with the expected outcome of the theoretical model.

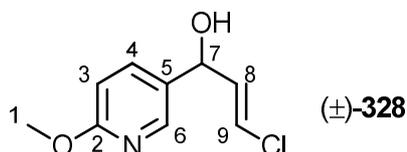
*(R)*-1-(6-Methoxypyridin-3-yl)propan-1-ol, (*R*)-**327**.



This compound was prepared following the general procedure (C) for ketone transfer hydrogenation, using (*2E*)-3-chloro-1-(6-methoxypyridin-3-yl)prop-2-en-1-one, (*E*)-**320** (7 mg, 3.55 x 10<sup>-2</sup> mmol) and Ru(*R,R*)*teth*-TsDPEN (0.2 mg, 3.22 x 10<sup>-4</sup> mmol) in FA/TEA (18  $\mu$ L, 2M), following a reaction time of 24 h. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – hexane 1:1), product (*R*)-**327** (8 mg, 4.79 x 10<sup>-2</sup> mmol) was obtained as colourless oil; (found (ESI): M<sup>+</sup> + H, 168.1021. C<sub>9</sub>H<sub>14</sub>NO<sub>2</sub> requires M, 168.1019);  $\nu_{\max}$  3325 (OH st.), 1607 (C=C st.), 1574 (C=C st.), 1492 (C=C st.) cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 8.01 (1 H, d, *J* 2.3, H<sub>3</sub>), 7.53 (1 H, dd, *J* 8.5, 2.3, H<sub>2</sub>), 6.67 (1 H, d, *J* 8.5, H<sub>1</sub>), 4.50 (1 H, t, *J* 7.1, H<sub>4</sub>), 3.86 (3 H, s, CH<sub>3</sub>), 1.81 - 1.61 (2 H, m, H<sub>5</sub>), 0.84 (2 H, t, *J* 7.1, H<sub>6</sub>);  $\delta_C$  (101 MHz, CDCl<sub>3</sub>) 160.98 (C<sub>2</sub>), 144.77 (C<sub>6</sub>), 136.64 (C<sub>4</sub>), 132.43 (C<sub>5</sub>), 110.88 (C<sub>3</sub>), 73.46 (C<sub>1</sub>), 53.44 (C<sub>7</sub>), 31.60 (C<sub>8</sub>), 10.02 (C<sub>9</sub>). The ee of this sample was not

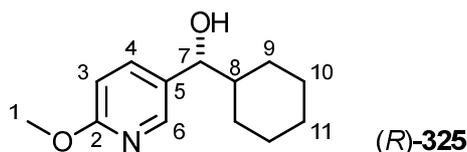
determined due to time constraints. The absolute configuration was assigned analogy with the expected outcome of the theoretical model.

*Cyclohexyl(6-methoxypyridin-3-yl)methanol, (±)-328.*



This compound was prepared following the general procedure for the reduction of ketones with NaBH<sub>4</sub>, using (2E)-3-chloro-1-(6-methoxypyridin-3-yl)prop-2-en-1-one, *E*-**320** (5 mg, 2.54 x 10<sup>-2</sup> mmol) and NaBH<sub>4</sub> (1 mg, 2.64 x 10<sup>-2</sup> mmol) in methanol (1 cm<sup>3</sup>) following a reaction time of 3½ h. Following concentration under reduced pressure, product (±)-**328** (4.2 mg, 2.11 x 10<sup>-2</sup> mmol, 80 %) was obtained as colourless oil; (found (ESI): M<sup>+</sup> + H, 200.0476. C<sub>9</sub>H<sub>11</sub><sup>35</sup>ClNO<sub>2</sub> requires M, 200.0473); ν<sub>max</sub> 3348 (OH st.), 1608 (C=C st.), 1574 (C=C st.), 1493 (C=C st.) cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 8.05 (1 H, s, H<sub>6</sub>), 7.52 (1 H, dd, *J* 8.5, 2.3, H<sub>4</sub>), 6.69 (1 H, d, *J* 8.8, H<sub>3</sub>), 6.29 (1 H, d, *J* 13.3, H<sub>9</sub>), 6.04 (1 H, dd, *J* 13.3, 6.3, H<sub>8</sub>), 5.17 (1 H, d, *J* 5.8, H<sub>7</sub>), 3.91 - 3.82 (3 H, m, H<sub>1</sub>), 1.97 (1 H, s, OH); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 164.18 (C<sub>2</sub>), 145.08 (C<sub>6</sub>), 137.02 (C<sub>4</sub>), 134.78 (C<sub>9</sub>), 129.85 (C<sub>5</sub>), 120.73 (C<sub>8</sub>), 111.20 (C<sub>3</sub>), 70.85 (C<sub>1</sub>), 53.57 (C<sub>7</sub>); *m/z* (ESI) 200.0 (M<sup>+</sup>[<sup>35</sup>Cl]<sup>+</sup> + 1), 202.0 (M<sup>+</sup>[<sup>37</sup>Cl]<sup>+</sup> + 1).

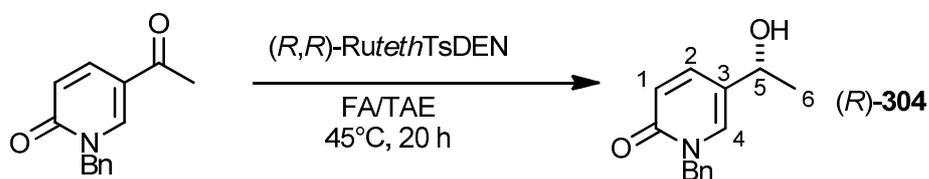
*(R)-Cyclohexyl(6-methoxypyridin-3-yl)methanol, (R)-325.*



This compound was prepared following the general procedure for ketone transfer hydrogenation, using cyclohexyl(6-methoxypyridin-3-yl)methanone **318** (26 mg,

0.119 mmol) and Ru(*R,R*)-*teth*-TsDPEN (0.7 mg,  $1.13 \times 10^{-3}$  mmol) in FA/TEA (58  $\mu$ L, 2M), following a reaction time of 24 h. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate – hexane 1:1), product (*R*)-**325** (27 mg, 0.122 mmol) was obtained as colourless oil;  $[\alpha]_D^{21} + 18.2$  ( $c$  0.70 in  $\text{CHCl}_3$ ) 35 % ee; (found (ESI):  $\text{M}^+ + \text{H}$ , 220.1490.  $\text{C}_{13}\text{H}_{20}\text{NO}_2$  requires  $\text{M}$ , 220.1489);  $\nu_{\text{max}}$  3335 (OH st.), 2922 (alkyl CH st.), 2850 (alkyl CH st.), 1606 (C=C st.), 1573 (C=C st.), 1492 (C=C st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 8.03 (1 H, d,  $J$  2.4,  $\text{H}_6$ ), 7.56 (1 H, dd,  $J$  8.5, 2.4,  $\text{H}_4$ ), 6.74 (1 H, d,  $J$  8.5,  $\text{H}_3$ ), 4.34 (1 H, dd,  $J$  7.3, 3.0,  $\text{H}_7$ ), 3.93 (3 H, s,  $\text{H}_1$ ), 1.87 (1 H, bs, OH), 1.83 - 1.73 (1 H, m,  $\text{H}_8$ ), 1.73 - 1.53 (4 H, m,  $\text{H}_9$ ), 1.32 - 0.82 (6 H, m,  $\text{H}_{10-11}$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 163.69 ( $\text{C}_2$ ), 145.16 ( $\text{C}_6$ ), 137.10 ( $\text{C}_4$ ), 131.55 ( $\text{C}_5$ ), 110.64 ( $\text{C}_3$ ), 76.65 ( $\text{C}_1$ ), 53.38 ( $\text{C}_7$ ), 44.71 ( $\text{C}_8$ ), 29.00 ( $\text{C}_9$ ), 26.30 ( $\text{C}_{10}$ ), 25.92 ( $\text{C}_{11}$ );  $m/z$  (ESI) 220.1 ( $\text{M}^+ + 1$ ). Enantiomeric separation was determined by HPLC analysis of the acetate derivative: (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 98 : 2, 0.5 mL/min,  $T = 28^\circ\text{C}$ , 13.0 min, 17.2 min.) 35 % ee (*R*). The absolute configuration was assigned analogy with the expected outcome of the theoretical model.

*1-Benzyl-5-(1-hydroxyethyl)piperidin-2-one*, (*R*)-**304**.



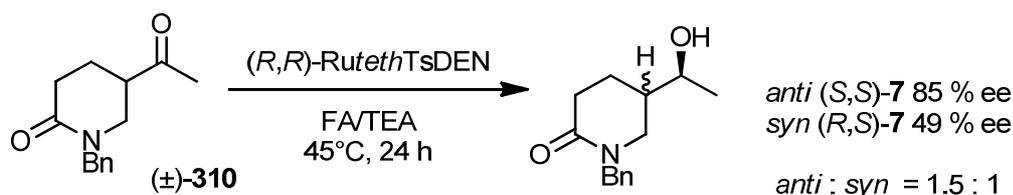
This compound was prepared following the general procedure (C) for ketone transfer hydrogenation, using 5-acetyl-1-benzylpyridin-2(1H)-one, **309** (45 mg, 0.198 mmol) and Ru(*R,R*)-*teth*-TsDPEN (1.2 mg,  $1.93 \times 10^{-3}$  mmol) in FA/TEA (198  $\mu$ L, 1M), following a reaction time of 20 h. Following concentration under reduced pressure

and purification by column chromatography (ethyl acetate – hexane 9:1), product (*R*)-**304** (17 mg, 0.074 mmol, 37 %) was obtained as colourless oil;  $[\alpha]_{\text{D}}^{22} + 3.6$  (*c*0.35 in CHCl<sub>3</sub>) 42 % ee; (found (ESI): M<sup>+</sup> + Na, 252.0995. C<sub>14</sub>H<sub>15</sub>NNaO<sub>2</sub> requires M, 252.0995);  $\nu_{\text{max}}$  3356 (OH st.), 1661 (C=O st.), 1578 (C=C st.), 1542 (C=C st.), 1497 (C=C st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz,) 7.41 - 7.22 (7 H, m, ArH, H<sub>2</sub>, H<sub>4</sub>), 6.60 (1 H, d, *J* 9.5, H<sub>1</sub>), 5.05 - 5.17 (2 H, s, CH<sub>2</sub>), 4.63 (1 H, q, *J* 6.2, H<sub>5</sub>), 2.02 - 2.11 (1 H, bs, OH), 1.40 (3 H, d, *J* 6.2, H<sub>6</sub>);  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>) 162.43 (CO), 138.30 (C<sub>4</sub>), 136.21 (Ar), 133.70 (C<sub>2</sub>), 128.80 (Ar), 128.01 (Ar), 127.96 (Ar), 124.30 (C<sub>1</sub>), 120.89 (C<sub>3</sub>), 66.76 (CH<sub>2</sub>Ph), 52.10 (C<sub>5</sub>), 24.14 (C<sub>6</sub>); *m/z* (ESI) 229.8 (M<sup>+</sup> +1). Enantiomeric separation was determined by HPLC analysis of the acetate derivative: (Chiralpak IC, 4.6 mm x 250 mm, hexane : IPA 80 : 20, 1.0 mL/min, T = 30 °C, *S* (minor) isomer 41.0 min, *R* (major) isomer 44.3 min.) 42 % ee. The configuration was determined by comparison of the optical rotation of a sample of (*R*)-**304**, formed from (*R*)-**303**. The synthesis of this compound is in the following section.

*AH of 1-benzyl-5-(1-hydroxyethyl)pyridin-2(1H)-one, 304.*

The AH catalyst screen of 1-benzyl-5-(1-hydroxyethyl)-pyridin-2(1H)-one **304** was carried out using the general procedure for alkene hydrogenation. Conversions were determined by <sup>1</sup>H NMR.

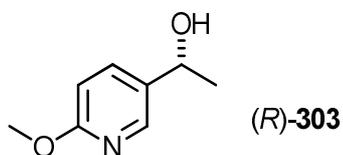
*1-Benzyl-5-(1-hydroxyethyl)pyridin-2(1H)-one, 7.*



This compound was prepared following the general procedure for ketone transfer hydrogenation, using 5-acetyl-1-benzylpiperidin-2-one ( $\pm$ )-**310** (7.5 mg, 0.032 mmol) and Ru(*R,R*)-*teth*-TsDPEN (0.2 mg,  $3.22 \times 10^{-4}$  mmol) in FA/TEA (32  $\mu$ L, 1M), following a reaction time of 24 h. Following concentration under reduced pressure and removal of the catalyst by column chromatography (ethyl acetate – hexane 9:1), a mixture containing diastereomers (*anti* / *syn* = 1.39:1, as determined by GC) (D1)-**7a** and (D2)-**7b** (10 mg, 0.043 mmol) was obtained as a colourless oil. No separation of the diastereomers was attempted. De and ee was determined by GC analysis of the isolated mixture of diastereomers: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25  $\mu$ m, gas: He, T = 200  $^\circ$ C, P = 18 psi He, det = 220  $^\circ$ C, inj = 220  $^\circ$ C, (*S,R*) (minor) isomer 24.70 min., (*R,S*) (major) isomer 25.25 min., (*S,S*) (major) isomer 25.83 min., (*R,R*) (minor) isomer 26.19 min.) 20 % de; (*R,S*), 85 % ee; (*S,S*), 49 % ee. Full characterisation of the isomers **7a** and **7b** is detailed in the next section. Assignments of absolute and relative configurations were made through comparison of the GC traces of two enantiomerically enriched samples of (*R,R*)-**7b** and (*S,R*)-**7a**. Racemic samples of D2-**7b** and D1-**7a** prepared through the procedure shown in the next section were used as racemic standards during chiral GC analysis.

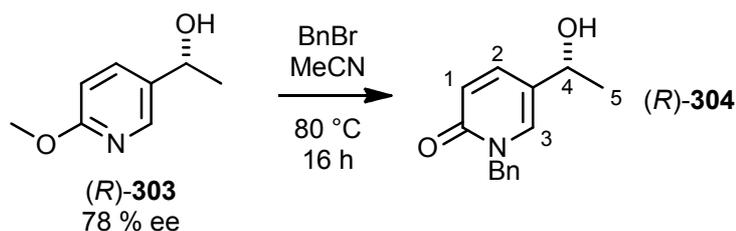
Section 3.5.3: Asymmetric Synthesis of Diastereomers **7a** and **7b**.

(*R*)-1-(6-Methoxypyridin-3-yl)ethanol, (*R*)-**303**.



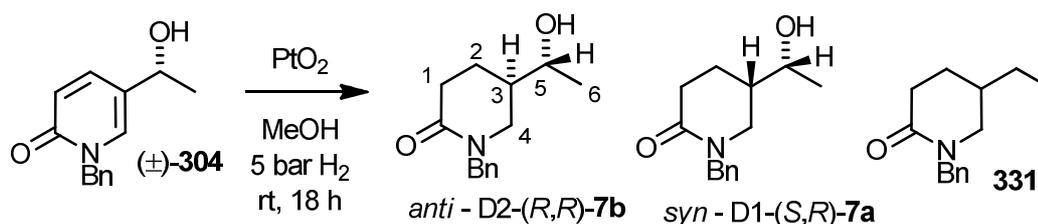
This procedure was used for the large scale asymmetric reduction of 1-(6-methoxypyridin-3-yl)ethanone **4**. Under nitrogen, FA/TEA (5:2, 9.93 cm<sup>3</sup>, 1M) was added to 1-(6-methoxypyridin-3-yl)ethanone, **4** (1.00 g, 6.62 mmol). Dissolution was aided by gently heating the mixture at 45 °C. The mixture was then allowed to cool to room temperature for 30 min. Ru(*R,R*)*teth*-TsDPEN (41.0 mg, 6.61 x 10<sup>-2</sup> mmol) was added and the solution was left stirring at room temperature for 5 min. The mixture was heated to 45 °C and stirred for 24 h before saturated aqueous sodium hydrocarbonate (20 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 20 cm<sup>3</sup>), the solution was concentrated under reduced pressure and purified by column chromatography (petroleum ether – ethyl acetate 1:1), to give the product (*R*)-**303** (0.960 g, 6.27 mmol, 95 % yield) as an oil; [ $\alpha$ ]<sub>D</sub><sup>15</sup> + 27.8 (c 0.60 in CHCl<sub>3</sub>) 78 % ee (lit. [ $\alpha$ ]<sub>D</sub><sup>206</sup> + 33.7 (c 2.70, CHCl<sub>3</sub>) 98.0 % ee (*R*)); Enantiomeric separation was determined by GC analysis of the acetate derivative: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25  $\mu$ m, gas: He, T = 180 °C, P = 18 psi He, det = 250 °C, inj = 220 °C, *S* (minor) isomer 3.23 min., *R* (major) isomer 3.30 min.) 78 % ee. Full characterisation data was given in the previous section.

*1-Benzyl-5-(1-hydroxyethyl)pyridin-2(1H)-one, (R)-304.*



A solution of benzyl bromide (0.77 cm<sup>3</sup>, 1.12 g, 6.47 mmol) and (*R*)-1-(6-methoxypyridin-3-yl)ethanone **303** (78 % ee, 0.910 g, 5.94 mmol) in dry acetonitrile (14 cm<sup>3</sup>) was stirred at 80 °C for 16 d before the mixture was concentrated under reduced pressure and purified by column chromatography (ethyl acetate – petroleum ether 1:1 to 1:0), to give product (*R*)-**304** (0.852 g, 3.72 mmol, 63 % yield) as a colourless oil;  $[\alpha]_D^{20} + 15.4$  ( $c$ 1.40 in CHCl<sub>3</sub>). The ee was not determined at this point and it was assumed to be unchanged. Conditions for chiral HPLC separation and full characterisation data were given in the previous section.

*(5R)*-1-benzyl-5-[(1*R*)-1-hydroxyethyl]piperidin-2-one (*R,R*)-(D2)-**7b** and *(5S)*-1-benzyl-5-[(1*R*)-1-hydroxyethyl]piperidin-2-one, (*S,R*)-(D1)-**7a**.



These compounds were prepared following the general procedure for alkene hydrogenation, using *syn* - 1-benzyl-5-(1-hydroxyethyl)pyridin-2(1*H*)-one, (*R*)-**304** (78 % ee, 0.810 g, 3.54 mmol) and platinum oxide (40 mg, 0.176 mmol) following a reaction time of 18 h, at room temperature and 5 bar of hydrogen. Following concentration under reduced pressure and purification by column chromatography (1 to 3 % methanol – DCM, slow gravity elution), two diastereomerically enriched

samples of the isomers D2-(*R,R*)-**7b** and D1-(*S,R*)-**7a** were obtained: D1-(*S,R*)-**7a** (100 % *syn* as determined by GC) (165 mg, 0.708 mmol, 20 % yield) was obtained as a colourless oil which solidified upon standing; 110-112 °C;  $[\alpha]_D^{22} - 30.1$  ( $c$ 0.75 in CHCl<sub>3</sub>) 78 % ee; (found (ESI): M<sup>+</sup> + Na, 256.1306. C<sub>14</sub>H<sub>19</sub>NNaO<sub>2</sub> requires M, 256.1308);  $\nu_{\max}$  3354 (OH st.), 1614 (C=O st.) cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.36 - 7.20 (5 H, m, ArH), 4.60 (1 H, d, *J* 14.6, CH<sub>2</sub>), 4.56 (1 H, d, *J* 14.6, CH<sub>2</sub>), 3.61 (1 H, quin, *J* 6.4, H<sub>5</sub>), 3.40 (1 H, ddd, *J* 12.2, 5.1, 1.8, H<sub>4A</sub>), 3.10 (1 H, dd, *J* 12.2, 10.2, H<sub>4B</sub>), 2.54 (1 H, ddd, *J* 18.1, 5.5, 3.0, H<sub>1A</sub>), 2.41 (1 H, ddd, *J* 18.1, 11.5, 6.0, H<sub>1B</sub>), 1.98 (1 H, bs, OH), 1.87 - 1.71 (2 H, m, H<sub>2</sub>), 1.60 - 1.47 (1 H, m, H<sub>3</sub>), 1.20 (3 H, d, *J* 6.4, H<sub>6</sub>);  $\delta_C$  (101 MHz, CDCl<sub>3</sub>) 169.86 (CO), 136.91 (Ar), 128.39 (Ar), 127.78 (Ar), 127.17 (Ar), 68.91 (C<sub>5</sub>), 50.27 (CH<sub>2</sub>Ph), 49.39 (C<sub>4</sub>), 41.14 (C<sub>3</sub>), 31.27 (C<sub>1</sub>), 23.82 (C<sub>2</sub>), 21.14 (C<sub>6</sub>); *m/z* (ESI) 234.1 (M<sup>+</sup> + 1), 256.1 (M<sup>+</sup> + 23). Enantiomeric separation was determined by GC analysis: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 μm, gas: H, T = 185 °C, P = 18 psi H, det = 250 °C, inj = 220 °C, (*S,R*) (major) isomer 18.61 min., (*R,S*) (minor) isomer 19.24 min.) 78 % ee. A racemic sample of the diastereomer D1-**7a** was used as a racemic standard during chiral GC analysis. Recrystallisation of a racemic sample of D1-**7a** (DCM-hexane) provided crystals of sufficient quality to undergo X-ray diffraction. Full details of this X-ray structure are shown in Appendix II. This confirmed the structure and enabled the relative configuration of this sample to be assigned as *cis* with respect to H<sub>3</sub> and H<sub>5</sub>. As the configuration at C(5) was known to be *R* (due to the configuration of the starting material), and the ee of the sample was known, this enabled the assignment of the configurations to be made. The <sup>1</sup>H NMR spectrum of this compound has been shown in Appendix I.

(*R,R*)-**7b** (72 % *anti*, as determined by GC) (266 mg, 1.14 mmol, 32 % yield) was obtained as a colourless oil;  $[\alpha]_D^{22} + 11.0$  (*c*1.00 in CHCl<sub>3</sub>) 78 % ee; (found (ESI): M<sup>+</sup> + Na, 256.1306. C<sub>14</sub>H<sub>19</sub>NNaO<sub>2</sub> requires M, 256.1308);  $\nu_{\max}$  3368 (OH st.) 1612 (C=O st.) cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.37 - 7.22 (5 H, m, ArH), 4.64 (1 H, d, *J* 14.7, CH<sub>2</sub>), 4.55 (1 H, d, *J* 14.7, CH<sub>2</sub>), 3.68 (1 H, quin, *J* 5.8, H<sub>5</sub>), 3.17 (1 H, ddd, *J* 11.5, 5.8, 1.5, H<sub>4A</sub>), 3.07 (1 H, t, *J* 11.5, H<sub>4B</sub>), 2.61 (1 H, ddd, *J* 17.9, 5.5, 3.0, H<sub>1A</sub>), 2.42 (1 H, ddd, *J* 17.9, 11.8, 6.0, H<sub>1B</sub>), 1.79 (1 H, dqd, *J* 11.5, 5.8, 3.1, H<sub>3</sub>), 1.66 - 1.53 (2 H, m, H<sub>2</sub>), 1.15 (3 H, d, *J* 5.8, H<sub>6</sub>);  $\delta_C$  (101 MHz, CDCl<sub>3</sub>) 169.91 (CO), 137.05 (Ar), 128.58 (Ar), 127.99 (Ar), 127.36 (Ar), 68.55 (C<sub>5</sub>), 50.27 (CH<sub>2</sub>Ph), 49.19 (C<sub>4</sub>), 40.91 (C<sub>3</sub>), 31.53 (C<sub>1</sub>), 22.37 (C<sub>2</sub>), 20.97 (C<sub>6</sub>); *m/z* (ESI) 234.1 (M<sup>+</sup> + 1), 256.1 (M<sup>+</sup> + 23). Enantiomeric separation was determined by GC analysis: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25  $\mu$ m, gas: He, T = 200 °C, P = 18 psi He, det = 250 °C, inj = 220 °C, (*S,R*) (minor) isomer 24.70 min., (*R,S*) (major) isomer 25.25 min., (*S,S*) (minor) isomer 25.54 min., (*R,R*) (major) isomer 26.09 min.) 78 % ee. A racemic sample of the diastereomer D2-**7b** was used as a racemic standard during chiral GC analysis. The relative configuration of this sample was assigned in analogy to D1-**7b**. As configuration at C(5) was known, the absolute configuration of this sample was assigned accordingly. De was determined by GC analysis of the crude reaction mixture with the chiral GC method stated above: 31 % de. The <sup>1</sup>H NMR spectrum of this compound has been shown in Appendix I.

For future reference, enantiomerically and diastereomerically enriched samples of **7** will be referred to in terms of the absolute configuration of the major component present, with indication of the degree of purity, with the prefix of D2 or D1 for

clarity. Racemic and diastereomerically enriched samples of **7** will be referred to in terms of D2 and D1 with a prefix of ( $\pm$ ).

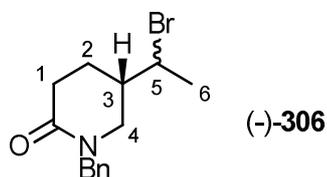
The hydrogenolysis product 1-benzyl-5-ethylpiperidin-2-one, **331** was also isolated from this reaction in variable yields. For the case of this experiment, 1-benzyl-5-ethylpiperidin-2-one (110 mg, 0.507 mmol, 14 % yield) was obtained as a colourless oil; (found (ESI):  $M^+ + Na$ , 240.1357.  $C_{14}H_{19}NNaO$  requires  $M$ , 240.1359);  $\nu_{max}$  2959 (alkyl CH st.), 2923 (alkyl CH st.), 2874 (alkyl CH st.), 1636 (C=O st.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.36 - 7.22 (5 H, m, ArH), 4.63 (1 H, d,  $J$  14.2,  $CH_2$ ), 4.55 (1 H, d,  $J$  14.2,  $CH_2$ ), 3.20 (1 H, ddd,  $J$  12.0, 5.1, 1.8,  $H_{4A}$ ), 2.85 (1 H, dd,  $J$  12.0, 10.3,  $H_{4B}$ ), 2.56 (1 H, ddd,  $J$  17.8, 5.8, 3.3,  $H_{1A}$ ), 2.42 (1 H, ddd,  $J$  17.8, 11.4, 6.5,  $H_{1B}$ ), 1.97 - 1.87 (1 H, m,  $H_{2A}$ ), 1.75 - 1.61 (1 H, m,  $H_3$ ), 1.43 (1 H, dtd,  $J$  13.1, 11.4, 5.8,  $H_{2B}$ ), 1.34 - 1.25 (2 H, m,  $H_5$ ), 0.87 (3 H, t,  $J$  7.5,  $H_6$ );  $\delta_C$  (101 MHz,  $CDCl_3$ ) 170.02 (CO), 137.22 (Ar), 128.51 (Ar), 127.96 (Ar), 127.25 (Ar), 52.52 ( $CH_2Ph$ ), 50.15 ( $C_4$ ), 35.49 ( $C_3$ ), 31.60 ( $C_2$ ), 26.01 ( $C_5$ ), 11.29 ( $C_6$ );  $m/z$  (ESI) 240.0 ( $M^+ + 1$ ).

*Synthesis of amines **308a** and **308b**, and attempted pyridone formation.*

Two separate syntheses of diastereomerically enriched samples of 5-(1-aminoethyl)-1-benzylpiperidin-2-one **308** originating from diastereomerically and enantiomerically enriched samples of the precursors, (*R,R*)-(D2)-**7b** and (*S,R*)-(D1)-**7a**. For simplicity, these have been shown in two separate sections. For future reference, enantiomerically and diastereomerically enriched samples of **306**, **333** or **308** will be referred to with an additional prefix of (D1) or (D2) to indicate that the sample had originated from a diastereomerically enriched sample of D1-**7a**, or (D2)-**7b** respectively; additionally, the sign of the optical rotation will also be used.

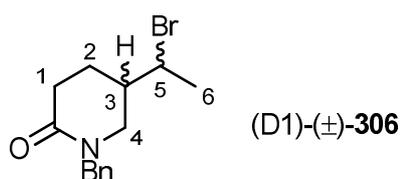
#### Section 3.5.4: Synthesis of Amine **308a**.

1-Benzyl-5-(1-bromoethyl)piperidin-2-one, (D1)-(-)-**306** via precursor alcohol D1-(*S,R*)-**7a**.



Under nitrogen, phosphorus tribromide (73  $\mu\text{L}$ , 210 mg, 0.777 mmol) was added to a solution of 1-benzyl-5-(1-hydroxyethyl)-piperidin-2-one (*S,R*)-(D1)-**7a** (100 % *syn*, as determined by GC) (78 % ee, 150 mg, 0.643 mmol) in toluene (6.00  $\text{cm}^3$ ) and the solution was stirred at 0  $^\circ\text{C}$  for 5 min. The solution was stirred at 80  $^\circ\text{C}$  for 50 min before water (5  $\text{cm}^3$ ) was added. Following extraction with ethyl acetate (3 x 10  $\text{cm}^3$ ), the organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to give a sample enriched in one diastereomer (75 % D1, as determined by  $^1\text{H}$  NMR), (D1)-(-)-**306** (147 mg, 0.498 mmol, 77 % yield) as an oil;  $[\alpha]_{\text{D}}^{22} - 12.9$  ( $c$ 0.52 in  $\text{CHCl}_3$ ). This sample was characterised through the synthesis and purification of the racemic sample, (D1)-( $\pm$ )-**306**. This is shown in the next section. For the case of this experiment, no further purification or separation of the diastereomers was attempted.

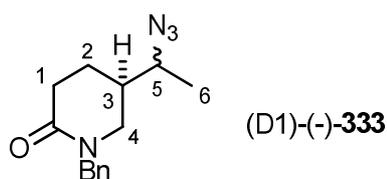
Synthesis of 1-benzyl-5-(1-bromoethyl)piperidin-2-one, (D1)-( $\pm$ )-**306** via precursor alcohol D1-( $\pm$ )-**7a**.



Under nitrogen, phosphorus tribromide (97  $\mu\text{L}$ , 279 mg, 1.03 mmol) was added to a solution of *anti*-1-benzyl-5-(1-hydroxyethyl)piperidin-2-one *anti*-D1-( $\pm$ )-**7a** (100 %

*anti*, as determined by GC) (198 mg, 0.850 mmol) in toluene (4.3 cm<sup>3</sup>) and the solution was stirred at 0 °C for 5 min. The solution was stirred at 80 °C for 1 h before water (5 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 5 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (ethyl acetate – petroleum ether 1:1), to give a sample enriched in one diastereomer (68 % D1, as determined by <sup>1</sup>H NMR), (D1)-( $\pm$ )-**306** (38 mg, 0.129 mmol, 15 % yield) as an oil; (found (ESI): M<sup>+</sup> + Na, 318.0465. C<sub>14</sub>H<sub>18</sub><sup>79</sup>BrNNaO requires M, 318.0464);  $\nu_{\max}$  1636 (C=O st.), 1494 (C=C st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.38 - 7.20 (5 H, m, ArH), 4.73 (1 H, d, *J* 14.7, CH<sub>2</sub>), 4.46 (2 H, d, *J* 14.7, CH<sub>2</sub>), 4.11 - 3.99 (1 H, m, H<sub>5</sub>), 3.27 - 3.10 (2 H, m, H<sub>4</sub>), 2.68 - 2.54 (1 H, m, H<sub>1A</sub>), 2.51 - 2.39 (1 H, m, H<sub>1B</sub>), 2.09 - 1.92 (2 H, m, H<sub>2</sub>), 1.66 (3 H, d, *J* 7.5, H<sub>6</sub>) 1.80 - 1.62 (1 H, m, H<sub>3</sub>);  $\delta_{\text{C}}$  (101 MHz, CDCl<sub>3</sub>) 169.35 (CO), 136.86 (Ar), 128.61 (Ar), 127.99 (Ar), 127.43 (Ar), 59.52 (CH<sub>2</sub>Ph), 51.59 (C<sub>5</sub>), 50.03 (C<sub>4</sub>), 41.53 (C<sub>3</sub>), 31.19 (C<sub>1</sub>), 24.08 (C<sub>2</sub>), 23.57 (C<sub>6</sub>); *m/z* (ESI) 318.0 (M[<sup>79</sup>Br]<sup>+</sup> +23).

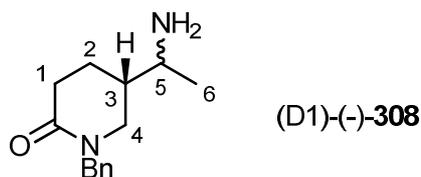
5-(1-Azidoethyl)-1-benzylpiperidin-2-one, (D1)-(-)-**333**.



Under nitrogen, a solution of (-)-1-benzyl-5-(1-bromoethyl)piperidin-2-one, (D1)-(-)-**306** (75 % D1, as determined by <sup>1</sup>H NMR) (78 % ee, 137 mg, 0.464 mmol) and NaN<sub>3</sub> (45 mg, 0.692 mmol) in acetone (0.9 cm<sup>3</sup>) and water (0.6 cm<sup>3</sup>) was stirred at 45 °C for 24 h before water (5.0 cm<sup>3</sup>) was added. Following extraction with ethyl acetate (3 x 10 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>), concentrated under reduced pressure and purified by column chromatography (ethyl acetate - petroleum ether 1:9 to 1:1), to give the product (D1)-(-)-**333** (82 % D1, as determined by <sup>1</sup>H

NMR) (16 mg, 0.062 mmol, 13 % yield) as an oil;  $[\alpha]_D^{22} - 24.0$  ( $c$ 0.70 in  $\text{CHCl}_3$ ); (found (ESI):  $\text{M}^+ + \text{Na}$ , 281.1373.  $\text{C}_{14}\text{H}_{18}\text{N}_4\text{NaO}$  requires  $\text{M}$ , 281.1373);  $\nu_{\text{max}}$  2101 ( $\text{N}_3$  st.), 1637 ( $\text{C}=\text{O}$  st.),  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.30 - 7.14 (5 H, m,  $\text{ArH}$ ), 4.66 (1 H, d,  $J$  14.8,  $\text{CH}_2$ ), 4.39 (1 H, d,  $J$  14.8,  $\text{CH}_2$ ), 3.99 (1 H, quin,  $J$  6.9,  $\text{H}_5$ ), 3.20 - 3.05 (2 H, m,  $\text{H}_4$ ), 2.56 (1 H, ddd,  $J$  17.7, 5.8, 3.5,  $\text{H}_{1\text{A}}$ ), 2.39 (1 H, ddd,  $J$  17.7, 11.5, 6.3,  $\text{H}_{1\text{B}}$ ), 2.01 - 1.85 (2 H, m,  $\text{H}_2$ ), 1.73 - 1.62 (1 H, m,  $\text{H}_3$ ), 1.59 (3 H, d,  $J$  6.9,  $\text{H}_6$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 169.40 (CO), 136.89 (Ar), 128.62 (Ar), 128.02 (Ar), 127.43 (Ar), 59.60 ( $\text{CH}_2\text{Ph}$ ), 51.60 ( $\text{C}_4$ ), 50.07 ( $\text{C}_5$ ), 41.57 ( $\text{C}_1$ ), 31.14 ( $\text{C}_3$ ), 24.14 ( $\text{C}_6$ ), 23.60 ( $\text{C}_2$ );  $m/z$  (ESI) 259.0 ( $\text{M}^+ + 1$ ), 281.0 ( $\text{M}^+ + 23$ ).

*5-(1-aminoethyl)-1-benzylpiperidin-2-one*, (D1)-(-)-**308**.

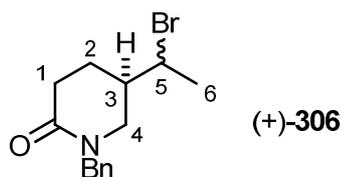


This compound was prepared following the general procedure for alkene hydrogenation, using (D1)-(-)-(1-azidoethyl)-1-benzyl-piperidin-2-one, (D1)-(-)-**333** (82 % D1, as determined by  $^1\text{H}$  NMR) (78 % ee, 14 mg, 0.054 mmol) and platinum oxide (0.6 mg,  $2.64 \times 10^{-3}$  mmol) following a reaction time of 14 h, at room temperature and 5 bar of hydrogen. Following filtration with celite, the resulting filtrate was passed through an Isolute-XL SCX amine scavenger resin and the resin was washed with DCM ( $3 \times 1 \text{ cm}^3$ ). The free amine was liberated by passing a solution of approx. 2 %  $\text{NH}_4\text{OH}$  in methanol through the resin, followed by washing with DCM ( $3 \times 1 \text{ cm}^3$ ). Following concentration under reduced pressure, an impure sample containing what was characterised to be the product (D1)-(-)-**308** (67 % D1, as determined by  $^1\text{H}$  NMR) (78 % ee, 10.6 mg, 0.046 mmol, 85 % yield) was

obtained as colourless oil;  $[\alpha]_D^{22} - 24.0$  ( $c0.05$  in  $\text{CHCl}_3$ ); (found (ESI):  $\text{M}^+ + \text{H}$ , 233.1643.  $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}$  requires  $\text{M}$ , 233.1648);  $\nu_{\text{max}}$  3441 (NH st.), 1638 (C=O st.)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.40 - 7.19 (5 H, m, ArH), 4.73 (1 H, d,  $J$  14.8,  $\text{CH}_2$ ), 4.46 (1 H, d,  $J$  14.8,  $\text{CH}_2$ ), 4.11 - 4.01 (1 H, m,  $\text{H}_5$ ), 3.30 - 3.08 (2 H, m,  $\text{H}_4$ ), 2.68 - 2.55 (1 H, m,  $\text{H}_{1\text{A}}$ ), 2.52 - 2.39 (1 H, m,  $\text{H}_{1\text{B}}$ ), 2.10 - 1.91 (2 H, m,  $\text{H}_2$ ), 1.66 (3 H, d,  $J$  7.0,  $\text{H}_6$ ), 1.71 - 1.56 (1 H, m,  $\text{H}_3$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 162.55 (CO), 136.88 (Ar), 128.81 (Ar), 127.91 (Ar), 127.47 (Ar), 51.56 ( $\text{C}_5$ ), 50.40 ( $\text{CH}_2\text{Ph}$ ), 50.13 ( $\text{C}_4$ ), 41.54 ( $\text{C}_1$ ), 31.23 ( $\text{C}_6$ ), 24.14 ( $\text{C}_3$ );  $m/z$  (ESI) 233.1 ( $\text{M}^+ + 1$ ).

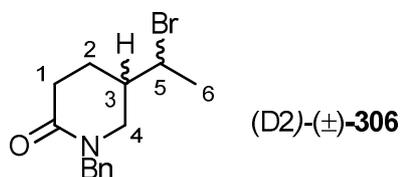
### Section 3.5.5: Synthesis of Amine **308b**.

#### *1-Benzyl-5-(1-bromoethyl)piperidin-2-one*, (D2)-(+)-**306**.



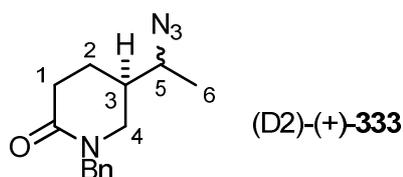
Under nitrogen, phosphorus tribromide (120  $\mu\text{L}$ , 346 mg, 1.28 mmol) was added to a solution of 1-benzyl-5-(1-hydroxyethyl)piperidin-2-one, (*R,R*)-**7b** (72 % *anti*, as determined by GC) (78 % ee, 246 mg, 1.06 mmol) in toluene (10.6  $\text{cm}^3$ ) and the solution was stirred at 0  $^\circ\text{C}$  for 5 min. The solution stirred at 80  $^\circ\text{C}$  for 50 min before water (5  $\text{cm}^3$ ) was added. Following extraction with ethyl acetate (3 x 10  $\text{cm}^3$ ), the organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to give a sample enriched in one diastereomer (68 % D2, as determined by  $^1\text{H}$  NMR), the product (D2)-(+)-**306** (190 mg, 0.644 mmol, 61 % yield) as an oil;  $[\alpha]_D^{22} + 10.6$  ( $c0.50$  in  $\text{CHCl}_3$ ). Full characterisation data was shown in the previous section. This sample was characterised through the synthesis and purification of the racemic sample, (D2)-( $\pm$ )-**306** which is shown in the next section. For the case of this experiment, no further purification or separation of the diastereomers was attempted.

Synthesis of 1-benzyl-5-(1-bromoethyl)piperidin-2-one, (D2)-( $\pm$ )-**306** via precursor alcohol D2-( $\pm$ )-**7b**.



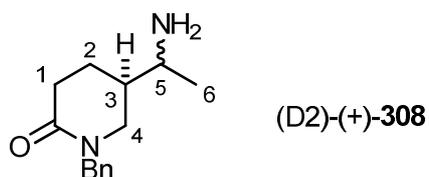
Under nitrogen, phosphorus tribromide (95  $\mu$ L, 274 mg, 1.01 mmol) was added to a solution of racemic *anti*-1-benzyl-5-(1-hydroxyethyl)-piperidin-2-one *syn*-D2-( $\pm$ )-**7b** (100 % *syn*, as determined by GC) (194 mg, 0.832 mmol) in toluene (4.0 cm<sup>3</sup>) and the solution was stirred at 0 °C for 5 min. The solution was stirred at 80 °C for 1 h before water (5 cm<sup>3</sup>) was added. Following extraction with DCM (3 x 5 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure and purified by column chromatography (ethyl acetate – petroleum ether 1:1), to give a sample enriched in one diastereomer (74 % D2, as determined by <sup>1</sup>H NMR), (D2)-( $\pm$ )-**306** (95 mg, 0.322 mmol, 39 % yield) as an oil; (found (ESI): M<sup>+</sup> + Na, 318.0461. C<sub>14</sub>H<sub>18</sub><sup>79</sup>BrNNaO requires M, 318.0464);  $\nu_{\max}$  1636 (C=O st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.37 - 7.23 (5 H, m, ArH), 4.68 (1 H, d, *J* 14.6, CH<sub>2</sub>), 4.53 (1 H, d, *J* 14.6, CH<sub>2</sub>), 4.04 (1 H, quin, *J* 6.9, H<sub>5</sub>), 3.42 (1 H, ddd, *J* 12.1, 5.1, 1.9, H<sub>4A</sub>), 3.15 (1 H, dd, *J* 12.1, 10.3, H<sub>4B</sub>), 2.60 (1 H, ddd, *J* 17.6, 5.8, 3.3, H<sub>1A</sub>), 2.45 (1 H, ddd, *J* 17.6, 11.5, 6.3, H<sub>1B</sub>), 2.11 - 1.92 (2 H, m, H<sub>2A</sub>, H<sub>3</sub>), 1.71 (3 H, d, *J* 6.9, H<sub>6</sub>), 1.75 - 1.62 (1 H, m, H<sub>2B</sub>);  $\delta_{\text{C}}$  (176 MHz, CDCl<sub>3</sub>) 169.25 (CO), 136.91 (Ar), 128.65 (Ar), 128.06 (Ar), 127.45 (Ar), 52.17 (C<sub>5</sub>), 50.53 (CH<sub>2</sub>Ph), 50.25 (C<sub>4</sub>), 42.00 (C<sub>3</sub>), 31.19 (C<sub>1</sub>), 25.44 (C<sub>2</sub>), 23.92 (C<sub>6</sub>); *m/z* (ESI) 296.0 (M[<sup>79</sup>Br]<sup>+</sup> +1), 298.0 (M[<sup>81</sup>Br]<sup>+</sup> +1).

5-(1-Azidoethyl)-1-benzylpiperidin-2-one, (D2)-(+)-**333**.



Under nitrogen, a solution of (+)-1-benzyl-5-(1-bromoethyl)piperidin-2-one, (D2)-(-)-**306** (66 % D2, as determined by  $^1\text{H}$  NMR) (78 % ee, 180 mg, 0.610 mmol) and  $\text{NaN}_3$  (60 mg, 0.923 mmol) in acetone (1.2  $\text{cm}^3$ ) and water (0.8  $\text{cm}^3$ ) was stirred at 45  $^\circ\text{C}$  for 24 h before water (5.0  $\text{cm}^3$ ) was added. Following extraction with ethyl acetate (3 x 10  $\text{cm}^3$ ), the organic extracts were dried ( $\text{MgSO}_4$ ), concentrated under reduced pressure and purified by column chromatography (ethyl acetate - petroleum ether 1:0 to 1:1), to give a diastereomerically enriched sample of (D2)-(+)-**333** (86 % D2, as determined by  $^1\text{H}$  NMR) (38 mg, 0.147 mmol, 24 % yield) as an oil;  $[\alpha]_{\text{D}}^{22} + 17.9$  ( $c$  0.76 in  $\text{CHCl}_3$ ); (found (ESI):  $\text{M}^+ + \text{Na}$ , 281.1370.  $\text{C}_{14}\text{H}_{18}\text{N}_4\text{NaO}$  requires  $\text{M}$ , 281.1373);  $\nu_{\text{max}}$  2107 ( $\text{N}_3$  st.), 1637 (CO)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.31 - 7.14 (5 H, m, ArH), 4.61 (1 H, d,  $J$  14.5,  $\text{CH}_2$ ), 4.46 (1 H, d,  $J$  14.5,  $\text{CH}_2$ ), 3.97 (1 H, quin,  $J$  6.8,  $\text{H}_5$ ), 3.35 (1 H, ddd,  $J$  12.1, 5.1, 1.8,  $\text{H}_{4\text{A}}$ ), 3.07 (1 H, dd,  $J$  12.1, 10.0,  $\text{H}_{4\text{B}}$ ), 2.52 (1 H, ddd,  $J$  17.8, 5.8, 3.3,  $\text{H}_{1\text{A}}$ ), 2.38 (1 H, ddd,  $J$  17.8, 11.8, 6.3,  $\text{H}_{1\text{B}}$ ), 2.03 - 1.85 (2 H, m,  $\text{H}_{2\text{A}}$ ,  $\text{H}_3$ ), 1.63 (3 H, d,  $J$  6.8,  $\text{H}_6$ ), 1.68 - 1.55 (1 H, m,  $\text{H}_{2\text{B}}$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 169.25 (CO), 136.86 (Ar), 128.62 (Ar), 128.02 (Ar), 127.43 (Ar), 59.60 ( $\text{C}_5$ ), 52.18 ( $\text{C}_4$ ), 50.54 ( $\text{CH}_2\text{Ph}$ ), 50.39 ( $\text{C}_4$ ), 41.92 ( $\text{C}_3$ ), 31.15 ( $\text{C}_1$ ), 25.39 ( $\text{C}_2$ ), 23.90 ( $\text{C}_6$ );  $m/z$  (ESI) 258.9 ( $\text{M}^+ + 1$ ), 280.9 ( $\text{M}^+ + 23$ ).

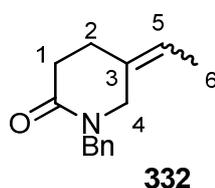
5-(1-aminoethyl)-1-benzylpiperidin-2-one, (D2)-(+)-**308**



This compound was prepared following the general procedure for alkene hydrogenation, using (D2)-(1-azidoethyl)-1-benzylpiperidin-2-one, (D2)-(+)-**333** (86% D<sub>2</sub>, as determined by <sup>1</sup>H NMR) (78 % ee, 38 mg, 0.147 mmol) and platinum oxide (1.6 mg, 7.05 x 10<sup>-3</sup> mmol) following a reaction time of 14 h, at room temperature and 5 bar of hydrogen. Following filtration with celite, the resulting filtrate was passed through an Isolute-XL SCX amine scavenger resin and the resin was washed with DCM (3 x 1 cm<sup>3</sup>). The free amine was liberated by passing a solution of approx. 2 % NH<sub>4</sub>OH in methanol through the resin, followed by washing with DCM (3 x 1 cm<sup>3</sup>). Following concentration under reduced pressure, the product (D2)-(+)-**308** (86% D<sub>2</sub>, as determined by <sup>1</sup>H NMR) (78 % ee, 21 mg, 0.090 mmol, 62 % yield) was obtained as a colourless oil; [ $\alpha$ ]<sub>D</sub><sup>22</sup> + 16.4 (c0.21 in CHCl<sub>3</sub>); (found (ESI): M<sup>+</sup> + H, 233.1643. C<sub>14</sub>H<sub>21</sub>N<sub>2</sub>O requires M, 233.1648);  $\nu_{\max}$  3412 (NH st.), 1638 (C=O st.) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.37 - 7.19 (5 H, m, ArH), 4.68 (1 H, d, *J* 14.8, CH<sub>2</sub>), 4.53 (1 H, d, *J* 14.6, CH<sub>2</sub>), 4.04 (1 H, quin, *J* 6.8, H<sub>5</sub>), 3.42 (1 H, ddd, *J* 12.1, 5.1, 1.9, H<sub>4A</sub>), 3.15 (1 H, dd, *J* 12.0, 10.3, H<sub>4B</sub>), 2.60 (1 H, ddd, *J* 18.1, 6.0, 3.0, H<sub>1A</sub>), 2.45 (1 H, ddd, *J* 17.6, 11.8, 6.0, H<sub>1B</sub>), 2.10 - 1.93 (2 H, m, H<sub>2</sub>, H<sub>3</sub>), 1.70 (3 H, d, *J* 6.8, H<sub>6</sub>), 1.74 - 1.62 (1 H, m, H<sub>2B</sub>);  $\delta_{\text{C}}$  (176 MHz, CDCl<sub>3</sub>) 169.29 (CO), 136.88 (Ar), 128.65 (Ar), 128.05 (Ar), 127.45 (Ar), 52.16 (C<sub>5</sub>), 50.53 (CH<sub>2</sub>Ph), 50.37 (C<sub>4</sub>), 41.97 (C<sub>3</sub>), 31.18 (C<sub>1</sub>), 25.42 (C<sub>2</sub>), 23.92 (C<sub>6</sub>); *m/z* (ESI) 233.1 (M<sup>+</sup>+1).

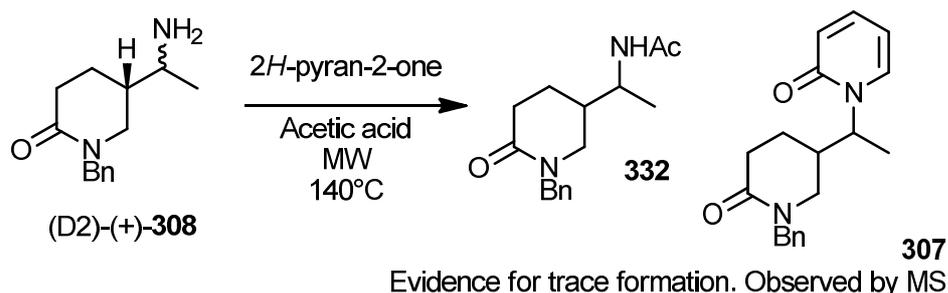
Section 3.5.6: Attempted Synthesis of Pyridone **307**.

1-benzyl-5-ethylidenepiperidin-2-one, **332**.



Under nitrogen, a solution of 2-hydroxypyridine (80 mg, 0.841 mmol), 1-benzyl-5-(1-bromoethyl)piperidin-2-one ( $\pm$ )-**306** (250 mg, 0.847 mmol), tetrabutylammonium bromide (27 mg, 0.084 mmol) and potassium carbonate (234 mg, 1.69 mmol) in toluene (7.0 cm<sup>3</sup>) and water (36  $\mu$ L) was heated at 110 °C for 18 h before the solution was allowed cool. Following filtration, concentration under reduced pressure and purification by column chromatography (ethyl acetate – petroleum ether 1:1 to 1:0), an impure and inseparable mixture of what was characterised to be isomers *E*-**332** and *Z*-**332** (100 mg, 0.465 mmol) was obtained as a colourless oil; (found (ESI):  $M^+ + Na$ , 238.1198.  $C_{14}H_{17}NNaO$  requires  $M$ , 238.1202);  $\nu_{max}$  1636 (C=O st.), 1489 (C=C st.)  $cm^{-1}$ ;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.38 - 7.20 (5 H, m, ArH), 5.41 - 5.31 (1 H, m, H<sub>5</sub>), 4.64 (2 H, s, CH<sub>2</sub>), 3.83 (2 H, s, *Z*-H<sub>4</sub>), 3.75 - 3.68 (2 H, m, *E*-H<sub>4</sub>), 2.55 - 2.39 (4 H, m, H<sub>1</sub>, H<sub>2</sub>), 1.62 (3 H, d,  $J$  6.8, H<sub>6</sub>);  $\delta_C$  (101 MHz,  $CDCl_3$ ) 170.59 (CO), 136.98 (Ar), 128.50 (Ar), 127.95 (Ar), 127.28 (Ar), 119.56 (C<sub>3</sub>), 119.39 (C<sub>5</sub>), 53.40 (CH<sub>2</sub>Ph), 47.29 (C<sub>4</sub>), 33.30 (C<sub>1</sub>), 30.17 (C<sub>2</sub>), 22.93 (C<sub>6</sub>);  $m/z$  (ESI) 215.8 ( $M^+ + 1$ ).

Procedure for the attempted formation of pyridone ( $\pm$ )-**307**.



Under nitrogen, a solution of 5-(1-aminoethyl)-1-benzylpiperidin-2-one, (D2)-( $\pm$ )-**308** (30 mg, 0.129 mmol) and 2*H*-pyran-2-one (37 mg, 0.390 mmol) in acetic acid (0.8 cm<sup>3</sup>) was irradiated at 140 °C for 3 h before saturated sodium hydrogen carbonate (5 cm<sup>3</sup>) was added. Following extraction with ethyl acetate (3 x 5 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give a sample containing an inseparable mixture of what was characterised to be the product **334** (30 mg). Data for **334** obtained from this mixture:  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.31 - 7.14 (5 H, m, ArH), 4.61 (1 H, d, *J* 14.5, CH<sub>2</sub>), 4.46 (1 H, d, *J* 14.5, CH<sub>2</sub>), 3.90 (1 H, quin, *J* 6.8, H<sub>5</sub>), 3.20 - 3.10 (1 H, m, H<sub>4A</sub>), 3.00 - 2.90 (1 H, m, H<sub>4B</sub>), 2.55 - 2.45 (1 H, m, H<sub>1A</sub>), 2.40 - 2.30 (1 H, m, H<sub>1B</sub>), 1.80 (3 H, s, CH<sub>3</sub>), 1.90 - 1.70 (2 H, m, H<sub>2</sub>), 1.50 - 1.40 (1 H, m, H<sub>3</sub>), 1.00 (3 H, d, *J* 6.8, H<sub>6</sub>); *m/z* (ESI) 275.1 (M<sup>+</sup>+1), 297.1 (M<sup>+</sup>+23). A signal corresponding to the indented product **307** was observed by MS; *m/z* (ESI) 313.1 (M<sup>+</sup>+1), 333.1 (M<sup>+</sup>+23).

## References.

- <sup>1</sup> Biot, J. B. *Bull. Soc. Philomath. Paris.*, **1815** 190-190.
- <sup>2</sup> Eliel, E. L. (1962) *Stereochemistry of carbon compounds*. USA: McGraw-Hill Book Company, Inc.
- <sup>3</sup> Van't Hoff, J. R. *Bull. Soc. Chim. France.*, **1875**, 23, 295-295.
- <sup>4</sup> Le Bel, J. A. *Bull. Soc. Chim. France.*, **1874**, 22, 337-337.
- <sup>5</sup> Burley, D. M.; Lenz, W. *Lancet*, **1962**, 279, 271-272.
- <sup>6</sup> Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.*, **2009**, 52, 6752-6756.
- <sup>7</sup> (a) Ojima, I. (2000). *Catalytic Asymmetric Synthesis*, 2<sup>nd</sup> edition. USA: Wiley-VCH; (b) Morrison, J. D. (1985). *Asymmetric Synthesis, volume 5*, 1<sup>st</sup> edition. UK: Academic Press INC. (London) ltd; (c) Morrison, J. D. (1984). *Asymmetric Synthesis, volume 3*, 1<sup>st</sup> edition. UK: Academic Press INC. (London) ltd.
- <sup>8</sup> (a) Krtiger, J.; Carreira, E. M. *Tetrahedron Lett.*, **1998**, 39, 7013-7016; (b) Krtiger, J.; Carreira, E. M. *J. Am. Chem. Soc.*, **1998**, 120, 837-838.
- <sup>9</sup> List, B.; Lerner, A.; Barbas, C. F. *J. Am. Chem. Soc.*, **2000**, 122, 2395-2396.
- <sup>10</sup> (a) Chen, G.; Fu, X.; Li, C.; Wu, C.; Miao, Q. *J. Organomet. Chem.*, **2012**, 702 19-26; (b) Paradowska, J.; Pasternak, M.; Gut, B.; Gryz, B.; Mlynarski, J. *J. Org. Chem.*, **2012**, 77, 173-187; (c) Fanton, J.; Camps, F.; Castillo, J. A.; Guérard-Hélaine, C.; Lemaire, M.; Charmantray, F.; Hecquet, L. *Eur. J. Org. Chem.*, **2012**, 1, 203-210.
- <sup>11</sup> (a) Georgiou, I.; Whiting, A. *Org. Biomol. Chem.*, **2012**, 10, 2422-2430; (b) Arnold, K.; Batsanov, A. S.; Davies, B.; Grosjean, C.; Schütz, T.; Whiting, A.; Zawatzky, K. *Chem. Commun.*, **2008**, 3879-3881.
- <sup>12</sup> Moteki, S. A.; Han, J.; Arimitsu, S.; Akakura, M.; Nakayama, K.; Maruoka, K. *Angew. Chem. Int. Ed.* **2012**, 51, 1187-1190.
- <sup>13</sup> Gosiewska, S.; Soni, R.; Clarkson, G. J.; Wills, M. *Tetrahedron Lett.*, **2010**, 51, 4214-4217.
- <sup>14</sup> (a) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.*, **1998**, 120, 6488-6499; (b) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Tetrahedron Lett.*, **1993**, 34, 4219-4222; (c) Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.*, **1994**, 116, 11737-11748.
- <sup>15</sup> Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem. Int. Ed.*, **1996**, 35, 200-202.
- <sup>16</sup> Duff, M. G.; Grayson, D. H. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 1555-1563.

- 
- <sup>17</sup> (a) Yang, Z.; Zhou, S. *J. Am. Chem. Soc.*, **2012**, *134*, 11833-11835.
- <sup>18</sup> Mochizuki, T.; Kondo, Y.; Abe, H.; Tovey, S. C.; Dedos, S. G.; Taylor, C. W.; Paul, M.; Potter, B. V. L.; Matsuda, A.; Shuto, S. *J. Med. Chem.*, **2006**, *49*, 5750-5758.
- <sup>19</sup> Mazuela, J.; Tolstoy, P.; Pàmies, O.; Andersson, P. G.; Diéguez, M. *Org. Biomol. Chem.*, **2011**, *9*, 941-946.
- <sup>20</sup> Nubbemeyer, U. *Synthesis*, **2003**, 961-1008.
- <sup>21</sup> Felix, R. J.; Weber, D.; Gutierrez, O.; Tantillo, D. J.; Gagne, M. J. *Nat. Chem.* **2012**, *4*, 405-409.
- <sup>22</sup> Quartieri, F.; Mesiano, L. E.; Borghi, D.; Desperati, V.; Gennari, C.; Papeo, G. *Eur. J. Org. Chem.*, **2011**, *33*, 6794-6801.
- <sup>23</sup> Çelebi-Ölçüm, N.; Lam, Y -H.; Richmond, E.; Ling, K. B.; Smith, A. D.; Houk, K. N. *Angew. Chem. Int. Ed.*, **2011**, *50*, 11478 -11482.
- <sup>24</sup> Li, Z.; Boyarskikh, Z.; Hansen, J. H.; Autschbach, J.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.*, **2012**, *134*, 15497-15504.
- <sup>25</sup> (a) Sheldon, R. A.; van Bekkum, H. (2001). *Fine chemicals through Heterogeneous catalysis*, 1<sup>st</sup> edition. Germany: WILEY-VCH Verlag GmbH; (b) Wilkinson, G.; Jardine, F. H.; Osborn, G. F. *Chem. Ind. (London)*, **1965**, 560.
- <sup>26</sup> (a) Horner, L. Siegel, H.; Buthe, H. *Angew. Chem. Int. Ed.*, **1968**, *7*, 942-942.; (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.*, **1977**, *99*, 5946-5952.
- <sup>27</sup> Andersson, P. G.; Munslow, I. J. (2008). *Modern reduction methods*. Weinheim: Wiley-VCH.
- <sup>28</sup> Knowles, W. S. *J. Chem. Educ.*, **1986**, *63*, 222-225.
- <sup>29</sup> Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.*, **1987**, *52*, 3174-3176.
- <sup>30</sup> Noyori, R. *Angew. Chem. Int. Ed.*, **2002**, *41*, 2008-2022.
- <sup>31</sup> Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijanit, A. *J. Am. Chem. Soc.*, **1994**, *116*, 4062-4066.
- <sup>32</sup> Spindler, F.; Malan, C.; Lotz, M.; Kesselgruber, M.; Pittelkow, U.; Rivas-Nass, A.; Briel, O.; Blaser, H. -H. *Tetrahedron: Asymmetry*, **2004**, *15*, 2299-2306.
- <sup>33</sup> Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.*, **2007**, *40*, 1278-1290.

- 
- <sup>34</sup> Boaz, N. W.; Mackenzie, E. B.; Debenham, S. D.; Large, S. E.; Ponasik, Jr., J. A. *J. Org. Chem.* **2005**, *70*, 1872-1880.
- <sup>35</sup> Wada, Y.; Imamoto, T.; Tsuruta, H. *Adv. Synth. Catal.*, **2004**, *346*, 777-777.
- <sup>36</sup> Yamanoi, Y.; Imamoto, T. *J. Org. Chem.*, **1999**, *64*, 2988-2989.
- <sup>37</sup> (a) Burk, M. F.; Gross, J. P. *J. Am. Chem. Soc.*, **1995**, *117*, 9375-9376; (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.*, **1993**, *115*, 10125-10138.
- <sup>38</sup> Feldgus, S.; Landis, C. R. *J. Am. Chem. Soc.*, **2000**, *122*, 12714-12727.
- <sup>39</sup> Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, III, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.*, **2004**, *126*, 9918-9919.
- <sup>40</sup> Ohta, T.; Miyake, T.; Seido, T.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.*, **1995**, *60*, 357-363.
- <sup>41</sup> Le Gendre, P.; Braun, T.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.*, **1996**, *61*, 8453-8455.
- <sup>42</sup> Fehr, M. J.; Consiglio, G.; Scalone, M.; Schmid, R. *J. Org. Chem.* **1999**, *64*, 5768-5776.
- <sup>43</sup> Dobbs, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J. -V.; Genêt, J. -P.; Wiles, J.; Bergens, S. H. *Angew. Chem. Int. Ed.*, **2000**, *39*, 1992-1995.
- <sup>44</sup> Genêt, J. -P. *Acc. Chem. Res.*, **2003**, *36*, 908-918.
- <sup>45</sup> Stead, D.; O'Brien, P. *Tetrahedron*, **2007**, *63*, 1885-1897.
- <sup>46</sup> Okuda, S.; Tsuda, K.; Kataoka, T. *Chem. Ind. (London)*, **1961**, 1751.
- <sup>47</sup> Stead, D.; O'Brien, P.; Sanderson, A. *J. Org. Lett.*, **2005**, *7*, 4459-4462.
- <sup>48</sup> Nshimyumukiza, P.; Cahard, D.; Rouden, J.; Lasne, M.; Plaquevent, J. *Tetrahedron Lett.*, **2001**, *42*, 7787-7790.
- <sup>49</sup> Demers, S.; Stevenson, H.; Candler, J.; Bashore, C. G.; Arnold, E. P.; O'Neill, B. T.; Coe, J. W. *Tetrahedron Lett.*, **2008**, *49*, 3368-3371.
- <sup>50</sup> Imming, P.; Klaperski, P.; Stubbs, M. T.; Seitz, G.; Gündische, D. *Eur. J. Med. Chem.*, **2001**, *36*, 375-388.
- <sup>51</sup> Pabreza, L. A.; Dhawan, S. Kellar, K. J. *Mol. Pharmacol.*, **1991**, *39*, 9-12.
- <sup>52</sup> (a) Raynor, S. A.; Thomas, J. M.; Raja, R.; Johnson, B. F. G.; Bell, R. G.; Mantle, M. D. *Chem. Commun.*, **2000**, 1925-1926; (b) Blaser, H. -U.; Hönl, H.; Studer, M.; Wedemeyer-Exl, C. *J. Mol. Catal. A: Chem.*, **1999**, *139*, 253-257; (c) Studer, M.;

- 
- Wedemeyer-Exl, C.; Spindler, F.; Blaser, H. –U. *Monatsh. Chem.* **2000**, *131*, 1335-1343.
- <sup>53</sup> (a) Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehmann, C. W. *Angew. Chem. Int. Ed.*, **2004**, *43*, 2850-2852; (b) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.*, **2005**, *127*, 8966-8967.
- <sup>54</sup> Govindachari, S.; Rajadurai, M.; Subramanian, M.; Thyagarajan, B. S. *J. Chem. Soc.*, **1957**, 3839-3844.
- <sup>55</sup> Bohlmann, F.; Englisch, A.; Ottawa, N.; Sander, H. *Chem. Ber.*, **1956**, *89*, 792-799.
- <sup>56</sup> Bohlman, F.; Winterfeldt, E.; Overwien, H.; Pagel, H. *Chem. Ber.*, **1958**, *91*, 2194-2205.
- <sup>57</sup> O'Neill, B. T.; Yohannes, D.; Bundesmann, M. W.; Arnold, E. P. *Org. Lett.* **2000**, *2*, 4201-4204.
- <sup>58</sup> Nshimyumukiza, P.; Cahard, D.; Rouden., J.; Lasne, M.; Plaquevent, J. *Tetrahedron Lett.*, **2001**, *42*, 7787-7790.
- <sup>59</sup> (a) van Tamelen, E.; Baran, J. *J. Am. Chem. Soc.*, **1955**, *77*, 4944-4945; (b) van Tamelen, E. E.; Baran, J. S. *J. Am. Chem. Soc.*, **1958**, *80*, 4659-4670.
- <sup>60</sup> Danieli, D.; Lesma, G.; Passarella, D.; Silvani, A. *J. Org. Chem.*, **1998**, *63*, 3492-3496.
- <sup>61</sup> Danieli, B.; Lesma, G.; Passarella, D.; Sacchetti, A.; Silvani, A.; Viridis, A. *Org. Lett.*, **2004**, *6*, 493-496.
- <sup>62</sup> Honda, T.; Takahashi, R.; Namiki, H. *J. Org. Chem.*, **2005**, *70*, 499-504.
- <sup>63</sup> Gallagher, T.; Galley, C.; Botuha, C. *Org. Biomol. Chem.*, **2004**, *2*, 1825-1826.
- <sup>64</sup> Cook, G.; Beholz, L.; Stille, J. *J. Org. Chem.*, **1994**, *59*, 3575-3584.
- <sup>65</sup> Owen, M. R.; Luscombe, C.; Lai, L. –W.; Godbert, S.; Crookes, D. L.; Emiabata-Smith, D. *Org. Process Res. Dev.*, **2001**, *5*, 308-323.
- <sup>66</sup> Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.*, **1998**, *63*, 6546-6553.
- <sup>67</sup> Satyanarayana, G.; Maier, M. E. *Tetrahedron*, **2008**, *64*, 356-363.
- <sup>68</sup> Gallagher, T.; Gray, D. *Angew. Chem. Int. Ed.*, **2006**, *45*, 2419-2423.
- <sup>69</sup> Gallagher, T.; Derrick, I.; Durkin, P. M.; Haseler, C. A.; Hirschhäuser, C.; Magrone, P. *J. Org. Chem.*, **2010**, *75*, 3766-3774.
- <sup>70</sup> Coe, J. W. *Org. Lett.*, **2000**, *2*, 4205-4208.

- 
- <sup>71</sup> Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.*, **2008**, *37*, 29–41.
- <sup>72</sup> Kim, M. –H.; Park, Y.; Jeong, B. –S.; Park, H. –G.; Jew, S. –S. *Org. Lett.*, **2010**, *12*, 2826-2829.
- <sup>73</sup> Hayman, A. R.; Gray, D. O. *Phytochemistry*, **1989**, *28*, 673–675.
- <sup>74</sup> Yohannes, D.; Hansen, C. P.; Akireddy, S. R.; Hauser, T. A.; Kiser, M. N.; Gurnon, N. J.; Day, C. S.; Bhatti, B.; Caldwell, W. S. *Org. Lett.*, **2008**, *10*, 5353-5356.
- <sup>75</sup> Yohannes, D.; Procko, K.; Lebel, L. A.; Fox, C. B.; O’Neill, B. T. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 2316–2319.
- <sup>76</sup> Nemes, P.; Scheiber, P. *Arkivoc*, **2008**, (iii), 194-199.
- <sup>77</sup> Marrière, E.; Rouden, J.; Tadino, V.; Lasne, M. C. *Org. Lett.*, **2000**, *2*, 1121-1124.
- <sup>78</sup> (a) Allain-Barbier, L.; Lasne, M. C.; Perrio-Huard, C.; Moreau, B.; BarrŽ, L. *Acta Chem. Scand.*, **1998**, *52*, 480-489; (b) Forngren, T.; Andersson, Y.; Lamm, B.; Langstršm, B. *Acta Chem. Scand.* **1998**, *52*, 475-479.
- <sup>79</sup> Fitch, R. W.; Kaneko, Y.; Klaperski, P.; Daly, J. W.; Seitz, G.; Gündisch, D. *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 1221-1224.
- <sup>80</sup> Rouden, J.; Ragot, A.; Gouault, S.; Cahard, D.; Plaquevent, J. –C.; Lasne, M –C. *Tetrahedron: Asymmetry*, **2002**, *13*, 1299-1305.
- <sup>81</sup> Bondarenko, S. P.; Frasinuk, M. S.; Vinogradova, V. I.; Khilya, V. P. *Chemistry of Natural Compounds*, **2011**, *47*, 604-607.
- <sup>82</sup> Chellappan, S. K.; Xiao, Y.; Tueckmantel, W.; Kellar, K. J.; Kozikowski, A. P. *J. Med. Chem.*, **2006**, *49*, 2673-2676.
- <sup>83</sup> Abin-Carriquiry, J. A.; Zunini, M. P.; Cassels, B. K.; Wonnacott, S.; Dajas, F. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 3683-3687.
- <sup>84</sup> Marion, L.; Turcotte, F.; Ouellet, J. *Can. J. Chem.*, **1951**, *29*, 22-29.
- <sup>85</sup> Stenhouse, J. *Annalen*, **1851**, *78*, 1-30.
- <sup>86</sup> (a) Clemo, G.; Leitch, G. C. *J. Chem. Soc.*, **1928**, 1928; (b) Clemo, G.; Raper, R.; Tenniswood, C. *J. Chem. Soc.*, **1931**, 429-437.
- <sup>87</sup> Winterfeld, K.; Rauch, C. *Arch. Pharm.*, **1934**, *272*, 273-290.
- <sup>88</sup> Włodarczak, J.; Wysocka, W.; Katrusiak, A. *J. Mol. Struc.*, **2010**, *971*, 12-17.
- <sup>89</sup> Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem. Int. Ed. Engl.*, **1990**, *29*, 1422-1423.

- 
- <sup>90</sup> Demers, S.; Coe, J. *Tetrahedron Let.* **2008**, *49*, 3368
- <sup>91</sup> (a) Sorm, F.; Keil, B. *Coll. Czech. Chem. Com.*, **1947**, *12*, 655-655; (b) Sorm, F.; Keil, B. *Coll. Czech. Chem. Com.*, **1948**, *13*, 544-544.
- <sup>92</sup> Marion, L.; Turcotte, F.; Ouellet, J. *Can. J. Chem.*, **1951**, *29*, 22-22.
- <sup>93</sup> Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.*, **1950**, *72*, 1316-1323.
- <sup>94</sup> (a) Bohlmann, F.; Müller, H.; Schumann, D. *Chem. Ber.*, **1971**, *106*, 3026-3034; (b) Bohlmann, F.; Winterfeldt, E.; Overwien, H.; Pagel, H. *Chem. Ber.*, **1962**, *95*, 944-948.
- <sup>95</sup> Oinuma, H.; Dan, S.; Kakisawa, H. *J. Chem. Soc. Chem. Commun.*, **1983**, 654-655.
- <sup>96</sup> (a) Brown, A. M.; Rycroft D. S.; Robins, D. J. *J. Chem. Soc. Perkin Trans. 1.*, **1991**, 2353-2355; (b) Golebiewski, W. M.; Spense, I. D. *Can. J. Chem.*, **1988**, *66*, 1734-1741; (c) Golebiewski, M.W.; Spense, I. D. *J. Am. Chem. Soc.*, **1976**, *98*, 6726-6728.
- <sup>97</sup> Wanner, M. J.; Koomen, G. –K. *J. Org. Chem.*, **1996**, *61*, 5581-5586.
- <sup>98</sup> (a) Van Tamelen, E. E.; Foltz, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 7372-7377; (b) Van Tamelen, E. E.; Foltz, R. L. *J. Am. Chem. Soc.* **1960**, *82*, 2400-2400.
- <sup>99</sup> Schöpf, C.; Braun, F.; Koop, H.; Werner, G. *Liebigs Ann. Chem.*, **1962**, *658*, 156-168.
- <sup>100</sup> Smith, B. T.; Wendt, J. A.; Aub, J. *Org. Lett.*, **2002**, *4*, 2577-2579.
- <sup>101</sup> Hayashi, T. *Acta Chem. Scand.*, **1996**, *50*, 259-266.
- <sup>102</sup> Buttler, T.; Fleming, I. *Chem. Commun.*, **2004**, 2404-2405.
- <sup>103</sup> Norcross, N. R.; Melbardis, J. P.; Solera, M. F.; Sephton, M. A.; Kilner, C.; Zakharov, L. N.; Astles, P. C.; Warriner, S. L.; Blakemore, P. R. *J. Org. Chem.*, **2008**, *73*, 7939 – 7951.
- <sup>104</sup> Danieli, B.; Lesma, G.; Passarella, D.; Sacchetti, A.; Silvani, A. *Tetrahedron Lett.*, **2005**, *46*, 7121-7123.
- <sup>105</sup> Hermet, J. –P. R.; McGrath, M. J.; O'Brien, P.; Porter, D. W.; Gilday, J. *Chem Commun.*, **2004**, 1830-1831.
- <sup>106</sup> Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.*, **2004**, *69*, 5789-5792.
- <sup>107</sup> (a) O'Brien, P. *Chem. Commun.*, **2008**, 655-667.; (b) Dearden, M. J.; Firkin, C. R.; Hermet, J. –P. R.; O'Brien, P. *J. Am. Chem. Soc.*, **2002**, *124*, 11870-11871.
- <sup>108</sup> Brosius, A. D.; Overman, L. E. *J. Org. Chem.*, **1997**, *62*, 440-441.

- 
- <sup>109</sup> Van Tamelen, E.; Baran, J. *J. Am. Chem. Soc.*, **1958**, *80*, 4659-4670.
- <sup>110</sup> Goldberg, S. I.; Lipkin, A. H. *J. Org. Chem.*, **1972**, *37*, 1823-1825.
- <sup>111</sup> Padwa, A.; Heidelbaugh, T. M.; Kueth, J. T. *J. Org. Chem.*, **2000**, *65*, 2368-2378.
- <sup>112</sup> Majik, M. S.; Parameswaran, P. S.; Tilve, S. G. *J. Org. Chem.*, **2009**, *74*, 6378-6381.
- <sup>113</sup> He, Z. -T.; Wei, Y. -B.; Yu, H. -J.; Sun, C. -Y.; Feng, C. -Y.; Tian, P.; Lin, G. -Q. *Tetrahedron*, **2012**, *68*, 9186-9191.
- <sup>114</sup> Paraskar, A. S.; Sudalai, A. *Tetrahedron*, **2006**, *62*, 4907-4916.
- <sup>115</sup> Yu, M. S.; Lantos, I.; Peng, Z. -Q.; Yu, J.; Cacchio, T. *Tetrahedron Lett.*, **2000**, *41*, 5647-5651.
- <sup>116</sup> (a) Bower, J. F.; Švenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.*, **2004**, *6*, 4727-4730; (b) Williams, A. J.; Chakthong, S.; Gray, D.; Lawrence, R. M.; Gallagher, T. *Org. Lett.*, **2003**, *5*, 811-814.
- <sup>117</sup> Bower, J. F.; Szeto, P.; Gallagher, T. *Chem. Commun.*, **2005**, 5793-5795.
- <sup>118</sup> (a) Nakao, Y.; Chen, J.; Imanaka, H.; Hiyama, T.; Ichikawa, Y.; Duan, W. -L.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.*, **2007**, *129*, 9137-9143; (b) Jin, S. -S.; Wang, H.; Xu, M. -H. *Chem. Commun.*, **2011**, *47*, 7230-7232; (c) Gini, F.; Hessen, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.*, **2007**, 710-712.
- <sup>119</sup> Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.*, **2004**, *126*, 3734-3735.
- <sup>120</sup> (a) Albrecht, L.; Richter, B.; Krawczyk, H.; Jorgensen, K. A. *J. Org. Chem.*, **2008**, *73*, 8337-8343; (b) Číhalová, S.; Valero, G.; Schimer, J.; Humpl, M.; Dračinský, M.; Moyano, A.; Rios, R.; Vesely, J. *Tetrahedron*, **2011**, *67*, 8942-8950.
- <sup>121</sup> Latli, B.; Prestwich, G. D. *J. Org. Chem.*, **1988**, *53*, 4603-4605.
- <sup>122</sup> Chen, B. -F.; Tasi, M. -R.; Yang, C. -Y.; Chang, Y. -K.; Chang, N. -C. *Tetrahedron*, **2004**, *60*, 10223-10231.
- <sup>123</sup> Ito, M.; Sakaguchi, A.; Kobayashi, C.; Ikariya, T. *J. Am. Chem. Soc.*, **2007**, *129*, 290-291.
- <sup>124</sup> Zhang, J.; Senthilkumar, M.; Ghosh, S. C.; Hong, S. H. *Angew. Chem. Int. Ed.*, **2010**, *49*, 6391-6395.

- 
- <sup>125</sup> Bettoni, G.; Franchini, C.; Morlacchi, F.; Tangari, N.; Tortorella, V. *J. Org. Chem.*, **1976**, *41*, 2780-2782.
- <sup>126</sup> Chandrasekhar, S.; Takhi, M.; Uma, G. *Tetrahedron Lett.*, **1997**, *38*, 8089-8092.
- <sup>127</sup> Jeong, Y. -C.; Moloney, M. G. *J. Org. Chem.*, **2011**, *76*, 13420-1354.
- <sup>128</sup> Mayer, S. C.; Banker, A. L.; Boschelli, F.; Di, Li.; Johnson, M.; Kenny, C. H.; Krishnamurthy, G.; Kutterer, K.; Moy, F.; Petusky, S.; Ravi, M.; Tkach, D.; Tsou, H. -Ru.; Xu, W. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 3641-3645.
- <sup>129</sup> Jayaselli, J.; Cheemala, M. S.; Geetha Rani, D. P.; Pal, S. *J. Braz. Chem. Soc.*, **2008**, *19*, 509-515.
- <sup>130</sup> Mariano, P. S.; Kromml, R. B. *Tetrahedron*, **1979**, *34*, 2609-2609.
- <sup>131</sup> McKillop, A.; Ielesko, M. J.; Taylor, E. C. *Tetrahedron Lett.*, **1968**, *48*, 4945-4948.
- <sup>132</sup> Clausen, A. M.; Dziadul, B. *Org. Proc. Res. Dev.*, **2006**, *10*, 723-726.
- <sup>133</sup> (a) Hsu, R.; Cheng, Li. *J. Org. Chem.*, **2002**, *67*, 5044-5047; (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron*, **1985**, *41*, 4380-4381; (c) Speckamp, W. N.; Hubert, J. C. *Tetrahedron*, **1975**, *31*, 1437-1441.
- <sup>134</sup> Borch, R. F.; Durst, H. D. *J. Am. Chem. Soc.*, **1969**, *91*, 3996-3997.
- <sup>135</sup> Giblin, G. M. P.; Kirk, D. T. *Org. Lett.*, **2003**, *5*, 1673-1675.
- <sup>136</sup> Luche, J. L. *J. Am. Chem. Soc.*, **1978**, *100*, 2226-2227.
- <sup>137</sup> Steinhuebel, D. P.; Krska, S. W. *Org. Lett.* **2010**, *12*, 4201-4203.
- <sup>138</sup> (a) Wienhöfer, G.; Westerhaus, F. A.; Jagadeesh, R. V.; Junge, K.; Junge, H.; Beller, M. *Chem. Commun.*, **2012**, *48*, 4827-4829; (b) Horn, S.; Albrecht, M. *Chem. Commun.*, **2011**, *47*, 8802-8804; (c) Black, P. B.; Cami-Kobeci, G.; Edwards, M. G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. *J. Org. Biomol. Chem.*, **2006**, *4*, 116-125.
- <sup>139</sup> Xue, D.; Chen, Y. -C.; Cui, X.; Wang, Q. -W.; Zhu, J.; Deng, J. -G. *J. Org. Chem.*, **2005**, *70*, 3584-3591.
- <sup>140</sup> (a) Schneider, J. F.; Lauber, M. B.; Muhr, V.; Kratzer, D.; Paradies, J. *J. Org. Biomol. Chem.*, **2011**, *9*, 4323-4327; (b) Hopmann, K. H.; Bayer, A. *Organometallics*, **2011**, *30*, 2483-2497; (c) Tang, Y.; Xiang, J.; Cun, L.; Wang, Y.; Zhu, J.; Liao, J.; Deng, J. *Tetrahedron: Asymmetry*, **2010**, *21*, 1900-1905; (d) Soltani, O.; Ariger, M. A.; Carreira, E. M. *Org. Lett.*, **2009**, *11*, 4196-4198.

- 
- <sup>141</sup> (a) Rickerby, J.; Vallet, M.; Bernardinelli, G.; Viton, F.; Kündig, E. P. *Chem. Eur. J.*, **2007**, *13*, 3354-3368; (b) Thamapipol, S.; Kündig, E. P. *Org. Biomol. Chem.*, **2011**, *9*, 7564-7570.
- <sup>142</sup> (a) Xue, D.; Chen, Y.-C.; Cui, X.; Wang, X.-W.; Zhu, J.; Deng, J.-G. *J. Org. Chem.*, **2005**, *70*, 3584-3591. (b) Chen, Y.-C.; Xue, D.; Deng, J.-G.; Cui, X.; Zhu, J.; Jiang, Y.-Z. *Tetrahedron Lett.*, **2004**, *45*, 1555-1558.
- <sup>143</sup> (a) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.*, **1999**, *64*, 6907-6910.; (b) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.*, **2002**, *124*, 14552-14553.
- <sup>144</sup> Padwa, A.; Hertzog, D. L. *Tetrahedron*, **1993**, *49*, 2589-2600.
- <sup>145</sup> Mulzer, J.; Zuhse, R.; Schmiechen, R. *Angew. Chem. Int. Ed. Engl.*, **1992**, *31*, 870-871.
- <sup>146</sup> Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.*, **1980**, *102*, 6304-631.
- <sup>147</sup> Almeida, J. F.; Anaya, J.; Martin, N.; Grande, M.; Moran, J. R.; Carballero, M. C. *Tetrahedron: Asymmetry*, **1992**, *3*, 1431-1440.
- <sup>148</sup> Chang, D.; Witholt, B.; Li, Z. *Org. Lett.*, **2000**, *2*, 3949-3952.
- <sup>149</sup> (a) Koot, W.-J.; van Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.*, **1991**, *32*, 401-404; (b) Huang, P. Q.; Zheng, X.; Wang, S. L.; Ye, J. L.; Jin, L. R.; Chen, Z. *Tetrahedron: Asymmetry*, **1999**, *10*, 3309-3317.
- <sup>150</sup> Athanasellis, G.; Igglessi-Markopoulou, O.; Markopoulos, J. *Bioinorganic Chemistry and Application*. **2010**, *2010*, Article ID 315056, 11 pages.
- <sup>151</sup> Hamilakis, S.; Kontonassios, D.; Sandris, C. *J. Heterocyclic Chem.*, **1996**, *33*, 825-829.
- <sup>152</sup> Mulholland, T. P. C.; Foster, R.; Haydock, D. B. *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2121-2128.
- <sup>153</sup> (a) Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1177-1182; (b) Oba, M.; Ito, C.; Hayashi, T.; Nishiyama, K. *Tetrahedron Letters*, **2009**, *50*, 5053-5055.
- <sup>154</sup> Eustache, F.; Dalko, P. I.; Cossy, J. *Org. Lett.*, **2002**, *4*, 1263-1265.
- <sup>155</sup> Kumarasamy, E.; Jesuraj, J. L.; Omlid, J. N.; Ugrinov, A.; Sivaguru, J. *J. Org. Chem.*, **2011**, *133*, 17106-17109.

- 
- <sup>156</sup> (a) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. *Chem. Rev.*, **2009**, *109*, 2551–2651; (b) Bardot, V.; Gardette, D.; Gelas-Mialhe, Y.; Gramain, J. –C.; Remuson, R. *Heterocycles*, **1998**, *48*, 507-518.
- <sup>157</sup> Yazici, A.; Pyne, S. G. *Synthesis*, **2009**, *4*, 0513-0541.
- <sup>158</sup> Bennett, D. J.; Blake, A. J.; Cooke, P. A.; Godfrey, C. R. A.; Pickering, P. L.; Simpkins, N. S.; Walker, M. D.; Wilson, C. *Tetrahedron*, **2004**, 4491-4511.
- <sup>159</sup> Pereira, E.; de Fátima Alves, C.; Böckelmann, M. A.; Pilli, R. A. *Tetrahedron Lett.*, **2005**, *46*, 2691-2693.
- <sup>160</sup> Cheng, D.; Croft, L.; Abdi, M.; Lightfoot, A.; Gallagher, T. *Org. Lett.*, **2007**, *9*, 5175-5178.
- <sup>161</sup> Mellor, B. J.; Murray, P. E.; Thomas, E. J. *Tetrahedron*, **1998**, *54*, 243-256.
- <sup>162</sup> Kim, M. –H.; Park, Y.; Jeong, B. –S.; Park, H. –G.; Jew, S. –S. *Org. Lett.*, **2010**, *12*, 2826-2829.
- <sup>163</sup> Paquette, L. A. (1995) *Encyclopaedia of reagents for organic synthesis*. New York; Chichester: Wiley.
- <sup>164</sup> McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S. P.; Pfaltz, A. *Adv. Synth. Catal.*, **2005**, *347*, 282-288.
- <sup>165</sup> (a) Leonard, N. J.; Conrow, K.; Sauers, R. R. *J. Am. Chem. Soc.*, **1958**, *80*, 5185–5193; (b) Rice, L. M.; Grogan, C. H. *J. Org. Chem.*, **1958**, *23*, 844-846.
- <sup>166</sup> (a) Somaiah, S.; Sashikanth, S.; Raju, V.; Reddy, K. P. *Tetrahedron: Asymmetry*, **2011**, *22*, 1-3; (b) Gill, C. D.; Greenahlgh, D. A.; Simpkins, N. S. *Tetrahedron*, **2003**, *59*, 9213-9230.
- <sup>167</sup> Breugst, M.; Mayr, H. *J. Am. Chem. Soc.*, **2010**, *132*, 15380-15389.
- <sup>168</sup> Lanni, E. L.; Bosscher, M. A.; Ooms, B. D.; Shandro, C. A.; Ellsworth, B. A.; Anderson, C. E. *J. Org. Chem.*, **2008**, *73*, 6425-6428.
- <sup>169</sup> Igarashi, M.; Fuchikami, T. *Tetrahedron Lett.*, **2001**, *42*, 1945-1947.
- <sup>170</sup> (a) Potter, R.; Horti, A. G.; Ravert, H. T.; Holt, D. P.; Finley, P.; Scheffl, U.; Dannais, R. F.; Wahl, R. L. *Bioorg. Med. Chem.*, **2011**, *19*, 2368–2372; (b) Miller, J. F.; Turner, E. M.; Gudmundsson, K. S.; Jenkinson, S.; Spaltenstein, A.; Thomson, M.; Wheelan, P. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 2125–2128; (c) Hernando, J. L. M.; Ontoria, J. M.; Malancona, S.; Attenni, B.; Fiore, F.; Bonelli, F.; Koch, U.; Di Marco, S.; Colarusso, S.; Ponzi, S.; Gennari, N.; Vignetti, S. E.; Ferreira, M. R. R.; Habermann, J.; Rowley, M.; Narjes, F. *ChemMedChem*, **2009**, *4*, 1695–1713; (d)

---

Stansfield, I.; Pompei, M.; Conte, I.; Ercolani, C. Migliaccio, G.; Jairaj, M.; Giuliano, G.; Rowley, M.; Narjes, F. *Bioorg. Med. Chem. Lett.*, **2007**, *17*, 5143–5149; (e) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Tetrahedron: Asymmetry*, **1996**, *7*, 345-348; (f) Rivera, J.; Jayasuriya, N.; Rane, D.; Keertikar, K.; Ferreira, J. A.; Chao, J.; Minor, K.; Guzi, T. *Tetrahedron Lett.*, **2002**, *43*, 8917-8919; (g) Wirza, B.; Waltherb, W. *Tetrahedron: Asymmetry*, **1992**, *3*, 1049-1054; (h) Magnus, P.; Thurston, L. S. *J. Org. Chem.*, **1991**, *56*, 1166-1170.

<sup>171</sup> Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.*, **1981**, *22*, 3815-3818.

<sup>172</sup> (a) Wu, J.; Ji, J. –X.; Guo, R.; Yeung, C. –H.; Chan, A. S. C. *Chem. Eur. J.*, **2003**, *9*, 2963-2968; (b) Kwong, H. –L.; Lee, W. –S.; Lai, T. –S.; Wong, W. –T. *Inorg. Chem. Commun.*, **1999**, *2*, 66-69; (c) Nordin, S. J. M.; Roth, P.; Tarnai, T.; Alonso, D. A.; Brandt, P.; Andersson, P. G. *Chem. Eur. J.*, **2001**, *7*, 1431-1436.

<sup>173</sup> Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett.*, **2000**, *41*, 9277-9280.

<sup>174</sup> (a) Morris, D. J.; Hayes, A. M.; Wills, M. *J. Org. Chem.*, **2006**, *71*, 7035-7044; (b) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.*, **2005**, *127*, 7318-7319.

<sup>175</sup> Martins, J. E. D.; Clarkson, G. J.; Wills, M. *Org. Lett.*, **2009**, *11*, 847-850.

<sup>176</sup> Crabtree, R. H.; Davis, M. W. *J. Org. Chem.*, **1986**, *51*, 2655-2661.

<sup>177</sup> Tomohiro, O.; Zenyu, S.; Yuta, T.; Satoshi, S. *Fused Heterocyclic Ring Derivatives and use thereof*, RC. Patent EP2471789 (A1), July 4<sup>th</sup>, 2004.

<sup>178</sup> Bisset, A. A.; Shiibashi, A.; Desmond, J. L.; Dishington, A.; Jones, T.; Clarkson, G. J.; Ikariya, T.; Wills, M. *Chem. Commun.*, **2012**, *48*, 11978-11980.

<sup>179</sup> Burdzhiev, N. T.; Stanoeva, E. R. *Tetrahedron*, **2006**, *62*, 8318-8326.

<sup>180</sup> Cadoret, F.; Retaileau, P.; Six, Y. *Tetrahedron Lett.*, **2006**, *47*, 7749-7753.

<sup>181</sup> Azoulay, M.; Vilmont, M.; Frappier, F. *Eur. J. Med. Chem.*, **1991**, *26*, 201-205.

<sup>182</sup> Gigant, N.; Gillaizeau, I. *Org. Lett.*, **2012**, *12*, 3304-3307.

<sup>183</sup> Braibante, M. E. F.; Braibante, H. S.; Missio, L.; Andricopulo, A. *Synthesis*, **1994**, *9*, 898-900.

<sup>184</sup> (a) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.*, **1999**, *64*, 6907-6910.; (b) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.*, **2002**, *124*, 14552–14553.

<sup>185</sup> Padwa, A.; Hertzog, D. L. *Tetrahedron*, **1993**, *49*, 2589-2600.

- <sup>186</sup> Størgaard, M.; Dörwald, F. Z.; Peschke, B.; Tanner, D. *J. Org. Chem.*, **2009**, *74*, 5032–5040.
- <sup>187</sup> Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1177–1182.
- <sup>188</sup> Courcambeck, J.; Bihel, F.; De Michelis, C.; Quéléver, G.; Kraus, J. L. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 1421–1430.
- <sup>189</sup> Sartori, A.; Curti, C.; Battistini, L.; Burreddu, P.; Rassu, G.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Tetrahedron*, **2008**, *64*, 11697–11705.
- <sup>190</sup> Chang, D.; Witholt, B.; Li, Z. *Org. Lett.*, **2000**, *2*, 3949–3952.
- <sup>191</sup> Nair, V.; Chi, G.; Uchil, V. R. *Diketo acids on nucleobase scaffolds as inhibitors of Flaviviridae.*, US. Patent 20060223834 (A1). Oct. 5<sup>th</sup>, 2006.
- <sup>192</sup> Fujii, T.; Yoshifuji, S.; Tamai, A. *Chem. Pharm. Bull.*, **1971**, *19*, 396–376.
- <sup>193</sup> Dainter, R. S.; Suschitzky, H.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 227–233.
- <sup>194</sup> Zhang, Y.; Loertscher, B. M.; Castle, S. L. *Tetrahedron*, **2009**, *65*, 6584–6590.
- <sup>195</sup> Kozikowski, A. P.; Xia, Y.; Reddy, E. R.; Tuckmantel, W.; Hanin, I.; Tang, X. C. *J. Org. Chem.*, **1991**, *56*, 4636–4645.
- <sup>196</sup> Mellor, B. J.; Murray, P. E.; Thomas, E. J. *Tetrahedron*, **1998**, *54*, 243–256.
- <sup>197</sup> Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.*, **1994**, *59*, 3575–3584.
- <sup>198</sup> Lerchner, A.; Carreira, E. M. *Chem. Eur. J.*, **2006**, *12*, 8208 – 8219.
- <sup>199</sup> Lanni, E. L.; Bosscher, M. A.; Ooms, B. D.; Shandro, C. A.; Ellsworth, B. A.; Anderson, C. E. *J. Org. Chem.*, **2008**, *73*, 6425–6428.
- <sup>200</sup> Moenius, T.; Troxler, T.; Masero, R. *J. Label. Compd. Radiopharm.*, **2007**, *50*, 613–615.
- <sup>201</sup> Slowinski, F.; Ayad, O. B.; Vache, J.; Saady, M.; Leclerc, O.; Lohead, A. *J. Org. Chem.*, **2011**, *76*, 8336–8346.
- <sup>202</sup> Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Heterocycl. Chem.*, **1998**, *35*, 717–724.
- <sup>203</sup> Anderson, A. G.; Berkelhammer, G. *J. Am. Chem. Soc.*, **1958**, *80*, 992–999.
- <sup>204</sup> Rieke, R. D.; Suh, Y.; Kim, S. H. *Tetrahedron Lett.*, **2005**, *46*, 5961–5964.
- <sup>205</sup> Yamamoto, Y.; Kurihara, K.; Miyaura, N. *Angew. Chem. Int. Ed.*, **2009**, *48*, 4414–4416.
- <sup>206</sup> Stepanenko, V.; De Jesús, M.; Correa, W.; Guzmán, I.; Vázquez, C.; Ortiz, L.; Ortiz-Marciales, M. *Tetrahedron: Asymmetry*, **2007**, *18*, 2738–2745.

## Appendix I: NMR Spectra: Spectra from Section 2.1.

### (E)-1-benzyl-4-((2-oxopyridin-1(2H)-yl)methylene)piperidine-2,6-dione, 1.

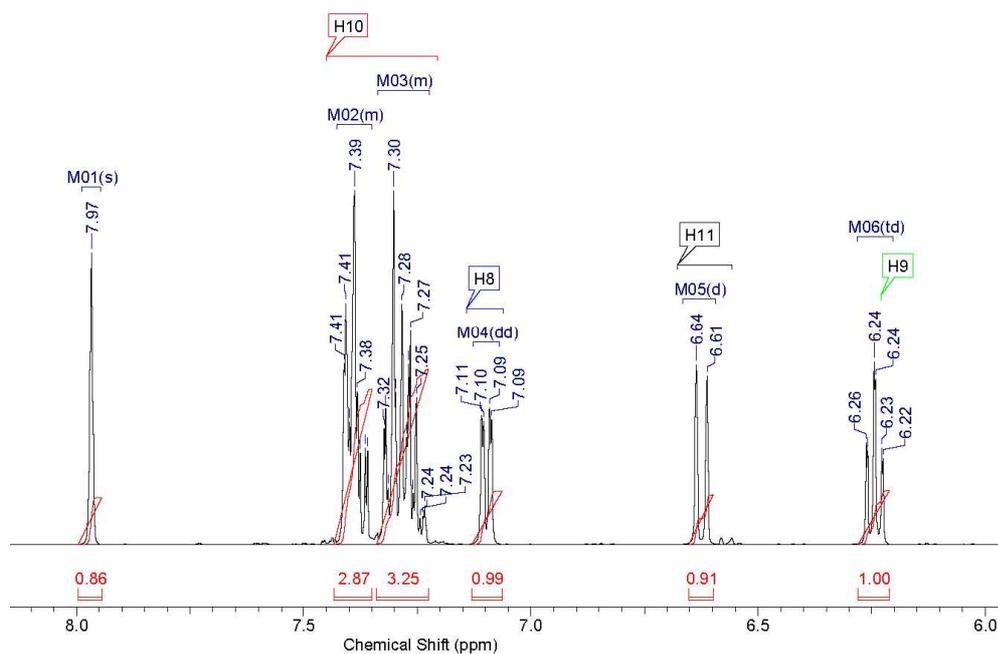
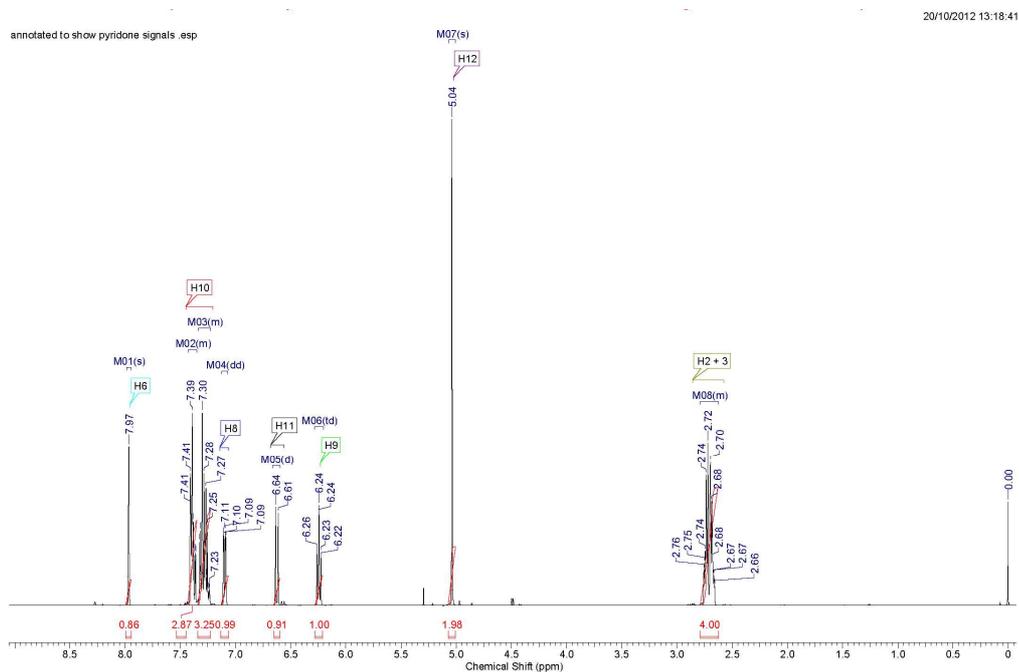
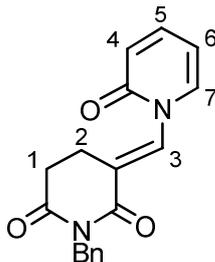


Figure 1:  $^1\text{H}$  NMR spectrum of **1**, 400 MHz,  $\text{CDCl}_3$ .



*1-benzyl-3-[(pyridin-2-yloxy)methyl]piperidine-2,6-dione, 227.*

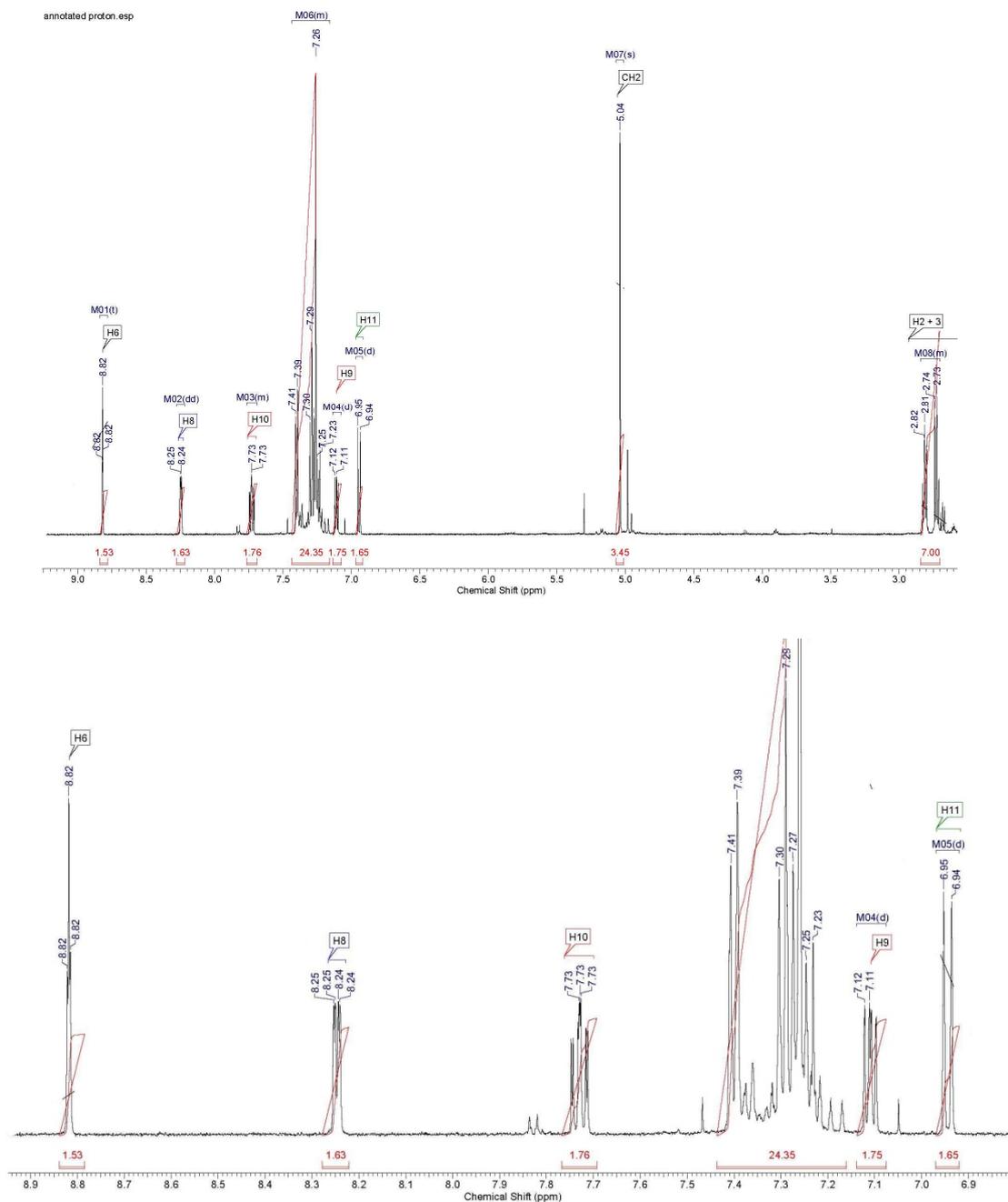
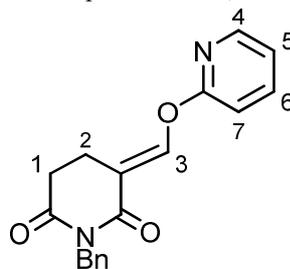


Figure 2: <sup>1</sup>H NMR spectra of 227, 500 MHz, CDCl<sub>3</sub>.



Spectra from Section 2.4.

1-((6-methoxypyridin-3-yl)methyl)pyridin-2(1H)-one **295**.

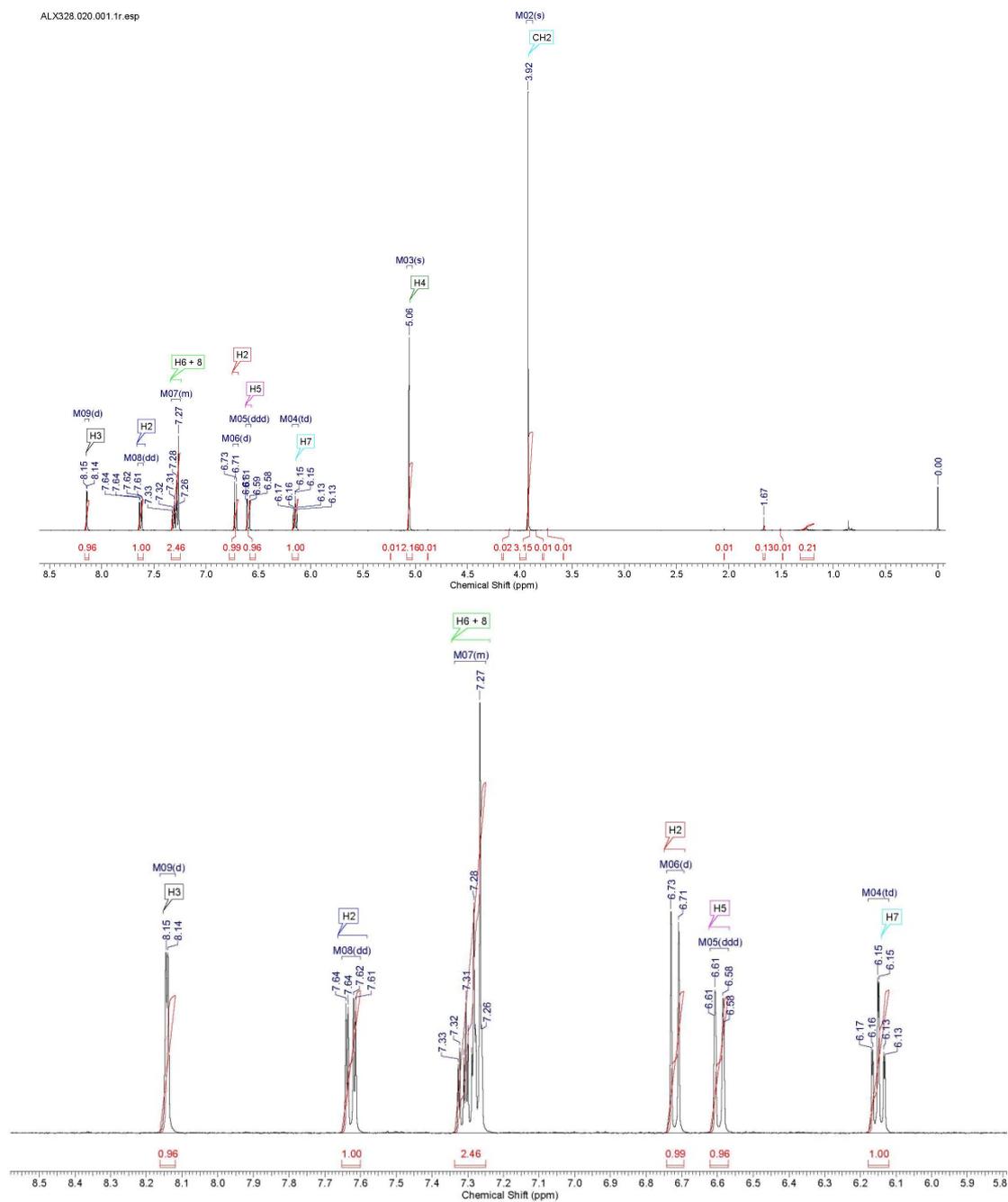
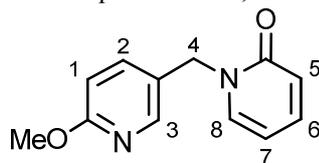


Figure 3:  $^1\text{H}$  NMR spectra of **295**, 400 MHz,  $\text{CDCl}_3$ .



2-methoxy-5-((pyridin-2-yloxy)methyl)pyridine, **297**.

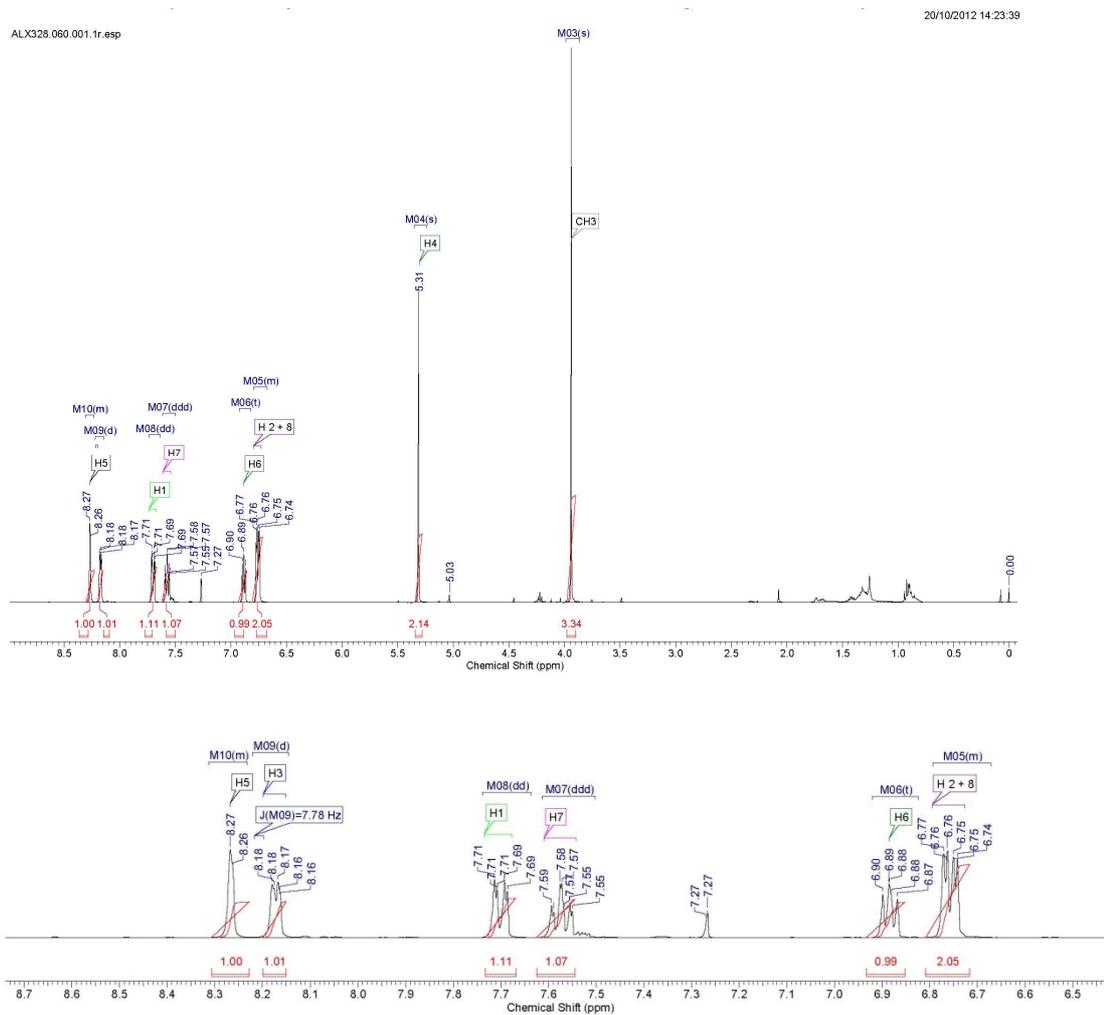
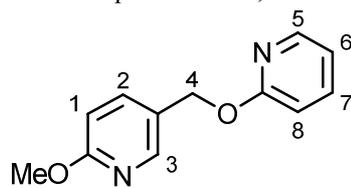


Figure 4:  $^1\text{H}$  NMR spectra of **297**, 400 MHz,  $\text{CDCl}_3$ .



*1-Benzyl-3-(piperidin-1-ylmethyl)piperidine, (±)-6.*

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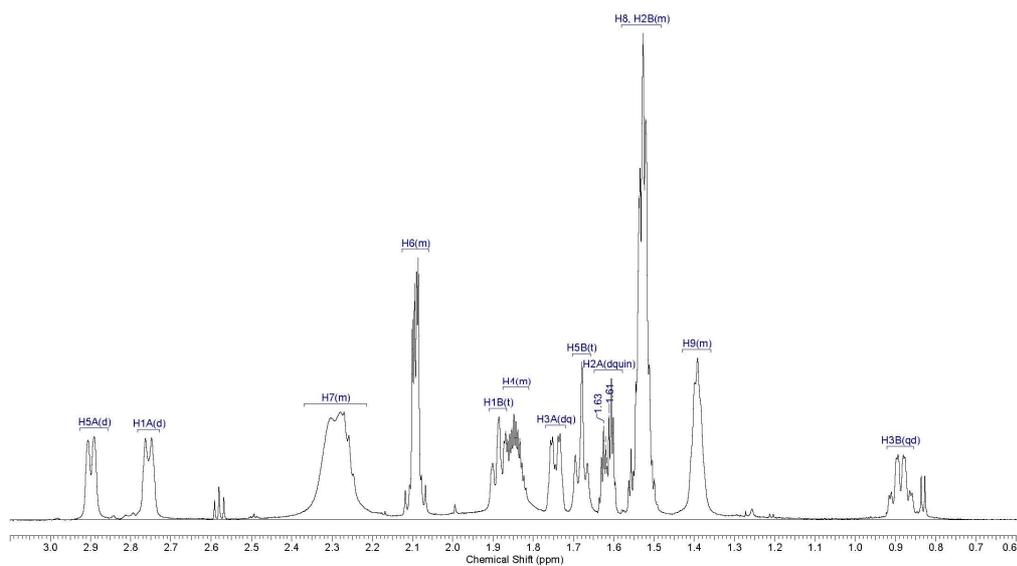
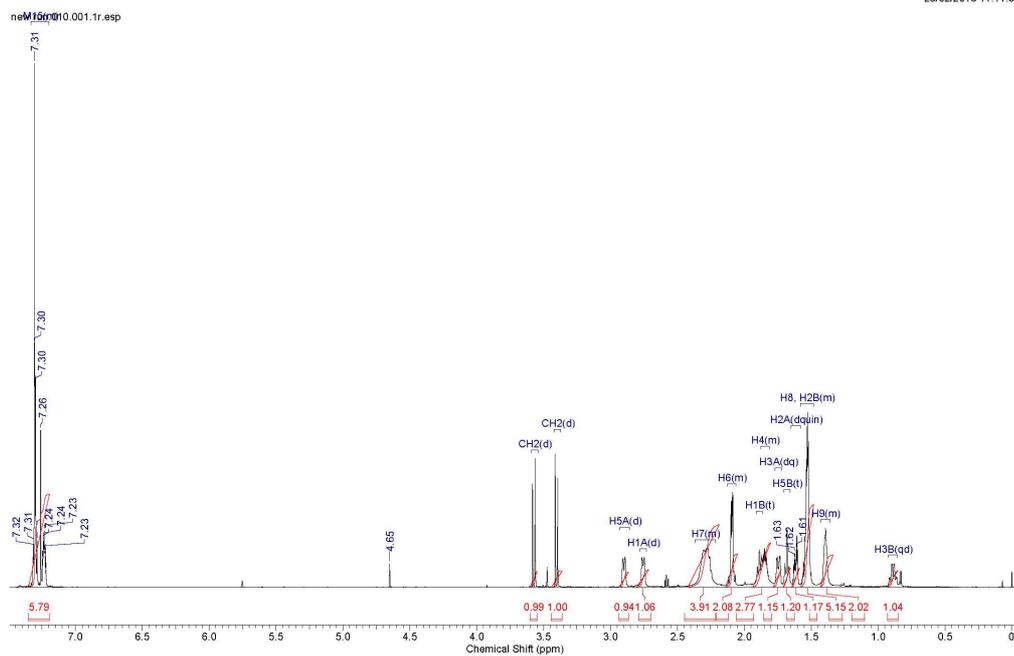
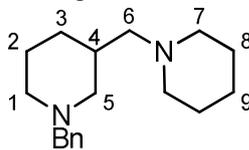


Figure 5:  $^1\text{H}$  NMR spectra of **6**, 700 MHz,  $\text{CDCl}_3$ .



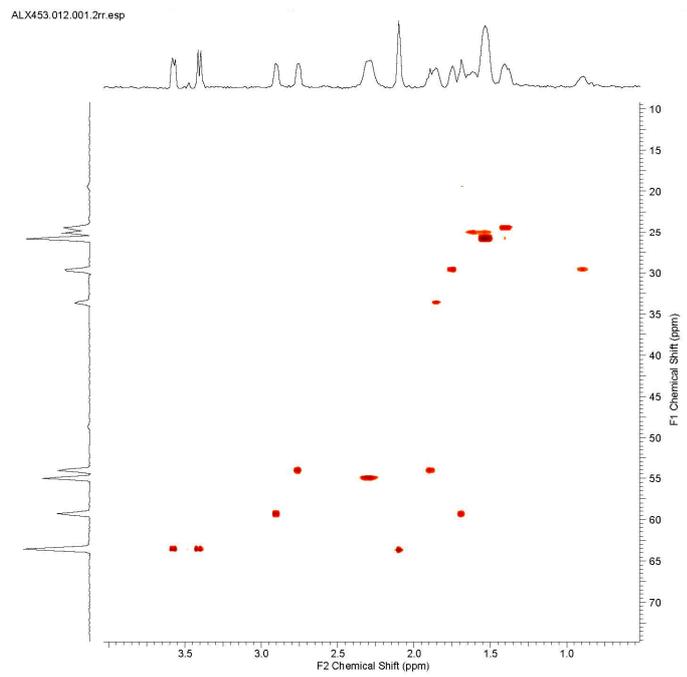


Figure 6: HMQC spectra of **6**, 700 MHz ( $^1\text{H}$ ), 176 MHz ( $^{13}\text{C}$ )  $\text{CDCl}_3$ .

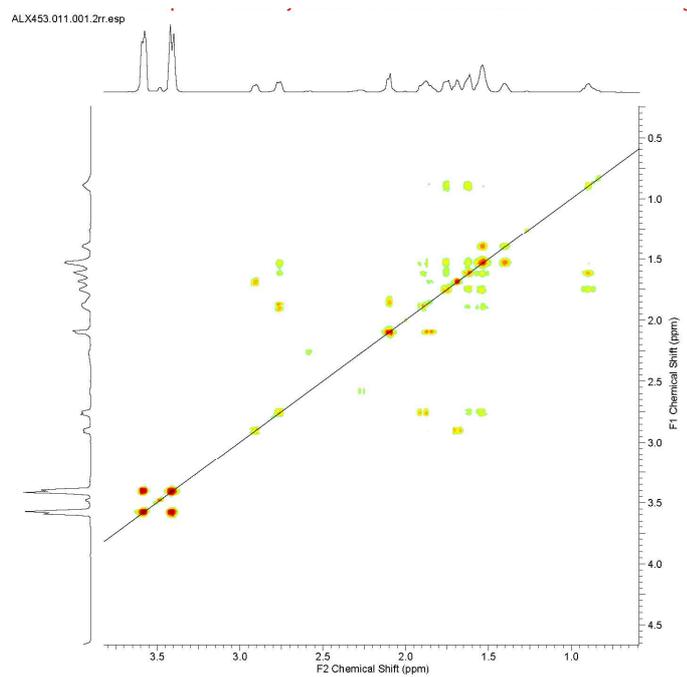


Figure 7: COSY spectra of **6**, 700 MHz ( $^1\text{H}_1$ ,  $^1\text{H}_2$ ),  $\text{CDCl}_3$ .

Spectra from Section 2.5.

1-benzyl-5-(1-hydroxyethyl)piperidin-2-one, D1-7.

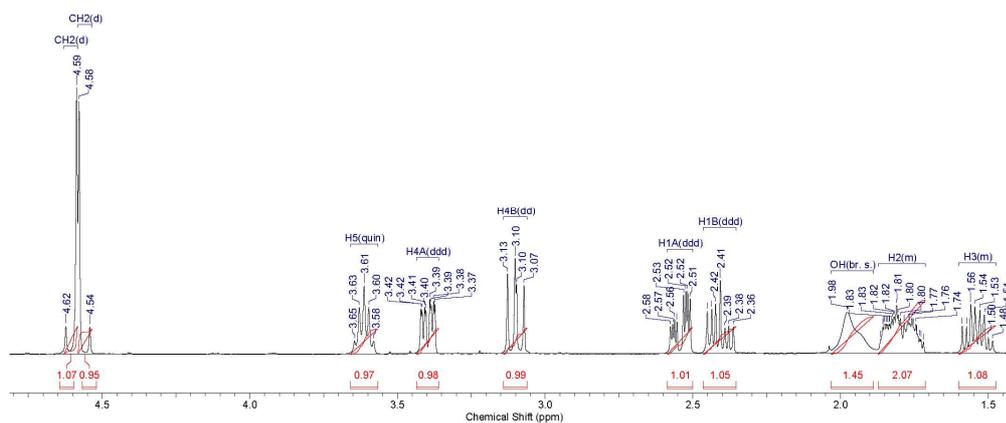
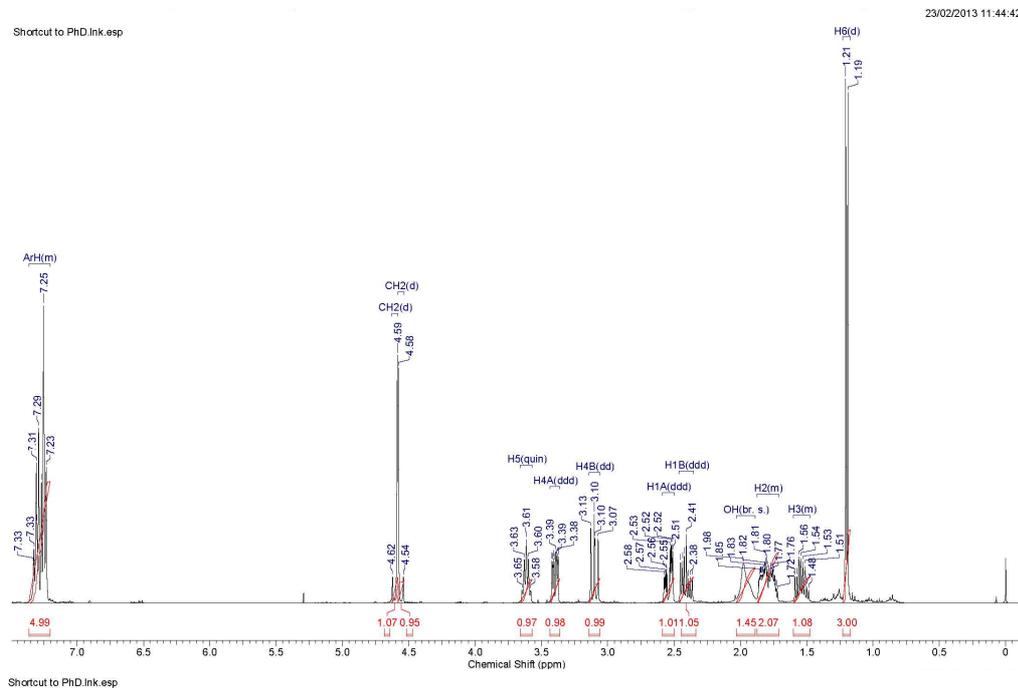
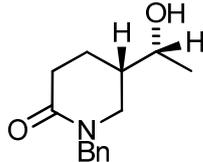


Figure 8:  $^1\text{H}$  NMR spectra of (D1)-7, 400 MHz,  $\text{CDCl}_3$ .



*1-benzyl-5-(1-hydroxyethyl)piperidin-2-one, D2-7.*

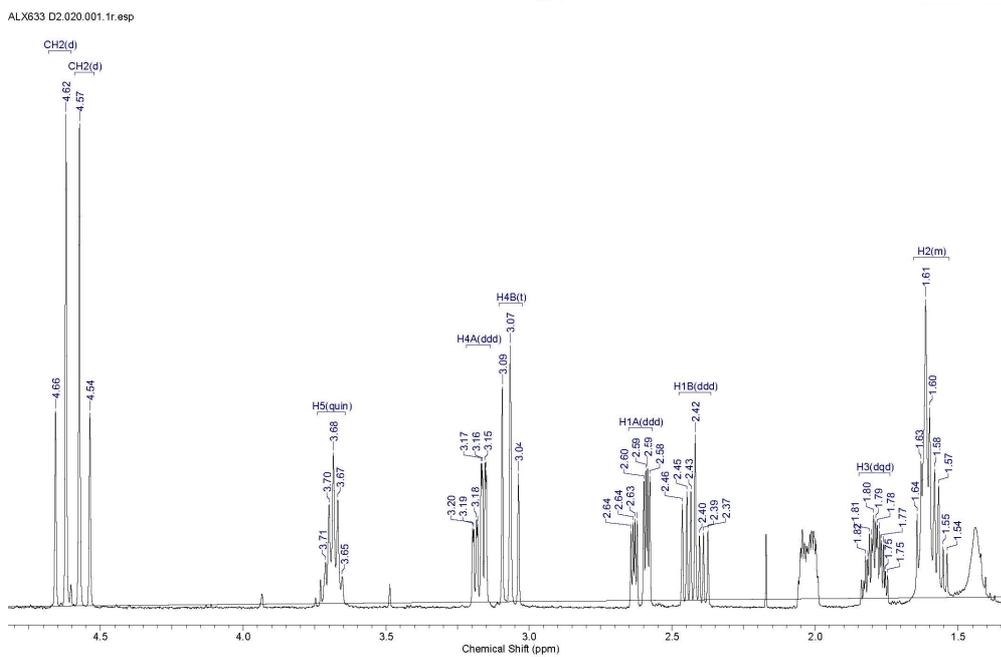
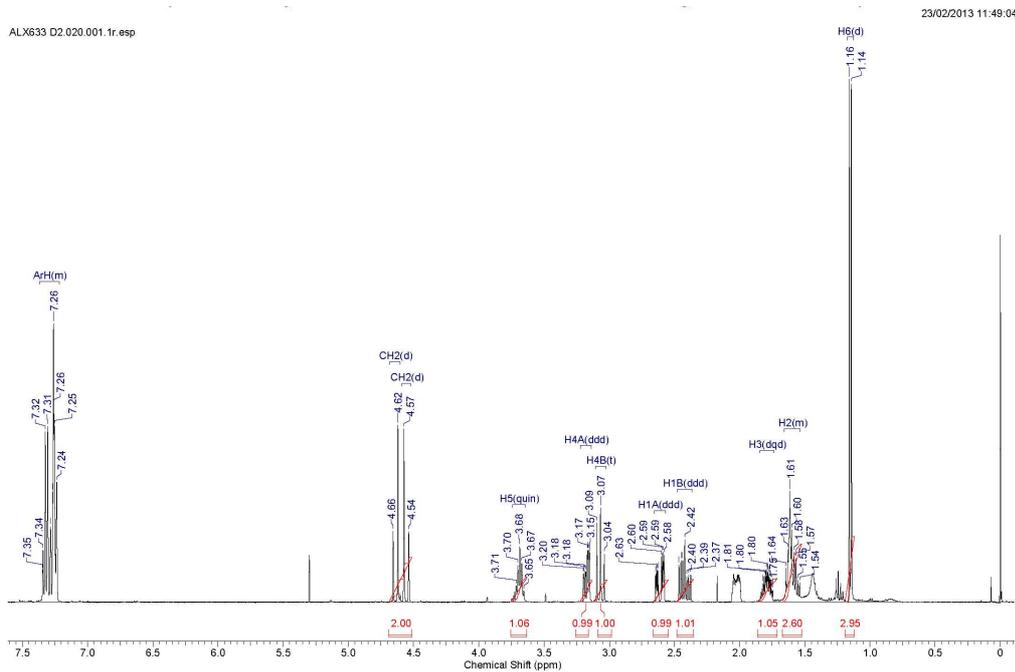
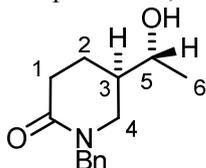


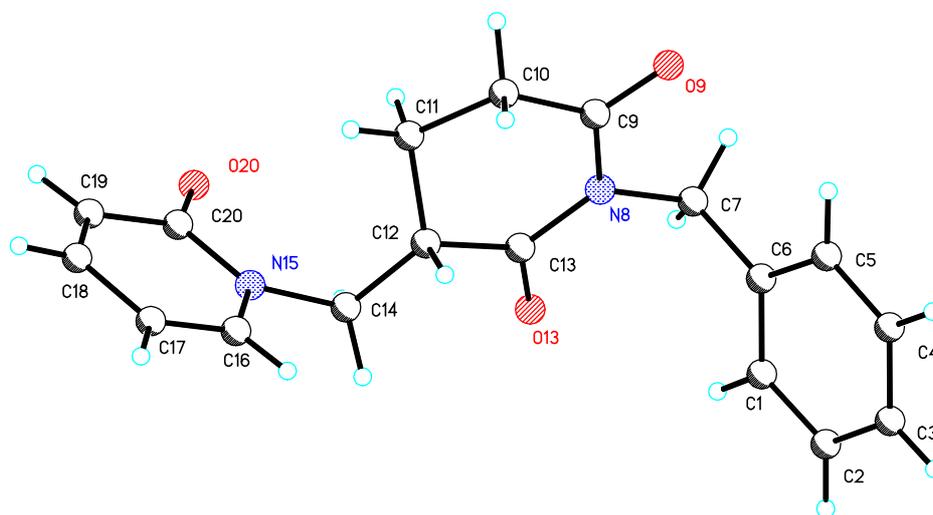
Figure 9:  $^1\text{H}$  NMR spectra of 7, 400 MHz,  $\text{CDCl}_3$ .



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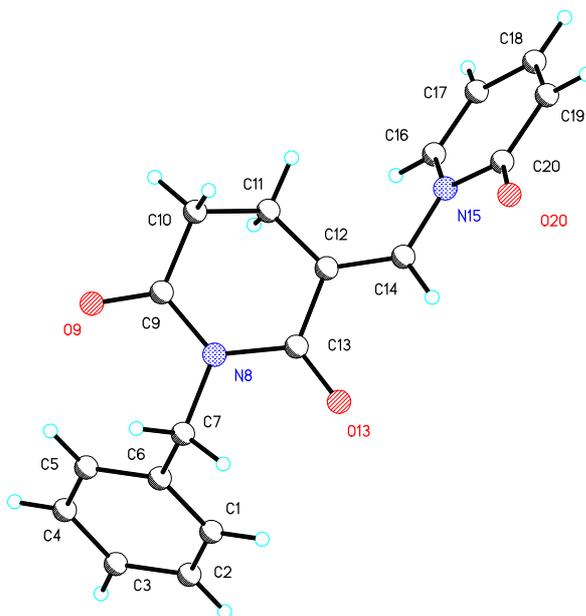
## Appendix II: X-Ray Crystal Structures.

### *1-Benzyl-3-((2-oxopyridin-1-yl)methyl)piperidine-2,6-dione, (±)-218.*



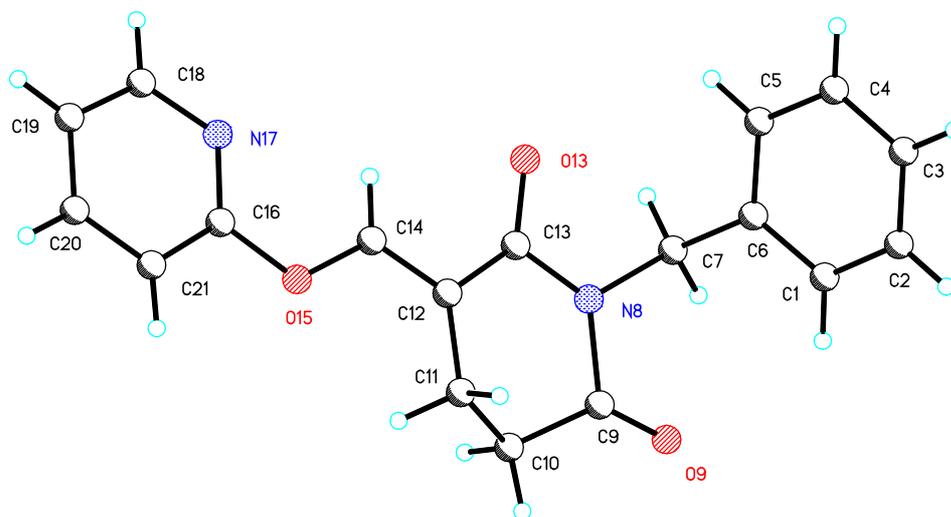
This structure was obtained from the diffraction of a crystal of racemic **218** which had formed from a sample of enantiomerically enriched **13** (90 % ee). The structure was found to have weak data, due to the overlapping presence of the two enantiomers. The pyridone ring was modeled due to disordered over these two positions. Crystallographic data for **218**:  $C_{18}H_{18}N_2O_3$ ,  $M = 310.34$ , Monoclinic, space group  $P2(1)/c$ ,  $a = 10.80640(10)$ ,  $b = 9.82230(10)$ ,  $c = 14.8463(2)$  Å,  $\alpha = 90$  deg.,  $\beta = 98.1460(10)$  deg.,  $\gamma = 90$  deg.,  $U = 1559.94(3)$  Å<sup>3</sup> (by least squares refinement on 14247 reflection positions),  $T = 100(2)$  K,  $\lambda = 1.54178$  Å,  $Z = 4$ ,  $D(\text{cal}) = 1.321$  Mg/m<sup>3</sup>,  $F(000) = 656$ .  $mv(\text{MoK-}\alpha) = 0.741$  mm<sup>-1</sup>. Crystal character: colourless block. Crystal dimensions 0.24 x 0.20 x 0.10 mm. 19357 reflections measured, 2425 unique [ $R(\text{int}) = 0.0293$ ].

*(E)*-1-Benzyl-3-((2-oxopyridin-1(2H)-yl)methylene)piperidine-2,6-dione, **1**.



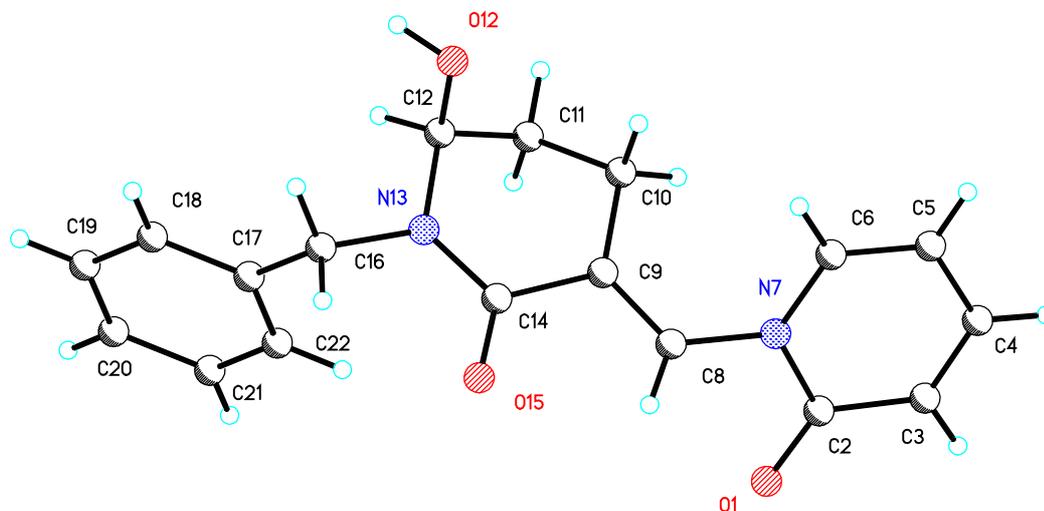
This structure was obtained by Akira Shiibashi. Crystallographic data for **1** (CCDC873751): C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>, M = 308.33, Monoclinic, space group P21/c, a = 13.8161(4), b = 9.6613(2), c = 11.7717(3) Å, α = 90 deg., β = 107.2680(10) deg., γ = 90 deg. U = 1500.48(7) Å<sup>3</sup> (by least squares refinement on 9224 reflection positions), T = 120(2) K, λ = 0.71073 Å, Z = 4, D(cal) = 1.365 Mg/m<sup>3</sup>, F(000) = 648. μ(MoK-α) = 0.094 mm<sup>-1</sup>. Crystal character: colourless block. Crystal dimensions 0.60 x 0.38 x 0.05 mm. 20600 reflections measured, 3425 unique [R(int) = 0.0430].

*(3E)*-1-benzyl-3-[(pyridin-2-yloxy)methylidene]piperidine-2,6-dione, **227**.



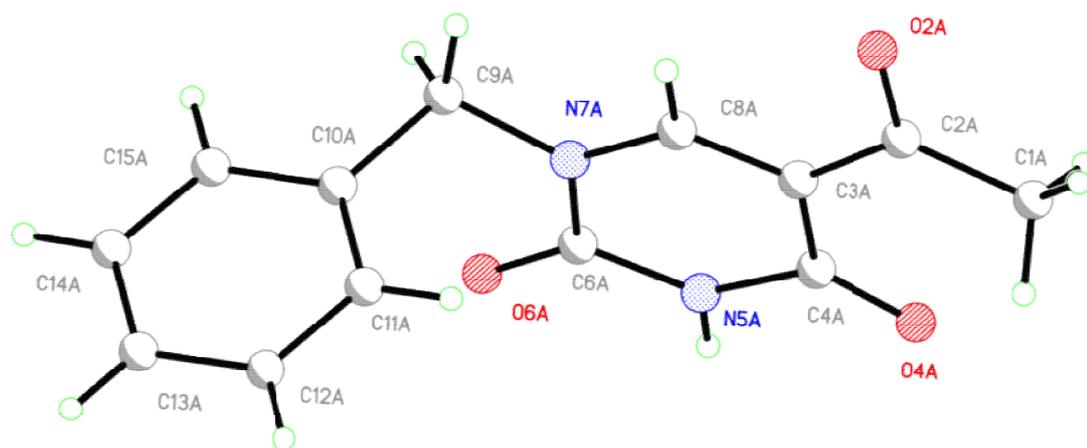
This structure was obtained by Akira Shiibashi. Crystallographic data for **227** (CCDC873752): C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>, M = 308.33, Monoclinic, space group P21/c, a = 14.0338(5) b = 8.3474(3), c = 13.1017(3) Å, α = 90 deg., β = 96.381(2) deg., γ = 90 deg. U = 1525.30(8) Å<sup>3</sup> (by least squares refinement on 13564 reflection positions), T = 298(2) K, lambda = 0.71073 Å, Z = 4, D(cal) = 1.343 Mg/m<sup>3</sup>, F(000) = 648. mu(MoK-α) = 0.093 mm<sup>-1</sup>. Crystal character: pale block. Crystal dimensions 0.58 x 0.38 x 0.25 mm. 27338 reflections measured, 3487 unique [R(int) = 0.0544].

*(Z)*-1-((1-Benzyl-6-hydroxy-2-oxopiperidin-3-ylidene)methyl)pyridin-2(1H)-one, **238**



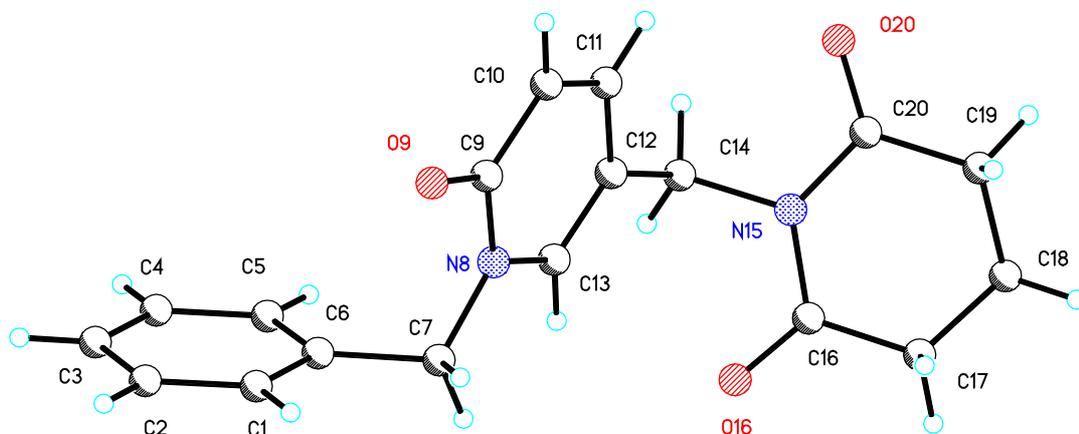
Crystallographic data for **238** (CCDC873750):  $C_{18}H_{18}N_2O_3$ ,  $M = 310.34$ , Tetragonal, space group P4122,  $a = 8.92910(10)$ ,  $b = 8.92910(10)$ ,  $c = 39.0823(7)$  Å,  $\alpha = 90$  deg.,  $\beta = 90$  deg.,  $\gamma = 90$  deg.  $U = 3115.99(7)$  Å<sup>3</sup> (by least squares refinement on 6800 reflection positions),  $T = 298(2)$  K,  $\lambda = 1.54184$  Å,  $Z = 8$ ,  $D(\text{cal}) = 1.323$  Mg/m<sup>3</sup>,  $F(000) = 1312$ .  $\mu$  (MoK- $\alpha$ ) =  $0.741$  mm<sup>-1</sup>. Crystal character: colourless block. Crystal dimensions  $0.20 \times 0.20 \times 0.20$  mm. 18002 reflections measured, 1852 unique [ $R(\text{int}) = 0.0443$ ].

*5-Acetyl-1-benzylpyrimidine-2,4(1H,3H)-dione*, **269**.



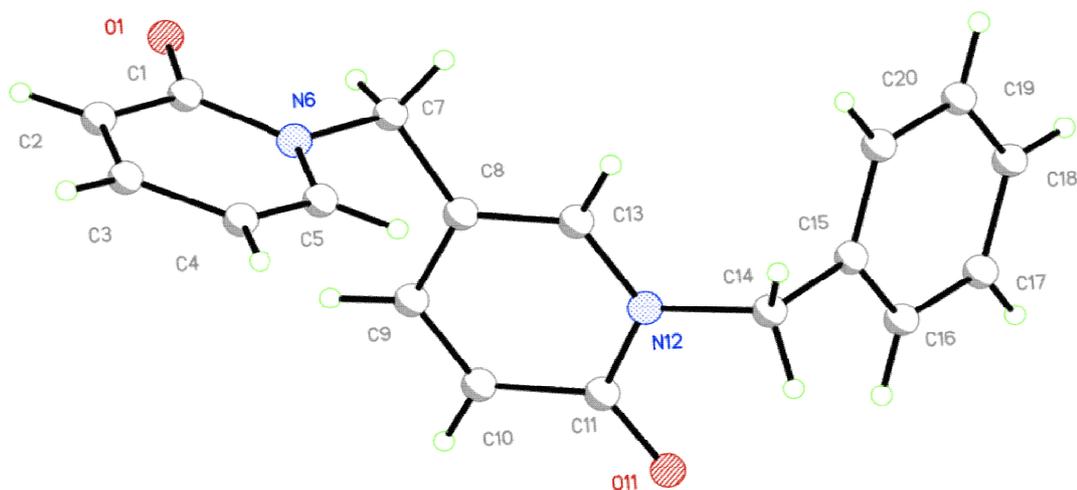
This structure was determined by the EPSRC Crystallographic Service. Crystallographic data for **269**: C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>, M = 244.25, Monoclinic, space group P2(1)/n, a = 9.680(15), b = 23.71(3), c = 10.025(13) Å, alpha = 90 deg., beta = 97.78(3) deg., gamma = 90 deg., U = 2280(5) Å<sup>3</sup> (by least squares refinement on 453 reflection positions), T = 100(2)K, lambda = 0.71075 Å, Z = 8, D(cal) = 1.423 Mg/m<sup>3</sup>, F(000) = 1024. mv (MoK-alpha) = 0.103 mm<sup>-1</sup>. Crystal character: colourless needle. Crystal dimensions 0.20 x 0.01 x 0.01 mm, 25462 reflections measured, 5220 unique [R(int) = 0.0623].

*1-[(1-Benzyl-6-oxo-1,6-dihydropyridin-3-yl)methyl]piperidine-2,6-dione, 2.*



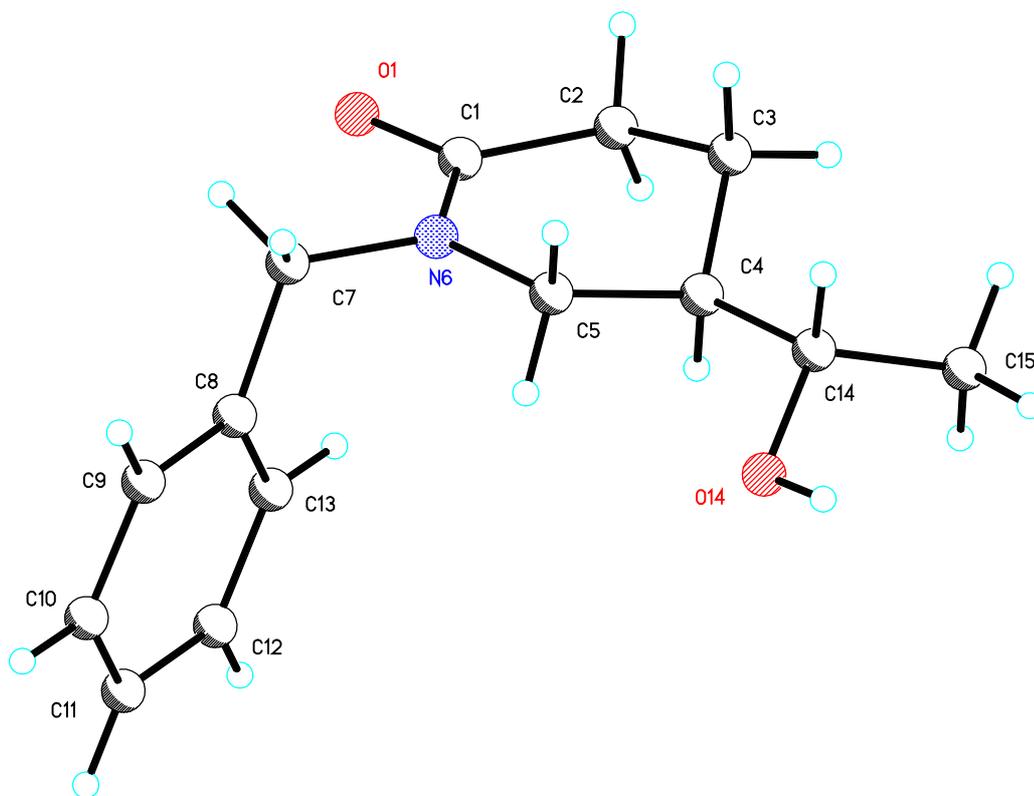
Crystallographic data for **2**:  $C_{18}H_{18}N_2O_3$ ,  $M = 310.34$ , Orthorhombic, space group  $Pbca$ ,  $a = 8.60003(9)$ ,  $b = 17.41730(19)$ ,  $c = 20.1379(3)\text{\AA}$ ,  $\alpha = 90\text{ deg.}$ ,  $\beta = 90\text{ deg.}$ ,  $\gamma = 90\text{ deg.}$ ,  $U = 3016.45(6)\text{ \AA}^3$  (by least squares refinement on 9775 reflection positions),  $T = 100(2)\text{K}$ ,  $\lambda = 1.54184\text{ \AA}$ ,  $Z = 8$ ,  $D(\text{cal}) = 1.367\text{ Mg/m}^3$ ,  $F(000) = 1312$ .  $mv(\text{MoK}\text{-}\alpha) = 0.766\text{ mm}^{-1}$ . Crystal character: colourless block. Crystal dimensions  $0.40 \times 0.40 \times 0.28\text{ mm}$ , 15826 reflections measured, 2892 unique [ $R(\text{int}) = 0.0173$ ].

*1-Benzyl-5-[(2-oxopyridin-1(2H)-yl)methyl]pyridin-2(1H)-one, 3.*



Crystallographic data for **3**. C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>, M = 292.33, Monoclinic, space group P2(1)/n, a = 13.0964(3), b = 7.73187(14), c = 15.1103(3) Å, alpha = 90 deg., beta = 108.983(2) deg., gamma = 90 deg., U = 1446.85(5) Å<sup>3</sup> (by least squares refinement on 2682 reflection positions), T = 150(2)K, lambda = 1.54184 Å, Z = 4, D(cal) = 1.342 Mg/m<sup>3</sup>, F(000) = 616. mv (MoK-alpha) = 0.714 mm<sup>-1</sup>. Crystal character: colourless plate. Crystal dimensions 0.20 x 0.20 x 0.01 mm. 5296 reflections measured, 2543 unique [R(int) = 0.0216].

*1-benzyl-5-(1-hydroxyethyl)piperidin-2-one, anti-D1-7a.*



Crystal Data for **7a**:  $C_{14}H_{19}NO_2$ ,  $M = 233.30$ , Orthorhombic, space group  $Pna2(1)$ ,  $a = 10.7915(2)$ ,  $b = 21.1078(5)$ ,  $c = 5.64620(18)$  Å,  $\alpha = 90$  deg.,  $\beta = 90$  deg.,  $\gamma = 90$  deg.,  $U = 1286.11(6)$  Å<sup>3</sup> (by least squares refinement on 5741 reflection positions),  $T = 150(2)$  K,  $\lambda = 1.54184$  Å,  $Z = 4$ ,  $D(\text{cal}) = 1.205$  Mg/m<sup>3</sup>,  $F(000) = 504$ .  $M_v$  (MoK- $\alpha$ ) =  $0.638$  mm<sup>-1</sup>. Crystal character: colourless needle. Crystal dimensions  $0.50 \times 0.01 \times 0.01$  mm, 10079 reflections measured, 2146 unique [ $R(\text{int}) = 0.0250$ ].

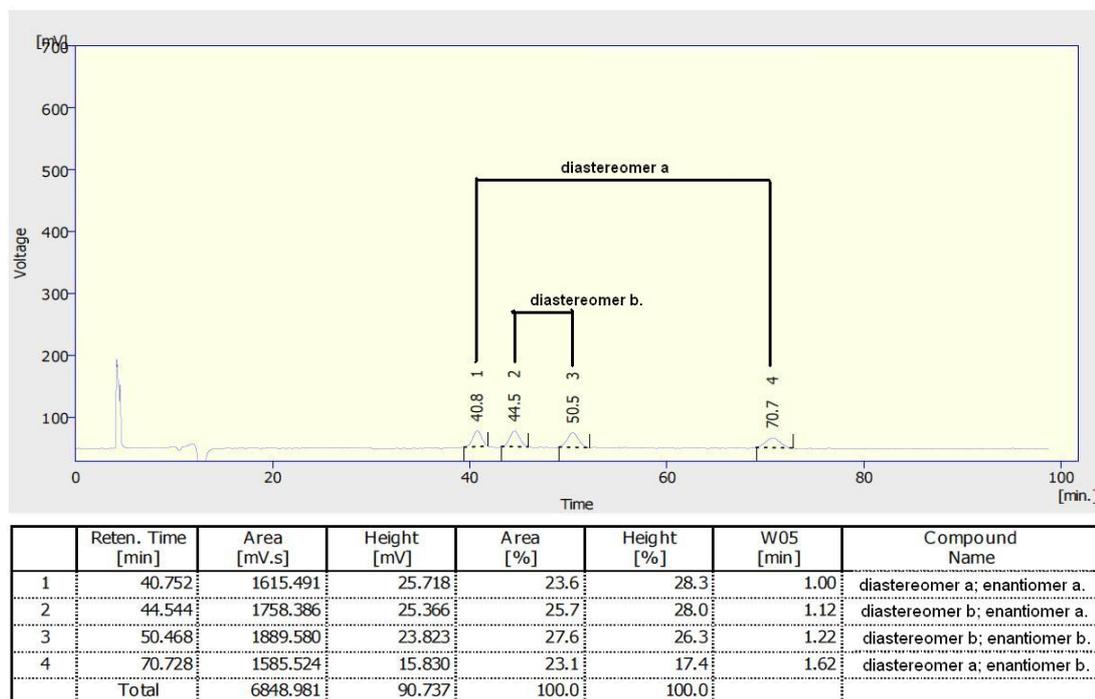
### Appendix III: Chiral HPLC and GC Traces.

HPLCs from Section 2.2: ATH of *N*-benzyl-5-acetyluracil.

In this section the HPLC traces of the reduction products formed by the ATH of *N*-benzyl-5-acetyluracil are shown. These reductions were shown in Table 2, section 2.2.3.

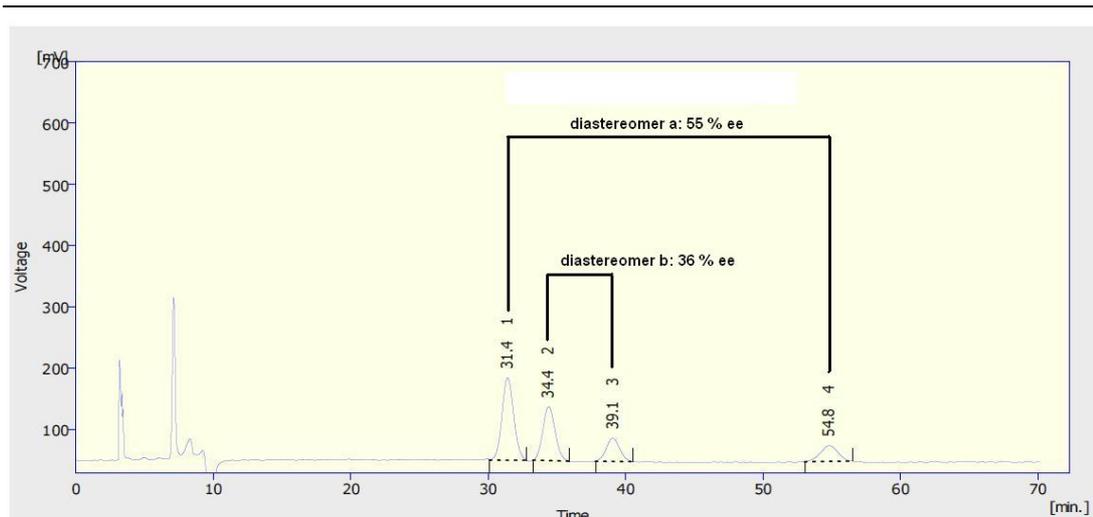
#### HPLC trace 1.

Reduction with the racemic catalyst, RuTsEN **249**, (entry 2, Table 2, section 2.2.3); chiral separation details: (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min, T = 30 °C, minor isomer 46.0 min, major isomer 51.9 min.) **271a** : **271b** dr = 1:1.



#### HPLC trace 2.

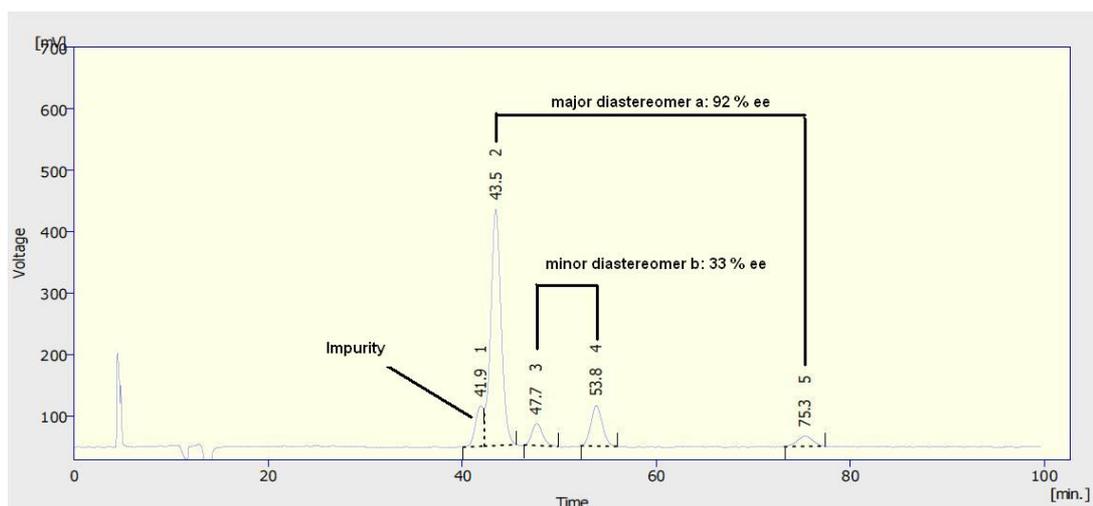
Reduction with the Noyori's catalyst (*R,R*)-**248**, (entry 3, Table 2, section 2.2.3); chiral separation details: (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min, T = 30 °C) **271a**: 55 % ee; **271b**: 36 % ee. a : b dr = 1.3:1.



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	31.416	7997.752	134.399	43.6	46.9	0.92	diastereomer a; enantiomer a.
2	34.404	5467.036	87.831	29.8	30.7	0.97	diastereomer b; enantiomer a.
3	39.076	2577.286	37.902	14.1	13.2	1.06	diastereomer b; enantiomer b.
4	54.792	2298.262	26.173	12.5	9.1	1.40	diastereomer a; enantiomer b.
	Total	18340.336	286.305	100.0	100.0		

### HPLC trace 3.

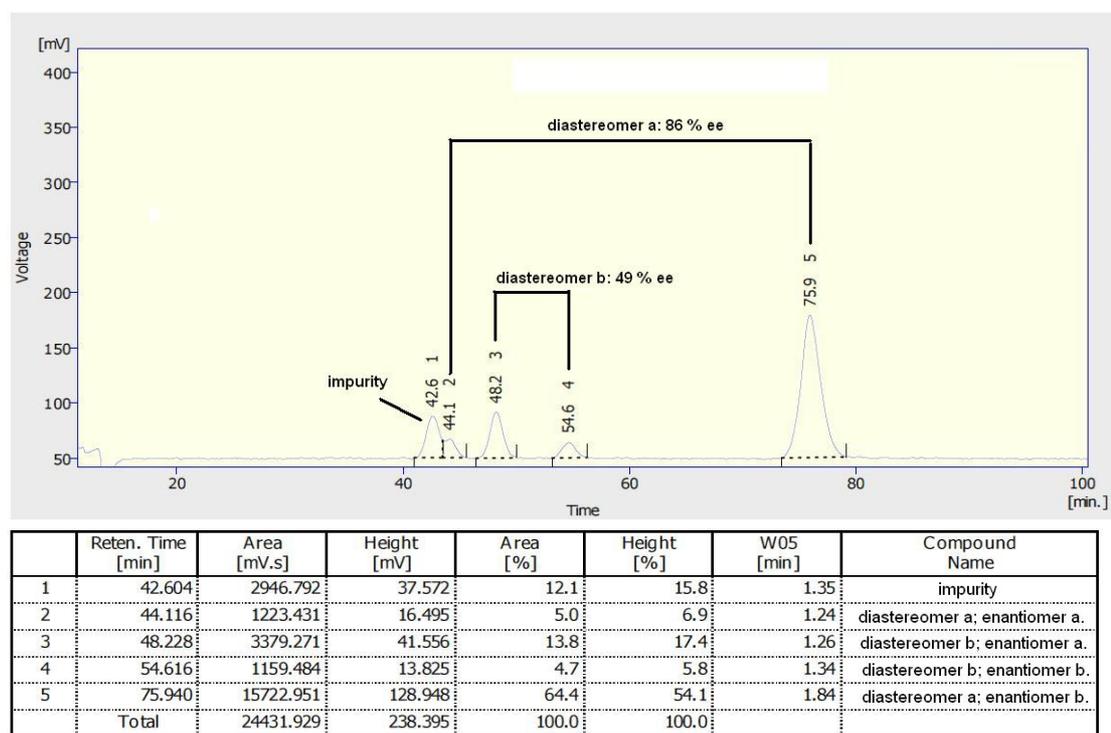
Reduction with (*R,R*)-RutethTsDPEN, (*R,R*)-**248**, (entry 4, Table 2, section 2.2.3); chiral separation details: (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min, T = 30 °C) **271a**: 92 % ee; **271b**: 33 % ee. a : b dr = 4:1.



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	41.936	3870.949	65.238	9.0	11.5	0.97	impurity
2	43.460	28903.698	384.210	67.6	67.7	1.14	diastereomer a; enantiomer a.
3	47.676	2752.056	35.332	6.4	6.2	1.18	diastereomer b; enantiomer a.
4	53.832	5388.335	65.920	12.6	11.6	1.27	diastereomer a; enantiomer b.
5	75.316	1871.360	16.953	4.4	3.0	1.74	diastereomer b; enantiomer b.
	Total	42786.397	567.652	100.0	100.0		

#### HPLC trace 4.

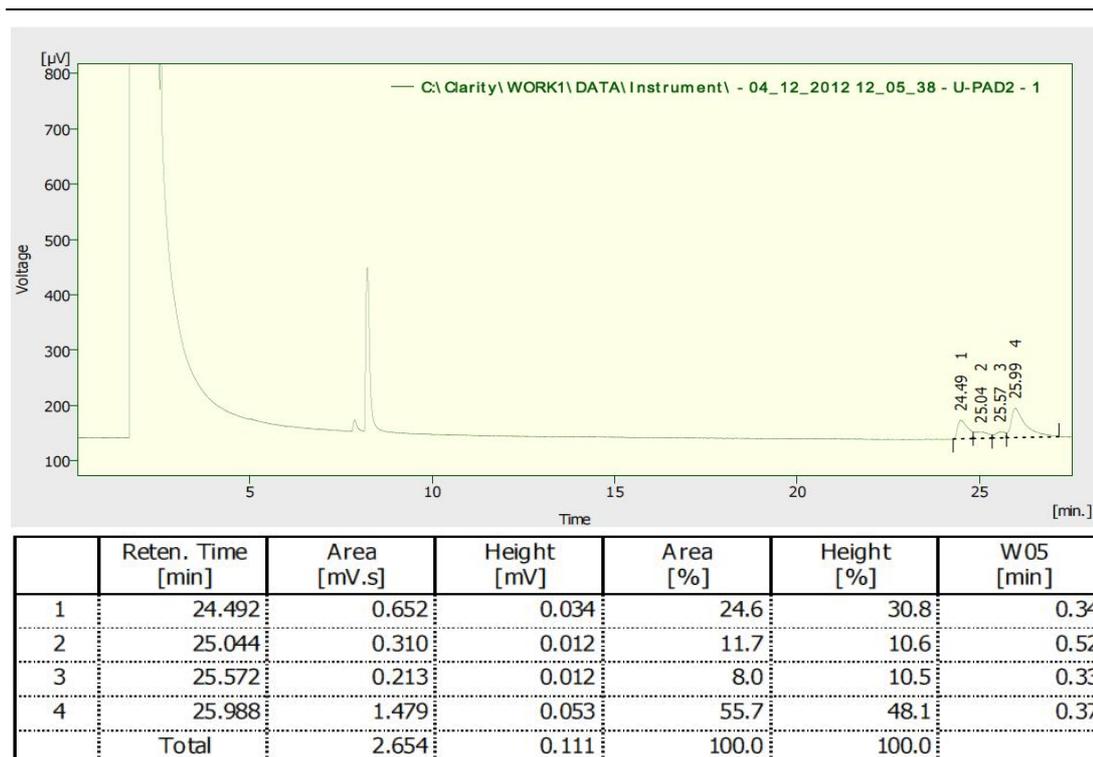
Reduction with (*S,S*)-RutethTsDPEN, (*S,S*)-**248**, (entry 5, Table 2, section 2.2.3); chiral separation details: (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min, T = 30 °C) **271a**: 86 % ee; **271b**: 49 % ee. **a** : **b** dr = 4:1.



#### GC traces from Section 2.5:

##### GC trace 1: crude reduction mixture of **7a** and **7b**

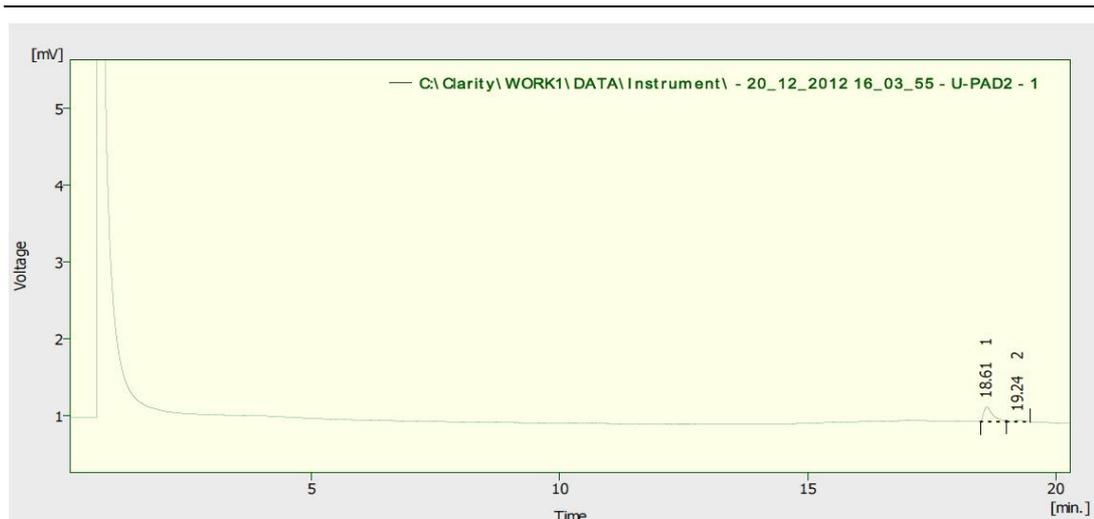
This GC trace was obtained from the crude reaction mixture of (D1)-**7a** and (D2)-**7b** resulting from the PtO<sub>2</sub> reduction of pyridone (R)-**304** (78 % ee). This was used to determine the dr of the reaction. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 μm, gas: He, T = 200 °C, P = 18 psi He, det = 250 °C, inj = 220 °C, (*S,R*) isomer 24.49 min., (*R,S*) isomer 25.04 min., (*S,S*) isomer 25.57 min., (*R,R*) isomer 25.99 min.) 31 % de.



The following chromatography of this crude mixture, the diastereomers **D1-7a** and **D2-7b** were obtained. The GC traces of these isomers are shown in the next two GC traces.

*GC trace 2: D1-7a, 78 % ee.*

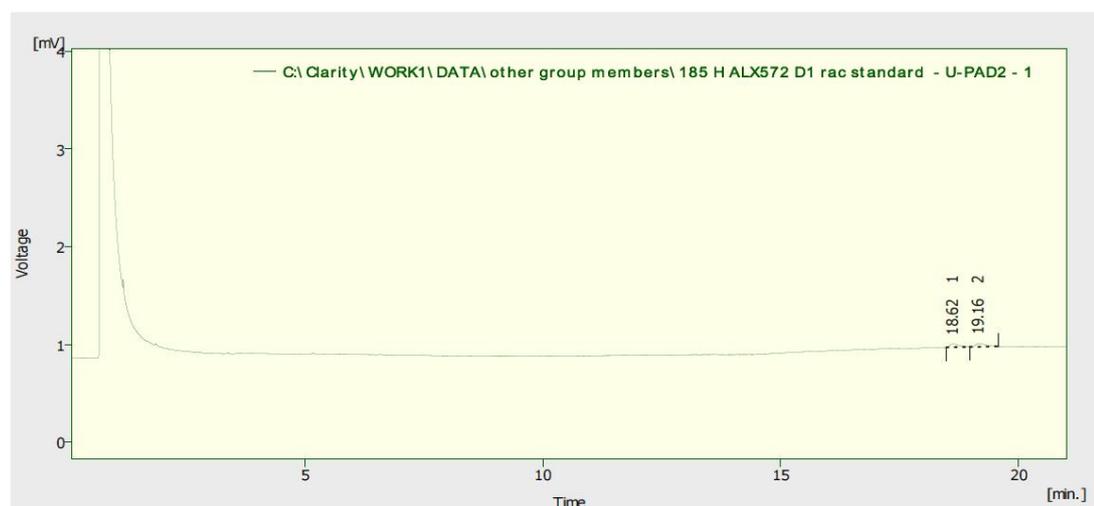
This GC trace was obtained from a chromatographically separated sample of **D1-7a**. Different GC conditions (to those in GC trace 1) were required for adequate separation. The racemic standard for this run is shown in GC trace 3. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 µm, gas: H, T = 185 °C, P = 18 psi H, det = 250 °C, inj = 220 °C, (*S,R*) isomer 18.61 min., (*R,S*) isomer 19.24 min.) 78 % ee.



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	18.608	2.437	0.189	89.4	91.2	0.19
2	19.236	0.289	0.018	10.6	8.8	0.22
	Total	2.726	0.207	100.0	100.0	

GC trace 3: ( $\pm$ )-(D1)-7a (racemic standard).

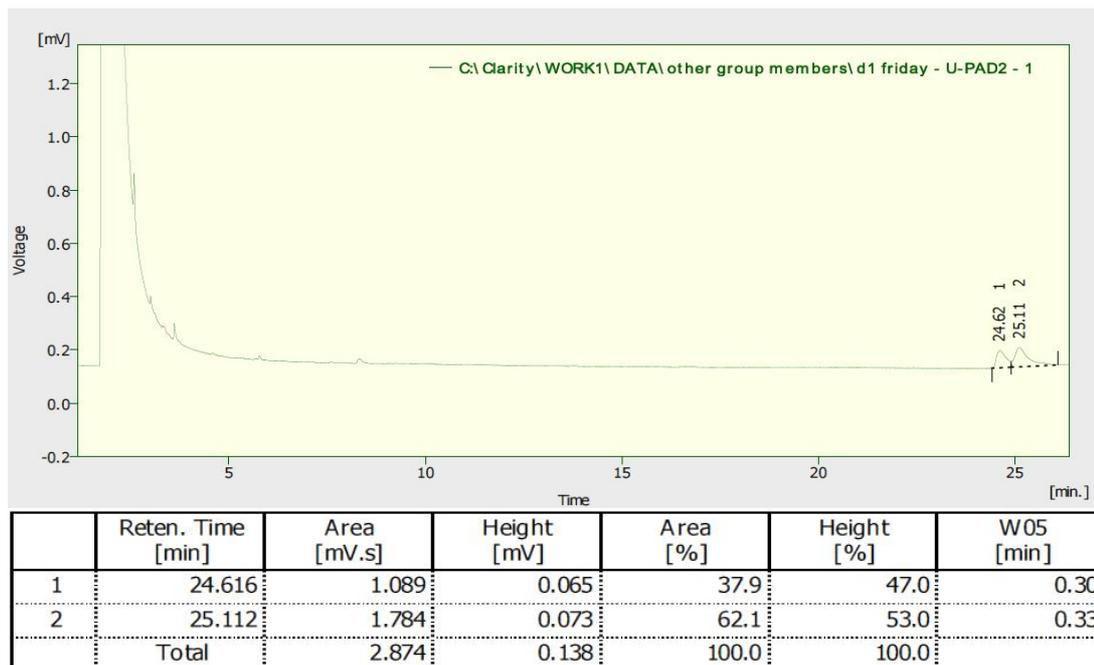
This GC trace of (D1)-7a was used as a racemic standard for GC trace 2: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25  $\mu$ m, gas: H, T = 185  $^{\circ}$ C, P = 18 psi H, det = 250  $^{\circ}$ C, inj = 220  $^{\circ}$ C, (S,R) isomer 18.64 min., (R,S) isomer 19.16 min.).



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	18.624	0.489	0.034	49.0	50.4	0.23
2	19.164	0.509	0.034	51.0	49.6	0.24
	Total	0.998	0.068	100.0	100.0	

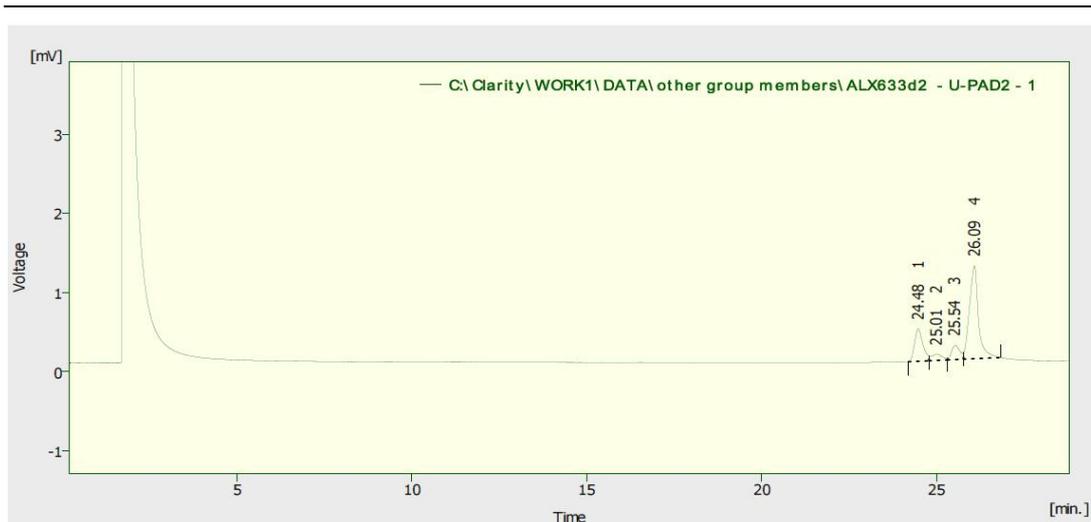
GC trace 4: ( $\pm$ )-D1-7a (in reference to GC 1).

This GC trace of racemic (D1)-7a was run at the same conditions as GC trace 1 to enable comparison. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25  $\mu$ m, gas: He, T = 200  $^{\circ}$ C, P = 18 psi He, det = 250  $^{\circ}$ C, inj = 220  $^{\circ}$ C, (*S,R*) isomer 24.62 min., (*R,S*) isomer 25.11 min.).



GC trace 5: D2-7b, 78 % ee.

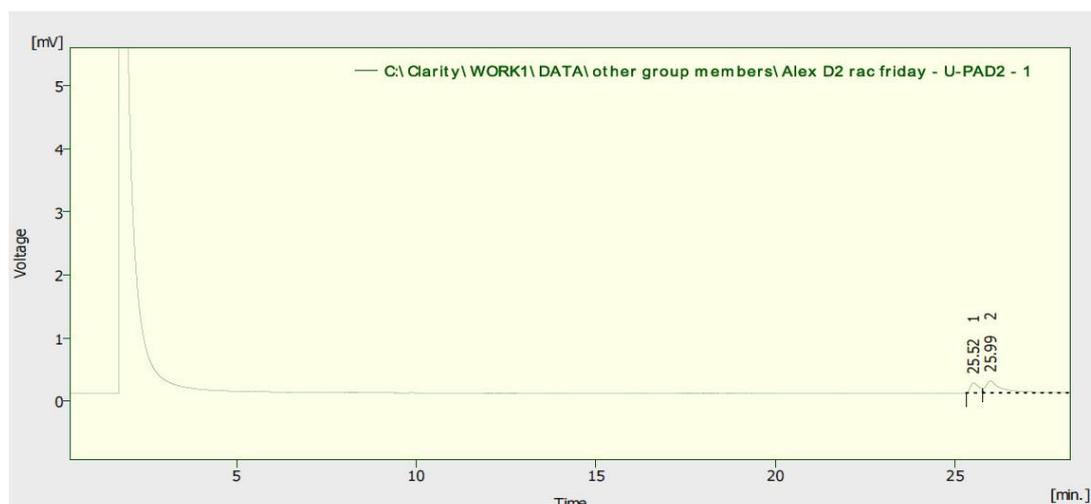
This GC trace was obtained from a chromatographically enriched sample of D2-7b (72 % D2). The racemic standard is shown in GC trace 6. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25  $\mu$ m, gas: H, T = 200  $^{\circ}$ C, P = 18 psi He, det = 250  $^{\circ}$ C, inj = 220  $^{\circ}$ C, (*S,R*) isomer 24.48 min., (*R,S*) isomer 25.00 min. (*S,S*) isomer 25.54 min., (*R,R*) isomer 26.09 min.) 78 % ee.



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	24.480	6.773	0.409	20.8	22.2	0.26
2	25.008	1.692	0.081	5.2	4.4	0.40
3	25.536	2.993	0.180	9.2	9.7	0.28
4	26.088	21.105	1.174	64.8	63.7	0.26
	Total	32.564	1.843	100.0	100.0	

GC trace 6: ( $\pm$ )-D2-7b.

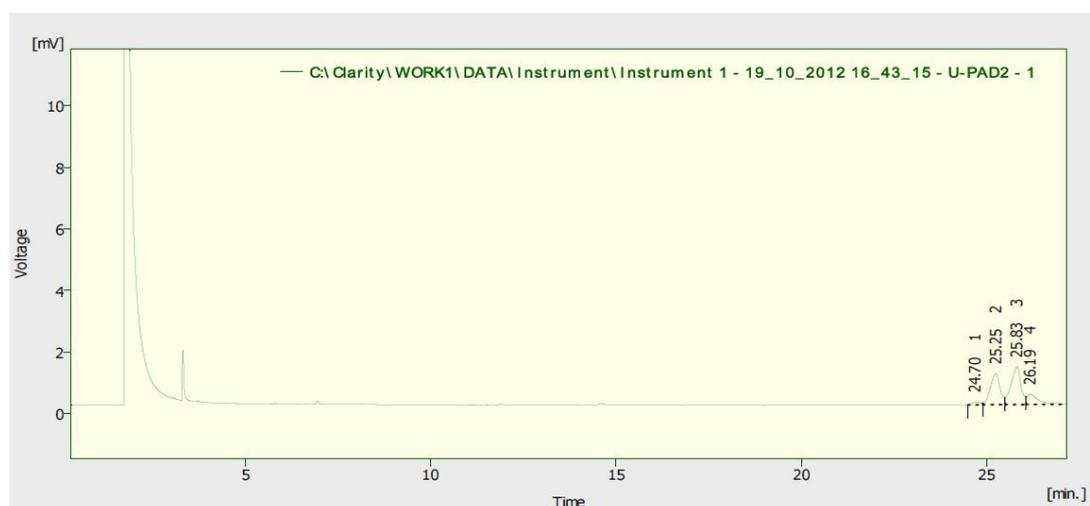
This GC trace of ( $\pm$ )-D2-7b was used as a racemic standard for GC trace 5. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25  $\mu$ m, gas: He, T = 200  $^{\circ}$ C, P = 18 psi He, det = 250  $^{\circ}$ C, inj = 220  $^{\circ}$ C, (*S,S*) isomer 25.52 min., (*R,R*) isomer 25.99 min.).



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	25.524	2.612	0.155	30.1	45.2	0.31
2	25.992	6.066	0.189	69.9	54.8	0.36
	Total	8.678	0.344	100.0	100.0	

GC trace 7: the ATH products of methyl lactam ketone **310**.

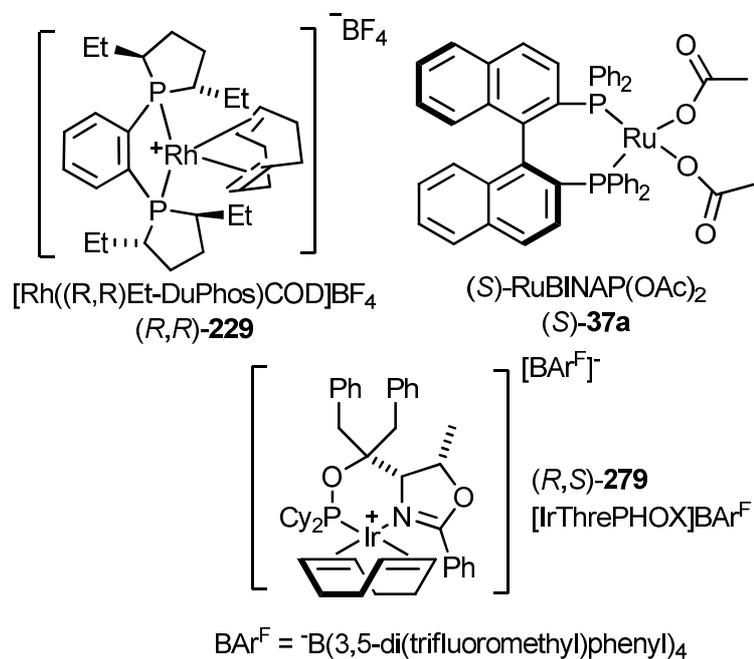
This GC trace was obtained from the unseparated mixture of diastereomers obtained from the ATH of methyl lactam ketone **310**. (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25  $\mu$ m, gas: He, T = 200 °C, P = 18 psi He, det = 220 °C, inj = 220 °C, (*S,R*) (minor) isomer 24.70 min., (*R,S*) (major) isomer 25.25 min., (*S,S*) (major) isomer 25.83 min., (*R,R*) (minor) isomer 26.19 min.) 20 % de; (*R,S*), 85 % ee; (*S,S*), 49 % ee.



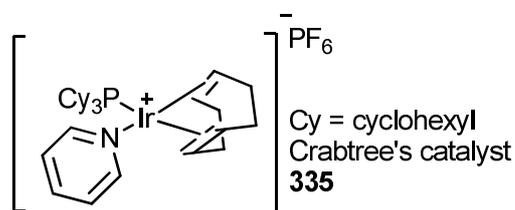
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	24.704	1.468	0.097	2.9	3.6	0.30
2	25.248	18.545	1.017	36.9	37.9	0.29
3	25.828	22.533	1.237	44.8	46.1	0.28
4	26.188	7.711	0.331	15.3	12.3	0.31
	Total	50.257	2.682	100.0	100.0	

## Appendix IV: Catalyst and Ligand Structures from Section 2.

*Asymmetric hydrogenation catalysts:*



*Non-chiral hydrogenation catalysts:*



*Asymmetric transfer hydrogenation catalysts:*

