Synthesis of Unnatural Enone-Containing α-Amino Acids: Precursors to Chiral *N*-Heterocycles

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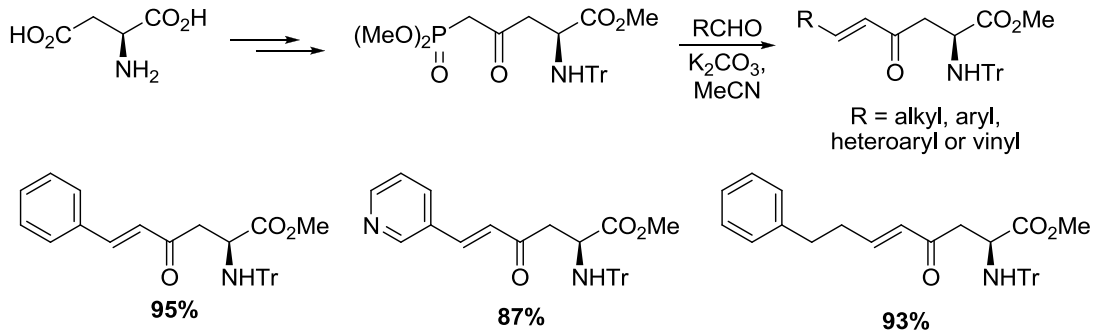
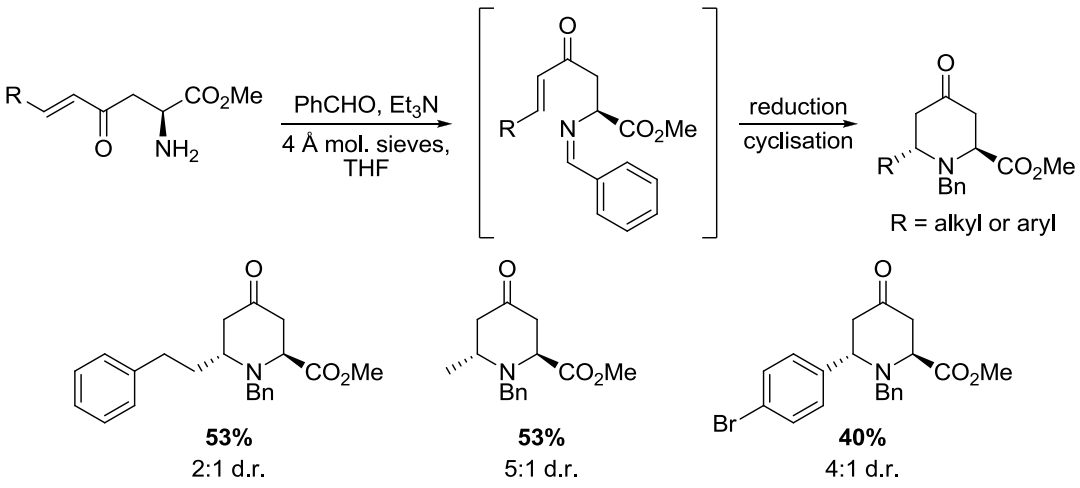
Abstract

A fast and efficient synthetic route was developed for the synthesis of a novel class of enone-containing α-amino acid. An amino acid-derived β-ketophosphonate ester was subjected to Horner-Wadsworth-Emmons conditions using a variety of aldehydes to produce a diverse library of α,β-unsaturated amino acids. *E*-Configured enone-containing amino acids were also deprotected using a two-stage approach to give the parent α-amino acids. A minor modification to the route enabled the synthesis of *Z*-configured enones *via* the Still-Gennari reaction. A small library of *Z*-enones was produced using various aldehydes.



Enone-functionalised α-amino acids were employed as substrates for an intramolecular cyclisation reaction to generate 6-substituted-4-oxopipecolic acids. A diastereoselective one-pot reductive amination/cyclisation strategy was developed to gain access to the *anti*-diastereomer of the chiral *N*-heterocycles. A small selection of 6-substituted-4-oxopipecolic acids was synthesised. 6-Substituted-4-oxopipecolic acids were also reduced diastereoselectively to generate 4-hydroxypipecolic acid analogues.



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Author's Declaration

This thesis represents the original work of Lindsay Sarah Fowler unless explicit reference is made to the contribution of others in the text. The research was carried out in the Loudon laboratory at the University of Glasgow under the supervision of Dr. Andrew Sutherland.

Certain aspects of this work have been published elsewhere as detailed below:

L. S. Fowler, D. Ellis and A. Sutherland, *Org. Biomol. Chem*., 2009, **7**, 4309.

Abbreviations

AIBN	2,2’-azobis(2-methylpropionitrile)
br	broad
c	concentration
CI	chemical ionisation
COSY	correlated spectroscopy
d	doublet
dd	double doublet
d.e.	diastereomeric excess
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,1’-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*-dimethylpropylene urea
DNA	deoxyribonucleic acid
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
EI	electron impact
FAB	fast atom bombardment
FTIR	Fourier transform infrared
h	hours
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital

Hz	hertz
LiHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet
MHz	mega hertz
mL	millilitres
mmol	millimoles
MOM	methoxymethyl
Mp	melting point
MW	microwave
NAD^+	nicotinamide adenine dinucleotide
NaHMDS	sodium bis(trimethylsilyl)amide
NMR	nuclear magnetic spectroscopy
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
r.t.	room temperature
S.M.	starting material
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilyl chloride
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	tri-*iso*-propylsilyl
TLC	thin layer chromatography

1 Saturated 6-Membered *N*-Heterocycles

1.1 Introduction

Within the structurally diverse field of organic chemistry, heterocyclic chemistry represents a vast and complex discipline of significant importance. A heterocycle can be defined as a ring system containing at least one heteroatom and can be subcategorised as either aromatic or non-aromatic. Six-membered non-aromatic *N*-heterocycles have warranted a great deal of attention due to their abundance in nature and synthetic utility in the pharmaceutical industry.

Representatives of the saturated six-membered *N*-heterocycle family include piperidine **1**, piperazine **2**, morpholine **3** and thiomorpholine **4** (Figure 1.1). An enormous array of permutations to the heterocyclic core exists with incorporation of different functional groups, various substitution patterns and stereogenic centres are also frequently observed. Structural variation of the heterocyclic scaffold can substantially alter the properties of the molecule.

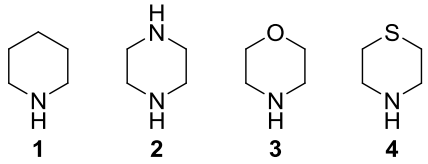


Figure 1.1 Saturated 6-membered *N*-heterocycles

Heterocycles are attractive targets for synthetic chemists because they possess broad and important biological properties. Many heterocyclic compounds are naturally occurring and their functions are fundamentally important to living systems. Alkaloid natural products contain nitrogen heterocycles as molecular scaffolds. Heterocycles have also been deemed privileged structures in the pharmaceutical industry as they often account for potent medicinal properties.[1] Within this group of saturated six-membered heterocyclic compounds, the piperidine core attracts considerable attention.

1.2 Piperidine

Piperidine is one of the most important members within the class of saturated six-membered *N*-heterocycles. The molecular fragment is widely distributed in nature within numerous plants, insects and amphibians. The chemical properties of the heterocyclic core have been extensively studied throughout the years.

Saturated heterocycles possess slightly different properties from their analogous open-chain derivatives. The most important factors that cause the distinction between cyclic and acyclic molecules are the size of the ring and the overall shape. Flexible molecules can adopt conformations to maximise bonding interactions and minimise repulsive interactions. In contrast, a ring system will impose certain constraints on these favourable interactions. Preferred features such as natural bond angles, intrinsic bond lengths and staggered hydrogen arrangements are often compromised and therefore ring systems can be strained. A cyclic molecule will still endeavour to adopt the lowest energy conformation possible.

Piperidine preferentially adopts a six-membered chair conformation equivalent to cyclohexane. The difference between the two arises as a result of the heteroatom. Unlike cyclohexane, two different types of conformational change can occur. Piperidine can undergo tetrahedral inversion of the nitrogen substituent (processes a and b) and also ring inversion (processes c and d) (Figure 1.2).[2] Equatorial positioning of the hydrogen atom with the lone pair axial (**6** and **7**) is more stable as 1,3-diaxial interactions are minimised. The barrier to tetrahedral inversion however is a low energy process and therefore piperidine can rapidly equilibrate, which means that nitrogen, unlike sulfur and phosphorus, cannot be chiral.

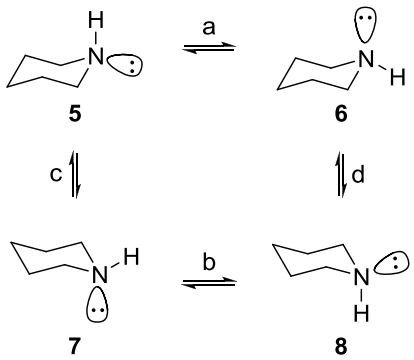
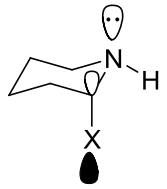


Figure 1.2 Tetrahedral inversion and ring inversion of piperidine

Another important feature of saturated heterocyclic compounds is the anomeric effect. This stereoelectronic effect was first recognised in carbohydrate chemistry, however is also observed in nitrogen and sulfur containing heterocycles. Saturated heterocycles bearing an electronegative substituent in the 2-position will prefer the substituent in an axial conformation (Figure 1.3). An antiperiplanar arrangement of the lone pair and exocyclic substituent is thermodynamically favoured as the lone pair can overlap with the parallel, low-lying anti-bonding orbital of the C–X bond to stabilise the molecule. Displacement of electron density from the nitrogen towards the electronegative substituent results in a stronger, shorter C–N bond and a longer, weaker C–X bond.



X = halogen or oxygen

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Figure 1.3 Anomeric effect in piperidine

Aside from the varied and interesting chemical properties that piperidine exhibits, the structurally diverse natural products containing piperidine also have an array of important biological properties. Alkaloid natural products are basic compounds derived from secondary metabolism of amino acids. A vast selection of alkaloids containing a piperidine ring have been isolated from plants (Figure 1.4). (−)-Coniine **10** is a member of the poisonous hemlock alkaloid family and was the first alkaloid to be chemically synthesised.[3] The neurotoxin disrupts the peripheral nervous system and is fatal to humans and livestock as respiratory paralysis causes death.[4] Atropine **11** and solanine **12** belong to the Solanaceae family and are also toxins. Atropine is found in deadly nightshade, *Atropa belladonna*, and the steroidal alkaloid, solanine, is present in unripe potatoes.[5] Several piperidine containing secondary metabolites have beneficial medicinal properties such as morphine **13**. Morphine is the major component of opium from the poppy, *Papaver somniferum,* and is known for its potent analgesic properties. Morphine acts on the central nervous system (CNS) to relieve pain. The disadvantages of this powerful opiate analgesic are the propensity for addiction, tolerance and psychological dependence. The macrolactone, carpaine **14**, contains two piperidine motifs. The pharmacology of carpaine includes use as a cardiac stimulant, an anti-hypertensive agent and a diuretic.[6] Piperine **15**, isolated from *Piper nigrum* (black pepper), has been found to possess antimicrobial activity.

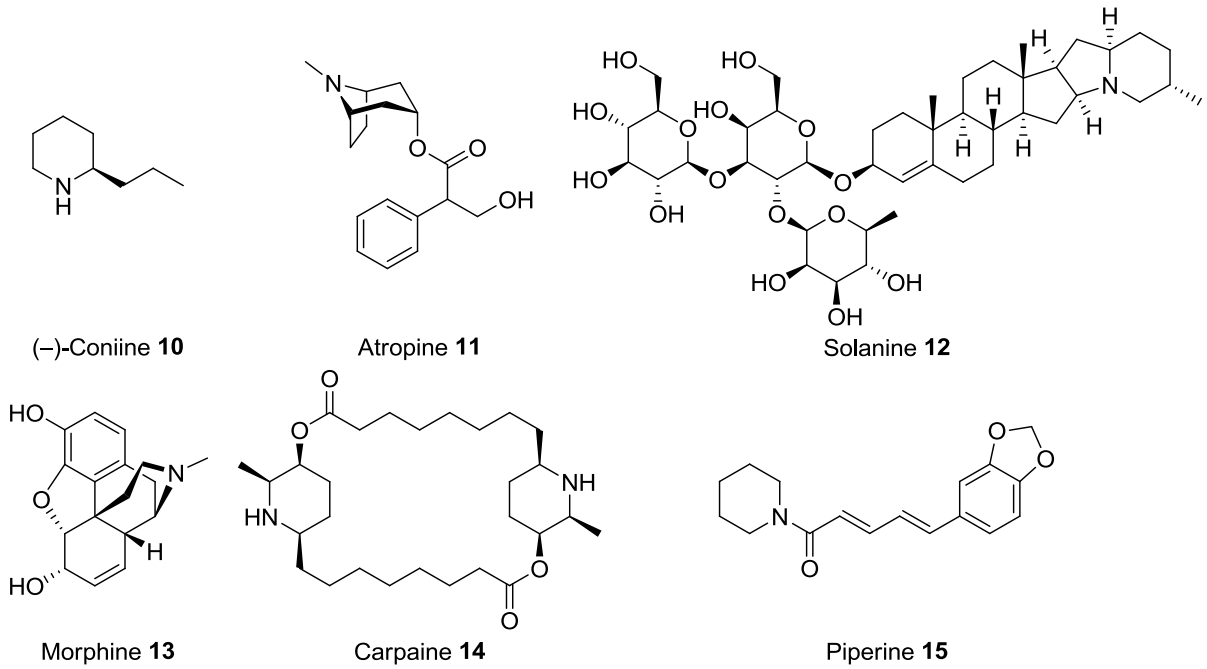


Figure 1.4 Secondary metabolites from plants containing piperidine

Many secondary metabolites derived from piperidine have also been identified in animal species (Figure 1.5). (+)-Stenusine **16** has been isolated as a diastereomeric mixture from the rove beetle genus, *Stenus*.[7] The compound displays a repellent activity against predators and also functions as a surface-active fluid to propel the beetle over water, as the beetle cannot swim.[8] Cryptophorine **17** is another animal natural product containing the saturated *N*-heterocycle.[9] Solenopsin A **18** is a constituent of fire ant venom, used as a defence mechanism against predators and possesses haemolytic, insecticidal and antibiotic properties.[10] Histrionicotoxin **19** is a spiropiperidine found in the skin of the Columbian frog, *Dendrobate histrionicus*.[11] The chemical functions as a defence mechanism and acts as a non-competitive inhibitor of the neuromuscular ganglionic and central neuronal nicotinic acetylcholine receptors.[12]

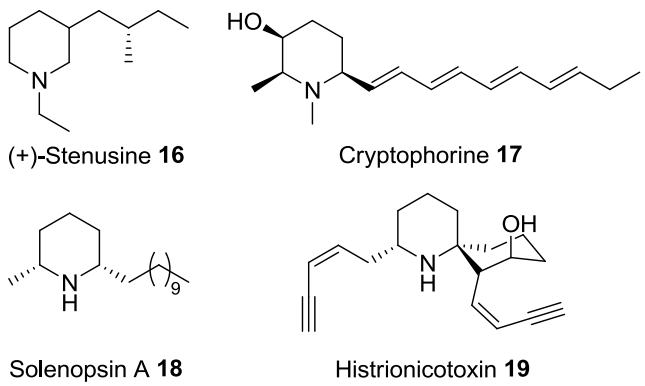


Figure 1.5 Secondary metabolites from animals containing piperidine

The piperidine scaffold is an essential pharmacophore in medicinal research with thousands of clinical and pre-clinical therapeutic agents containing the privileged structure.[13] Selected examples of drugs include paroxetine **20** produced by GlaxoSmithKline to treat depression and anxiety (Figure 1.6). Morphine analogues such as codeine **21**, heroin **22** and oxycodone **23,** used to relieve severe pain, contain the saturated *N*-heterocycle. Non-selective 5-HT/D_2 receptor antagonist, risperidone **24**, has proven effective to alleviate symptoms of schizophrenia.[14] 2,6-Disubstituted piperidine **25**, is a β_2-adrenoreceptor agonist which induces bronchodilation.[15] Many other pharmaceutically active compounds contain the piperidine nucleus with various substitution patterns.[16]

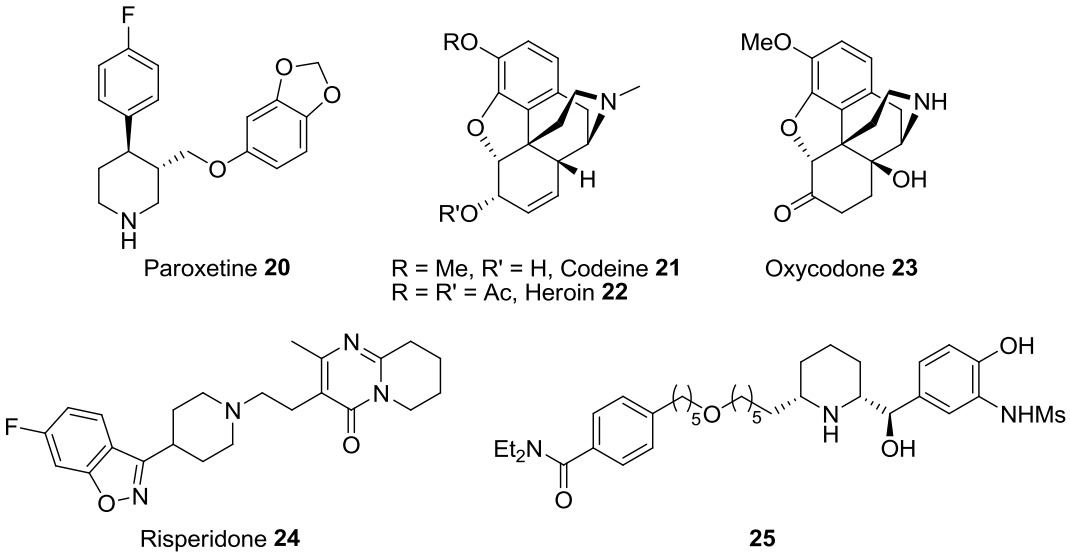


Figure 1.6 Therapeutic agents containing piperidine

The biological importance of piperidine derivatives has invoked substantial attention. Extensive research has been conducted into general approaches for the synthesis of the piperidine core. With increasing potential for applications in biological systems, the goal has been to develop enantioselective strategies to produce chiral piperidine derivatives. Another aspect for chemical syntheses is the ability to attain varied substitution patterns. These factors govern the direction of novel preparations and continue the drive for new methodologies. Many substitution patterns remain difficult to access and therefore new short, versatile, stereocontrolled routes are of great potential value.

1.2.1 Piperidine Synthesis

A great deal of research has been carried out in the field of piperidine synthesis.[17] Many different approaches to the *N*-heterocycle have been explored, however this is a demanding challenge and still has scope for improvement.

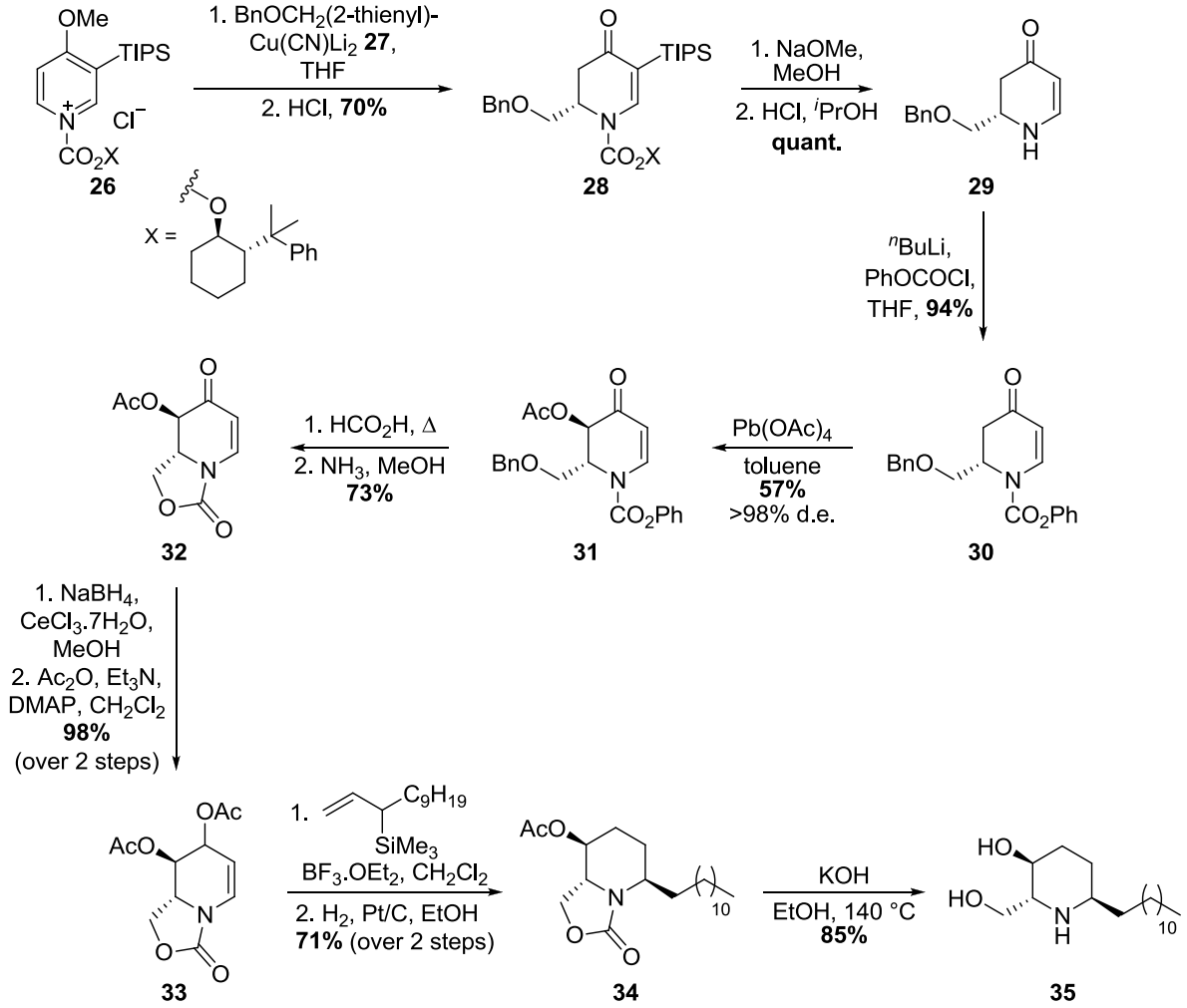
1.2.1.1 Reduction of Pyridine

Reduction of pyridine to synthesise piperidine derivatives has been extensively investigated. The strategy is efficient as the *N*-heterocyclic ring is already present, however it can be difficult to generate chirality in the molecule and therefore the approach is rarely employed in modern organic chemistry.

An example of pyridine reduction was presented by Comins and co-workers who devised an approach using an *N*-acylpyridinium salt containing a chiral auxiliary to induce asymmetry.[18] The objective of the work was to carry out a total synthesis of (+)-deoxoprosopinine **35**. Compound **35** is an analogue of the naturally occurring piperidine alkaloid, (+)-prosopinine, which exhibits antibiotic and anaesthetic properties.

Enantiopure pyridinium salt **26** was treated with cyanocuprate reagent **27** to introduce selectively the *C*-2 stereocentre and then acid-promoted tautomerism generated dihydropyridone **28** as a single diastereomer (Scheme 1.1). Hydrolysis of the chiral auxiliary was carried out using sodium methoxide, followed by acidic removal of the resultant carboxylic acid and the tri-*iso*-propylsilyl group to yield cyclic enone **29**. Protection of the amine with phenyl chloroformate and then diastereoselective acetoxylation using lead(IV) acetate gave intermediate **31**. Excellent diastereoselectivity to introduce the acetoxy group is achieved because the *C*-2 substituent exists

in an axial position as a result of allylic strain. A one-pot procedure to form bicyclic compound **32** involves cleavage of the benzyl ether, subsequent formation of a formate ester and then ammonia-induced ring closure. Generation of the oxazolidinone ring system is crucial for control of the final stereocentre. Chemoselective 1,2-reduction of the carbonyl followed by acetylation yields allylic acetate **33**. Treatment of **33** with a Lewis acid induces formation of an *N*-acyliminium ion *in situ* and then addition of the allylsilane occurs from the *Re* face. The stereoselectivity arises because the bicyclic system forces the *C*-2 stereogenic centre into a pseudo-equatorial position and therefore attack on the iminium species occurs in an axial manner to give **34**. Finally, basic hydrolysis of the acetate and opening of the oxazolidinone ring along with decarboxylation yields (2*R*,3*S*,6*R*)-(+)-deoxoprosopinine **35**.



Scheme 1.1 Total synthesis of (+)-deoxoprosopinine **35**

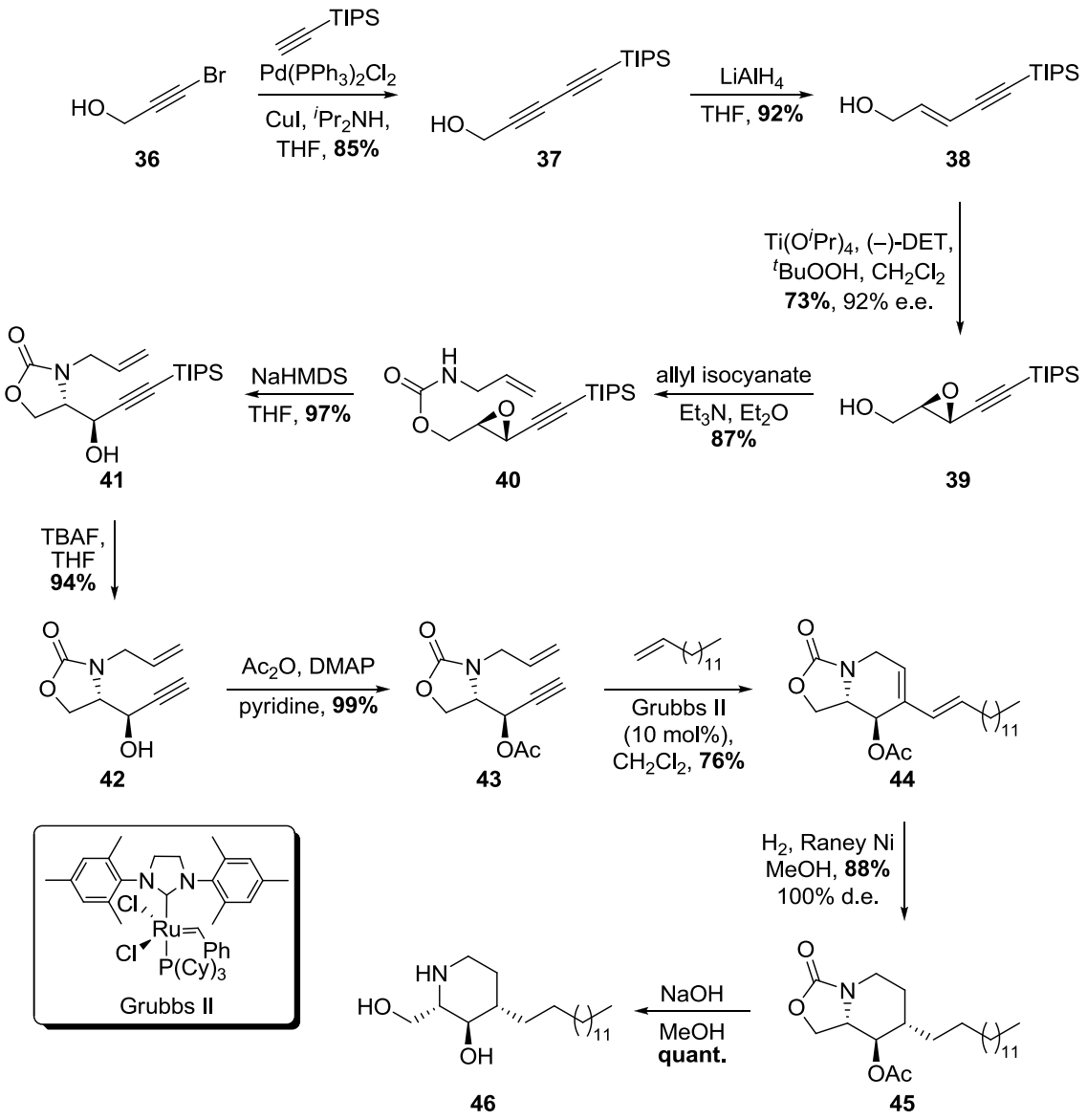
Comins and co-workers were able to synthesise the desired 2,3,6-trisubstituted piperidine natural product in 10 steps with 16% overall yield. The pyridinium reduction step is high yielding and generates a densely functionlised dihydropyridone **28** as a single stereoisomer. The group have shown that allylic acetate **33** can be readily further functionalised diastereoselectively and therefore, this approach is efficient and amenable for the generation of other analogues.

1.2.1.2 Heterocycle Construction

A variety of cyclisation reactions are frequently encountered for the synthesis of piperidine derivatives. Well-established transformations are employed in ring-closing reactions to generate the saturated *N*-heterocyclic core.

Kim and co-workers developed an elegant approach for the synthesis of conformationally constrained sphingoid base analogues containing a piperidine scaffold.[19] Naturally occurring sphingoid bases have several biological functions and can induce apoptotic cell death.[20] Conformationally restricted analogues of these bases exhibit potent cytotoxic activity and inhibit cancer cell growth. An efficient approach to synthesise the desired piperidine framework was investigated using a tandem enyne/diene-ene metathesis reaction.

The synthesis employed a Sonogashira cross-coupling reaction using 3-bromopropargyl alcohol **36** and silyl-protected acetylene to give diyne **37** (Scheme 1.2). Lithium aluminium hydride selectively reduced the alkyne with the pendant hydroxyl group to yield the *E*-isomer **38** in excellent yield. Allylic alcohol **38** was subjected to Sharpless asymmetric epoxidation conditions with (−)-diethyl tartrate to produce epoxy alcohol **39** in good yield with good enantiomeric excess. Epoxy alcohol **39** was reacted with allyl isocyanate to generate allyl carbamate **40**. Regioselective intramolecular ring-opening of the epoxide produced oxazolidinone **41** in excellent yield. Removal of the silyl protecting group, followed by acetylation of the free hydroxyl generated the substrate for the tandem ring-closing metathesis and subsequent cross-metathesis reaction. Enyne **43** was subjected to the metathesis conditions using Grubbs second-generation catalyst in the presence of 1-tetradecene to afford diene **44** in good yield and with complete *E*-selectivity of the external alkene. Completion of the synthesis involved hydrogenation of diene **44** using Raney nickel, which proceeded with complete facial selectivity. Finally, hydrolysis of the oxazolidinone ring and acetate group produced (2*S*,3*R*,4*S*)-trisubsituted piperidine **46** in 10 linear steps in 30% overall yield.



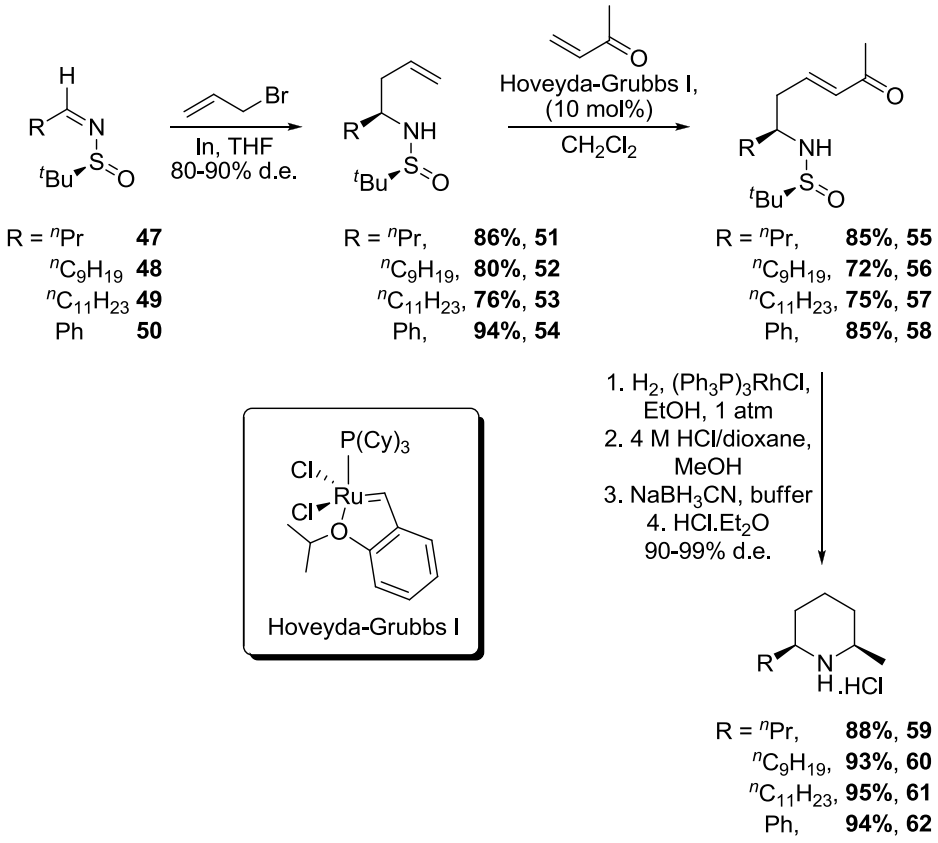
Scheme 1.2 Tandem ring-closing/cross-metathesis approach for the synthesis of trisubstituted piperidine **46**

This tandem metathesis approach provides the piperidine core highly efficiently. The chirality is achieved using asymmetric catalysis and therefore it would be feasible to use the opposite enantiomer of diethyl tartrate to obtain *ent*-**46**. The highly functionalised diene intermediate **44** may also allow variations to the piperidine template making this a versatile synthetic route.

Another recent synthetic strategy employing metathesis was developed by Davis and co-workers to allow entry to a potent neurokinin substance P receptor antagonist.[21]

A fast and efficient route was published by González-Gómez *et al* for the synthesis of highly desirable 2,6-*cis*-disubstituted piperidines.[22] 2-Methyl-6-alkylpiperidines are an important class of natural products. Dihydropinidine **59**[23] is produced by the Mexican bean beetle as a defense mechanism against predators and isosolenopsins **60** and **61**[24] are found in the venom of fire ants. The piperidine-containing alkaloid natural products were produced using a reductive amination strategy to form the *N*-heterocyclic core.

Indium-mediated allylation of (*S*)-*tert*-butylsulfinimines **47**-**50** with allyl bromide gave *N*-*tert*-sulfinylamines **51**-**54** in moderate to good diastereoselectivity (Scheme 1.3). Subsequent cross-metathesis of sulfinylamines **51**-**54** with methyl vinyl ketone using Hoveyda-Grubbs catalyst yielded enones **55**-**58**. Hydrogenation of the alkene was carried out with Wilkinson's catalyst. Acidic cleavage of the chiral auxiliary resulted in concurrent intramolecular imine formation, then subsequent reduction with sodium cyanoborohydride, followed by hydrochloride salt formation generated the *N*-heterocyclic core of piperidine derivatives **59**-**62** in excellent diastereomeric excess. The diastereoselective outcome is rationalised by the conformation adopted by the cyclic imine (Figure 1.7). Stereoelectronically favoured axial attack of the hydride on the most stable half-chair conformation **63**, where both substituents are pseudo-equatorial, results in the *cis*-configuration of piperidines. 2-Phenyl-6-methylpiperidine **62** has also been further transformed into 6-methylpipecolic acid in 41% yield over 3 steps.



Scheme 1.3 Reductive amination strategy to piperidine-containing alkaloid natural products

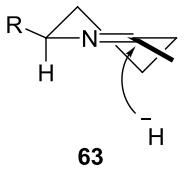


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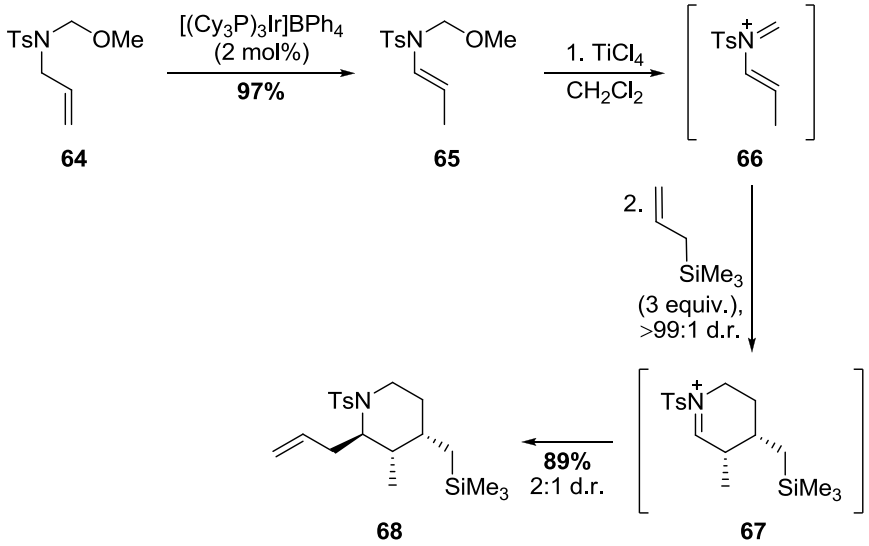
Figure 1.7 Axial attack on lowest energy conformation of cyclic imine

This reductive amination strategy is appealing because the piperidine ring is produced in 6 steps in 62% overall yield, on average. A range of substituents can be introduced at the 2-position as exemplified by the synthesis. Also, various 6-substituents could be incorporated by varying the enone employed for the cross-metathesis reaction and therefore the scope of this methodology is wide-ranging.

Using an intramolecular reductive amination reaction to form the piperidine core is a popular approach as illustrated by several recent syntheses.[25] Intramolecular nucleophilic substitution reactions also feature heavily in many modern piperidine syntheses.[26]

1.2.1.3 Cycloaddition

Cycloaddition reactions are often used as an efficient method to synthesise piperidine derivatives.[27] Nelson and co-workers published an expeditious route using a hetero Diels-Alder cyclisation to generate a highly functionalised piperidine skeleton.[28] Allylic sulfonamide **64** was subjected to an alkene isomerisation using an iridium-based catalyst to give enamine **65** with high *E*-selectivity (Scheme 1.4). In a one-pot process, cationic aza-diene **66** was formed by Lewis acid-mediated *N*,*O*-acetal ionisation of precursor **65**. Subsequent hetero Diels-Alder cycloaddition with allyltrimethylsilane produced *syn*-iminium cycloadduct **67** *via* an *endo* transition state. In the presence of excess allyltrimethylsilane, allylation of the iminium ion gave piperidine **68** with 2:1 diastereofacial control.



Scheme 1.4 Hetero Diels-Alder cycloaddition to generate trisubstituted piperidine **68**

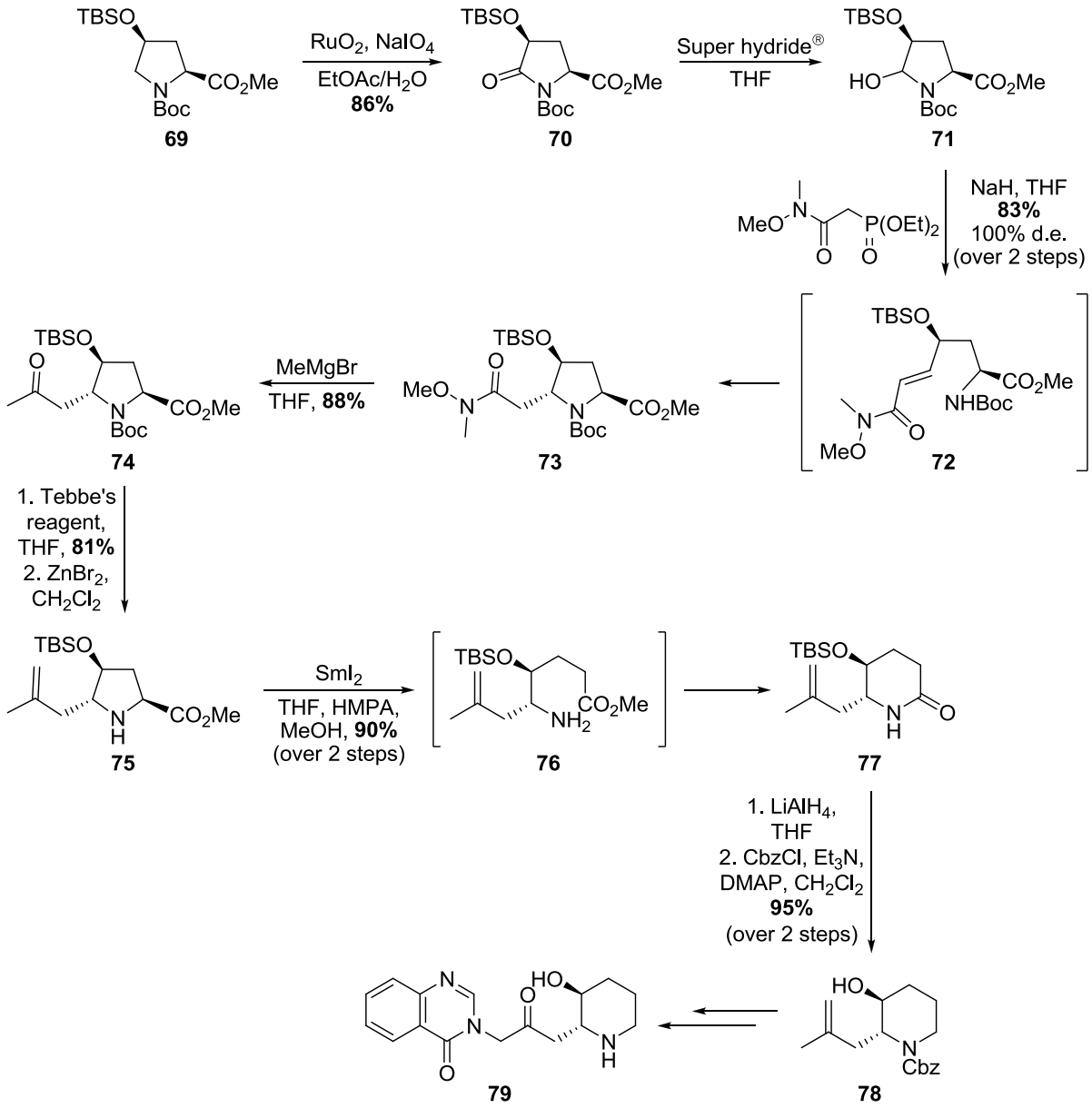
Nelson and co-worker's route provides a fast and efficient method to generate structurally diverse piperidines as various nucleophiles could be introduced at the 2-position. The disadvantage is that only relative stereochemistry is established in this case, however a chiral auxiliary in place of the *N*-tosyl group may induce asymmetry during the [4+2] cycloaddition.

1.2.1.4 Ring Expansion / Rearrangement

Rearrangement and ring expansion strategies are scarcely used for the synthesis of piperidines. They are usually employed in specific cases rather than as a general method.

Honda and co-workers devised a synthetic scheme for the synthesis of a potential antimalarial piperidine alkaloid, (+)-febrifugine **79**.[29] The sequence involved a samarium diiodide-promoted carbon–nitrogen bond cleavage of a five-membered ring, followed by ring-closure to produce a six-membered piperidine ring.

Starting from protected (4*S*)-4-hydroxy-L-proline **69**, ruthenium(IV) oxide oxidation produced lactam **70** (Scheme 1.5). Reduction of the lactam gave aminal **71**, which is in equilibrium with the corresponding aminoaldehyde. A one-pot Horner-Wadsworth-Emmons (HWE) reaction generated α,β-unsaturated amide **72** and then an intramolecular conjugate addition reaction yielded amide **73** in good yield. The stereochemistry arises from selective attack of the amine on the less hindered face to produce **73** as a single diastereomer. Methyl ketone **74** was generated by treatment of Weinreb amide **73** with methylmagnesium bromide. Methylenation of the ketone with Tebbe's reagent, followed by Boc deprotection yielded amine **75**. Reductive deamination using samarium diiodide as a one-electron reducing agent cleaved the *C*–*N* bond of the proline derivative to give intermediate **76**, which spontaneously cyclised *in situ* with expansion of the ring to produce piperidone **77** in excellent yield. Reduction of piperidone **77** with lithium aluminium hydride and simultaneous removal of the hydroxy-protecting group followed by protection of the secondary amine yielded 3-hydroxypiperidine **78**. Several transformations were required to convert piperidine **78** into the desired product, (+)-febrifugine **79**.



Scheme 1.5 Rearrangement reaction for the synthesis of (+)-febrifugine **79**

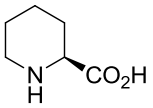
This approach is effective as the stereochemistry derived from the one-pot HWE/conjugate addition reaction proceeds with complete diastereoselectively. Also, the key reductive deamination step to rearrange the proline to the piperidine scaffold occurs in high yield. This method could enable the synthesis of a variety of analogues because piperidone **77** is suitably functionalised to allow subsequent transformations.

A review of recent literature demonstrates the wide selection of strategies available to synthetic chemists for the preparation of substituted piperidine scaffolds. The approaches illustrated

generally allow the target heterocycle to be synthesised in reasonable yields, however certain routes are long and inefficient. The drive towards short, enantiocontrolled strategies continues to be a priority within the field. Many variations to the piperidine core exist and therefore incorporation of diversity is another vital feature to enable the synthesis of important piperidine derivatives.

1.3 Pipecolic Acid

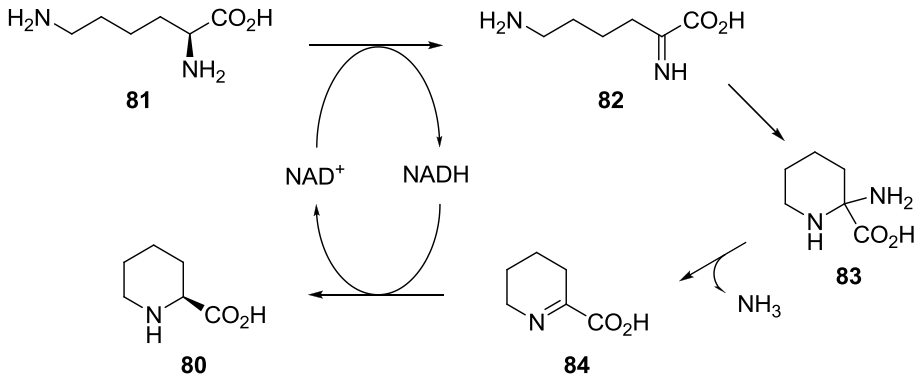
Pipecolic acid **80** is a naturally occurring non-proteinogenic α-amino acid that is widely distributed in plants, animals and microorganisms (Figure 1.8). The molecular scaffold consists of a saturated *N*-heterocycle substituted at the *C*-2 position with a carboxylic acid. Pipecolic acid has a wealth of different functions as it can be observed underivatised in biological systems or used as a natural or synthetic derivative.



80

Figure 1.8 (2*S*)-Pipecolic acid

Isotopic labelling studies have demonstrated that pipecolic acid is biosynthesised from lysine in mammals, higher plants and microbes.[30] Multiple putative pathways exist for lysine catabolism depending on the species.[31] Microbial biosynthesis occurs *via* a gene which codes for lysine cyclodeaminase. This enzyme is responsible for the NAD^+–dependant synthesis of the non-proteinogenic amino acid. The α-amino group of lysine **81** is oxidised to imine **82** using cofactor NAD^+, followed by cyclisation of the ε-amine onto the imine to generate the quaternary substituted *N*-heterocycle **83** (Scheme 1.6).[32] Subsequent loss of ammonia produces unsaturated piperidine **84**. Stereospecific reduction with NADH yields L-pipecolic acid **80** and recycles the coenzyme.



Scheme 1.6 Microbial biosynthesis of pipecolic acid **80** from lysine **81**

A similar metabolic pathway is currently accepted for pipecolic acid biosynthesis in mammals, however, 2-keto-6-amino caproic acid is thought to be the direct precursor of **84**.[33]

Metabolism of lysine into pipecolic acid has been observed in various human physiological fluids and in particular, in the brain. It has been suggested that pipecolic acid has a functional role in the mammalian central nervous system related to the GABAergic system, however much debate surrounds this hypothesis.[34,35] γ-Aminobutyric acid (GABA) is a fundamental neurotransmitter in the CNS, responsible for neuronal excitation and inhibition and therefore understanding the role of pipecolic acid in this critical pathway may lead to potential therapies for neurological disorders.[36]

(2*S*)-Pipecolic acid has also been incorporated into many elaborate structures which have a wide range of interesting biological properties. Several microbial secondary metabolites contain the pipecolic acid motif and these compounds possess significant pharmacological activity. Rapamycin **85**, FK506 **86** and FK520 **87** are macrolactone natural products that are primarily polyketide structures with the exception of a single pipecolic acid residue (Figure 1.9). Macrolides **85**-**87** exhibit potent anti-fungal and immunosuppressant activity and are currently used in transplant medicine, dermatology and cardiology.[37] The pipecolic acid moiety within the structures serves as a substrate mimic and is critical for affinity with the target FK506-binding proteins (FKBP12).[38,39,40]

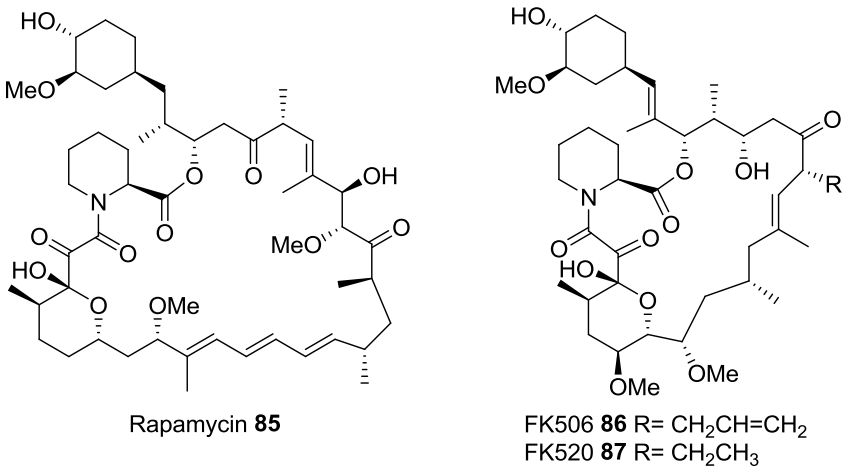
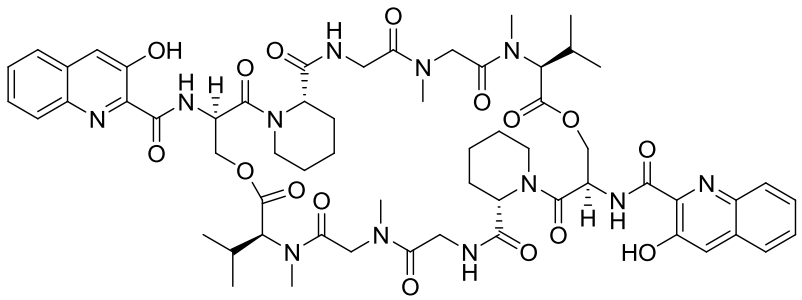


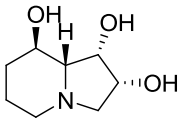
Figure 1.9 Immunosuppressant secondary metabolites containing the pipecolic acid motif

Two novel polyketides containing pipecolic acid; nocardiopsin A and B, have recently been identified from marine-derived microorganisms.[41] These are closely related structurally and biosynthetically to the immunosuppressants **85**-**87**, however as yet, no biological activity has been determined despite micromolar binding to FKBP12 proteins. The structures have been elucidated, although determination of the relative and absolute configurations of the stereogenic centres remains to be carried out.

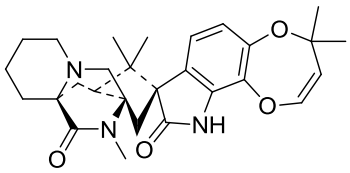
Sandramycin **88**, a potent anti-tumor antibiotic, is a cyclic decadepsipeptide with two pipecolic acid residues incorporated (Figure 1.10). The structure is C_2-symmetric and contains two heteroaromatic groups responsible for sequence-specific bis-intercalation with DNA.[42] This disrupts DNA replication within rapidly dividing cancerous cells. Pipecolic acid is also a precursor of other important naturally occurring secondary metabolites including the indolizidine alkaloid, swainsonine **89**, which exhibits potent antimetastatic, antiproliferative and immunomodulatory properties.[43] The anthelmintic agent marcfortine A **90**, used to expel parasitic worms, also uses pipecolic acid as a precursor.



Sandramycin **88**



Swainsonine **89**

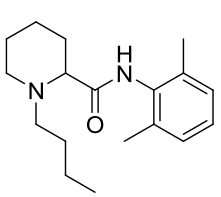


Marcfortine A **90**

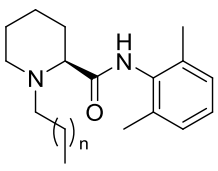
Figure 1.10 Secondary metabolites derived from pipecolic acid

Pipecolic acid has also been used as a scaffold for synthetic therapeutic agents such as the local anaesthetic analogues; bupivacaine **91**, ropivacaine **92** and levobupivacaine **93** administered *via* epidural or intrathecal injection (Figure 1.11). Bupivacaine was marketed as the racemic mixture, however, certain patients experienced cardiac arrest as a result of the anaesthetic. Employing the (*S*)-enantiomer of pipecolic acid in derivatives **92** and **93** prolonged the duration of action and reduced cardiotoxicity.[44] This illustrates the need for enantioselective syntheses of pipecolic acid for medicinal use.

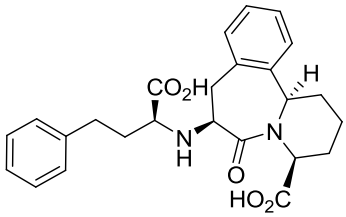
A potent angiotensin converting enzyme (ACE) inhibitor **94** was developed that contained a pipecolic acid motif to mimic binding of the endogenous ligand, angiotensin, to the positive *C*-terminus of the active site.[45] Synthetic ACE inhibitors have been widely employed to treat hypertension.



Bupivacaine **91**



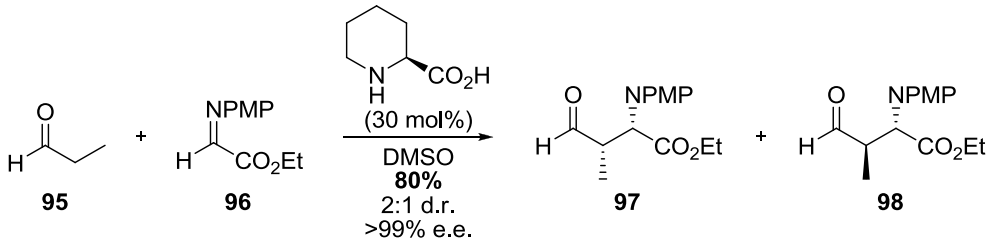
n = 1, Ropivacaine **92**
n = 2, Levobupivacaine **93**



ACE inhibitor **94**

Figure 1.11 Synthetic therapeutic derivatives containing the pipecolic acid motif

In modern organic synthesis, pyrrolidine-based organocatalysts have been extensively studied for use in asymmetric reactions.[46] (*S*)-Proline has been successfully employed as an organocatalyst, however, the six-membered analogue, pipecolic acid, has received limited attention.[47,48] Recent work published by Barbas and co-workers, revealed the potential to use (*S*)-pipecolic acid to catalyse a highly enantioselective Mannich reaction.[49] Reaction of aldehyde **95** with protected α-imino ethyl glyoxylate **96**, catalysed by pipecolic acid, gave a 2:1 mixture of *syn*:*anti* products in greater than 99% enantiomeric excess (Scheme 1.7). In light of this development, the full synthetic potential of pipecolic acid in organic chemistry is perhaps yet to be fully investigated.



Scheme 1.7 Pipecolic acid-catalysed asymmetric Mannich reaction

Pipecolic acid is a common structural element in peptide chemistry. Several conformationally constrained amino acids **99**-**102** have been devised to mimic turn motifs of biologically relevant peptides (Figure 1.12).[50] Pipecolic acid is often utilised within bicyclic structures as the heterocyclic amino acid is ideally positioned to mimic a peptidic β-turn. This expanding area of research will allow an enhanced understanding of interactions of small molecules with biological targets such as enzymes or receptors.

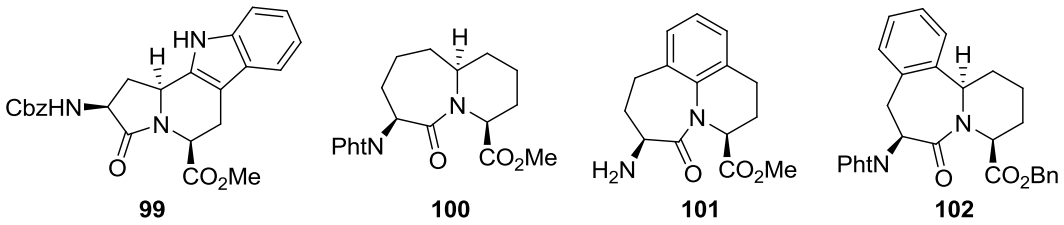
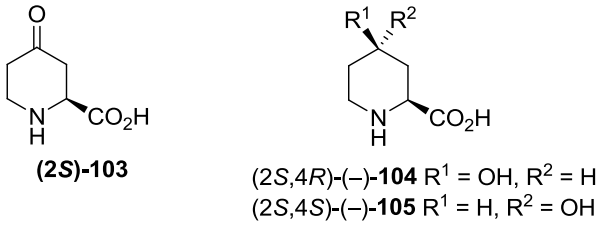


Figure 1.12 Pipecolic acid-derived peptidomimetics

The examples illustrated above demonstrate the significance of unfunctionalised pipecolic acid in the free form or as a structural element within natural or synthetic molecules for a wide range of roles. However, one of the largest classes of pipecolic acid derivatives studied is 4-substituted pipecolic acid, in particular, 4-oxygenated species **103**-**105** (Figure 1.13). These naturally occurring

pipecolic acid motifs have been extensively examined as they have interesting and potent biological activities.

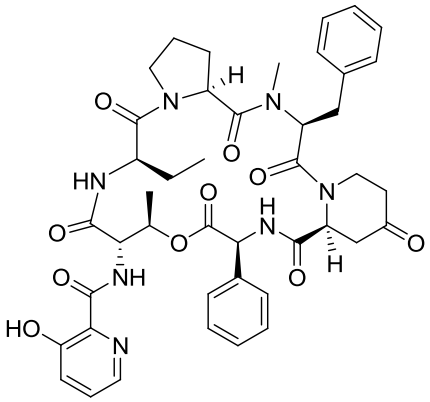


(2*S*)-103

(2*S*,4*R*)-(–)-**104** R^1 = OH, R^2 = H
(2*S*,4*S*)-(–)-**105** R^1 = H, R^2 = OH

Figure 1.13 4-Oxopipecolic acid and 4-hydroxypipecolic acids

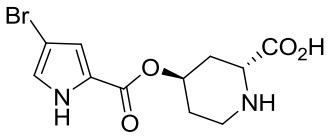
The 4-oxopipecolic acid moiety has been identified in the cyclic hexadepsipeptide antibiotic, virginiamycin S_2 **106** (Figure 1.14). Virginiamycin is a microbial secondary metabolite produced by *Streptomyces virginiae*, which has potent bactericidal properties against a wide spectrum of drug-resistant strains of gram-positive bacteria such as *Staphylococcus aureus*.[51] Other complex biologically active antibiotics containing the 4-oxopipecolic acid motif include virginiamycin S1, pristinamycin 1A, vernamycin B and ostreogrycin B3.[52]



Virginiamycin S_2 **106**

Figure 1.14 Antibiotic virginiamycin S_2

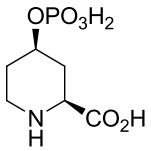
A secondary metabolite was identified from a marine sponge which contains a (2*R*,4*R*)-hydroxypipecolic acid residue. Damipipecolin **107** is a bromopyrrole alkaloid that exhibits a modulating effect on a serotonin receptor *in vitro* (Figure 1.15).[53]



Damipipecolin **107**

Figure 1.15 Marine alkaloid secondary metabolite with 4-hydroxpipecolic acid nucleus

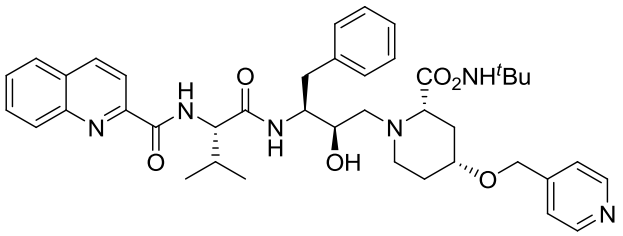
Synthetic therapeutic agents have been devised that possess 4-oxygenated pipecolic acid derivatives. Natural excitatory amino acids; aspartate and glutamate are important mediators of neuronal function in the mammalian CNS. They are agonists of the *N*-methyl-D-aspartic acid (NMDA) receptor that gates a calcium ion channel. Excessive stimulation by neurotransmitters is known to cause cell death in cerebral ischemia and is implicated in neurological disorders such as Alzheimer's disease and Huntington's chorea.[54] Antagonism of the NMDA receptor to block the over-excitation could potentially be a useful therapeutic tool to treat a range of neurodegenerative diseases. A potent and selective competitive NMDA receptor antagonist **108** has been developed that consists of a (4*R*)-hydroxypipecolic acid element (Figure 1.16).[55] Alternative analogues of NMDA antagonists have also been produced using 4-hydroxypipecolic acid as a synthetic intermediate.[54,56]



108

Figure 1.16 Competitive NMDA receptor antagonist

(4*R*)-Hydroxypipecolic acid is also present in the synthetic human immunodeficiency virus (HIV) protease inhibitor, palinavir **109** (Figure 1.17). HIV protease enzyme is responsible for producing mature protein components for the retrovirus and therefore is essential for the viral life cycle. Inhibition of HIV protease results in immature, non-infectious virions and suppresses viral replication.[57] Targeted inhibition of HIV protease has emerged as an effective strategy in HIV therapy.[58]



Palinavir **109**

Figure 1.17 HIV protease inhibitor, palinavir

As exemplified, the 4-oxygenated pipecolic acid moiety is an important element in a variety of medicinally relevant compounds. In general, the development of therapeutic agents requires asymmetric syntheses, as the unwanted enantiomer is regarded as a medicinal pollutant. Significant synthetic efforts have therefore been devoted to synthesise 4-oxo- and 4-hydroxypipecolic acids in high yield and with high enantioselectively.

1.3.1 4-Oxopipecolic Acid Synthesis

Pipecolic acid is a desirable target in organic synthesis as it is associated with three important families of natural products; α-amino acids, aza-sugars and alkaloids. Also, the biological significance of 4-oxygenated pipecolic acids makes them attractive synthetic targets. An efficient, stereocontrolled strategy to construct the *N*-heterocyclic product is crucial, however, enantioselective preparations of the 4-oxopipecolic acid skeleton remain a contemporary challenge.

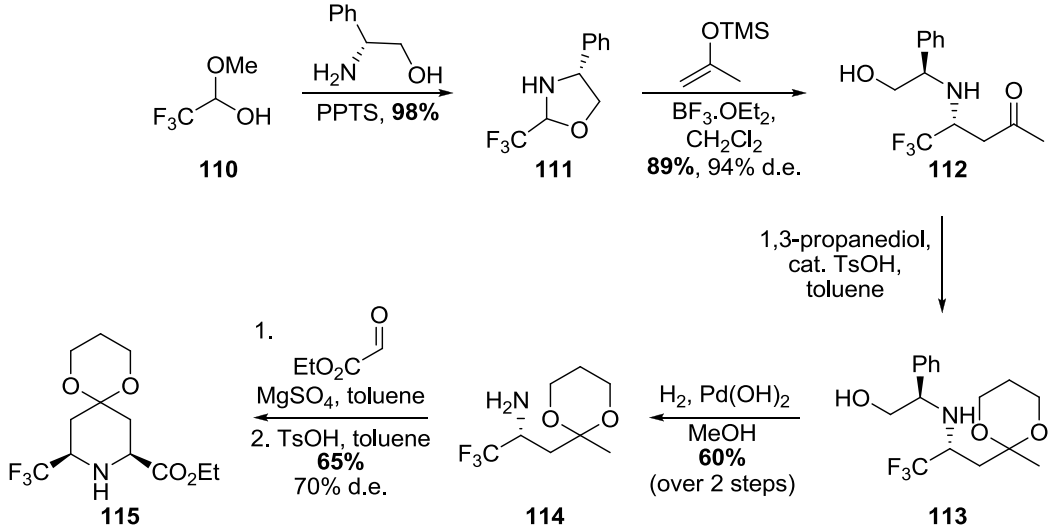
1.3.1.1 Heterocycle Construction

The most common method in the literature for the construction of the 4-oxopipecolic acid motif is to use an intramolecular cyclisation to synthesise the saturated *N*-heterocyclic core. Well-established, classical reactions are often employed for the ring-closing step, however, the difficultly remains to incorporate high levels of asymmetry.

An asymmetric synthesis of 4-oxopipecolic acid bearing a trifluoromethyl group was developed by Canet and co-workers.[59] Selective incorporation of fluorine atoms into small, therapeutic molecules can often lead to enhanced efficacy and therefore, the synthesis of saturated *N*-heterocycles containing fluorine is a topical field. Construction of the heterocyclic core of the 4-oxopipecolic acid derivative was carried out using an intramolecular Mannich reaction of an

enantiomerically pure α-trifluoromethyl-β-amino ketal. A β-amino alcohol was employed as the enantiopure starting material to enable asymmetric induction.

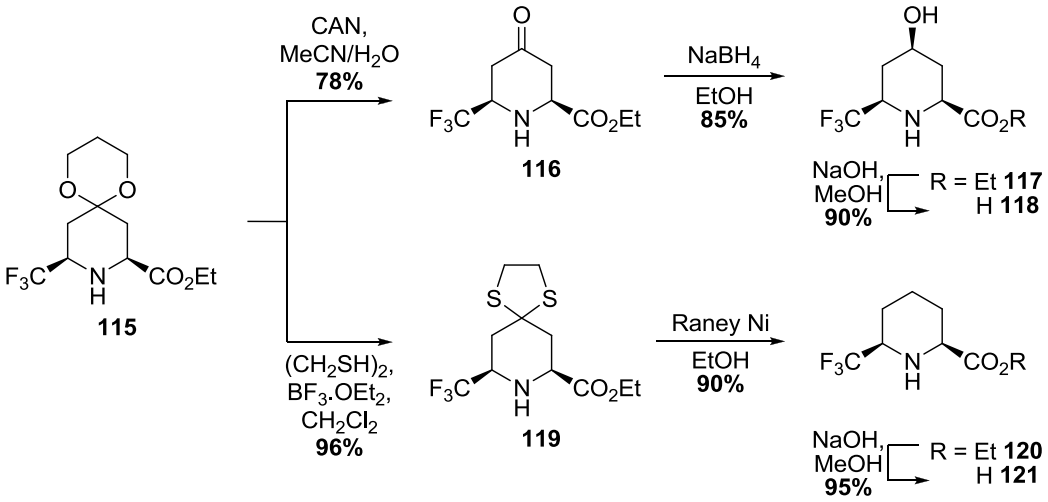
The synthetic route involved formation of oxazolidine **111** from trifluoroacetaldehyde methyl hemiacetal **110** and (*R*)-phenylglycinol (Scheme 1.8). This produced a 2:1 mixture of diastereomers in 98% yield. Subsequently, the diastereomeric mixture was treated with a silyl enol ether to give rise to β-amino ketone **112** with high diastereoselectivity. The high level of diastereoselectivity is accounted for by formation of a chiral imine which results from ring opening of the oxazolidine. This produces a rigid, ordered intermediate with the phenyl group blocking one face and therefore, selective attack occurs from the opposing face.[60] Protection of the carbonyl as ketal **113**, followed by hydrogenolysis generated substrate **114** for the intramolecular Mannich reaction. Formation of the pipecolic acid core was achieved using ethyl glyoxylate to give an imine. Under acidic conditions, the ketal ring-opened to give the corresponding enol ether, which cyclised onto the imine to produce the desired *N*-heterocycle and regeneration of the ketal protecting group occurred *in situ*. *Cis*-trifluoromethyl pipecolic acid **115** was the major diastereomer obtained as a result of the intramolecular Mannich reaction in an 85:15 *cis*:*trans* ratio.



Scheme 1.8 Synthetic route to trifluoromethyl-4-oxopipecolic acid derivative **115**

Canet and co-workers proceeded to demonstrate that the ketal-protected pipecolic acid scaffold **115** could be efficiently converted to desirable pipecolic acid congeners (Scheme 1.9). Oxidative cleavage of the ketal moiety with cerium ammonium nitrate (CAN) generated 4-oxopipecolic acid **116** and then reduction with sodium borohydride gave the (4*R*)-hydroxypipecolic acid analogue

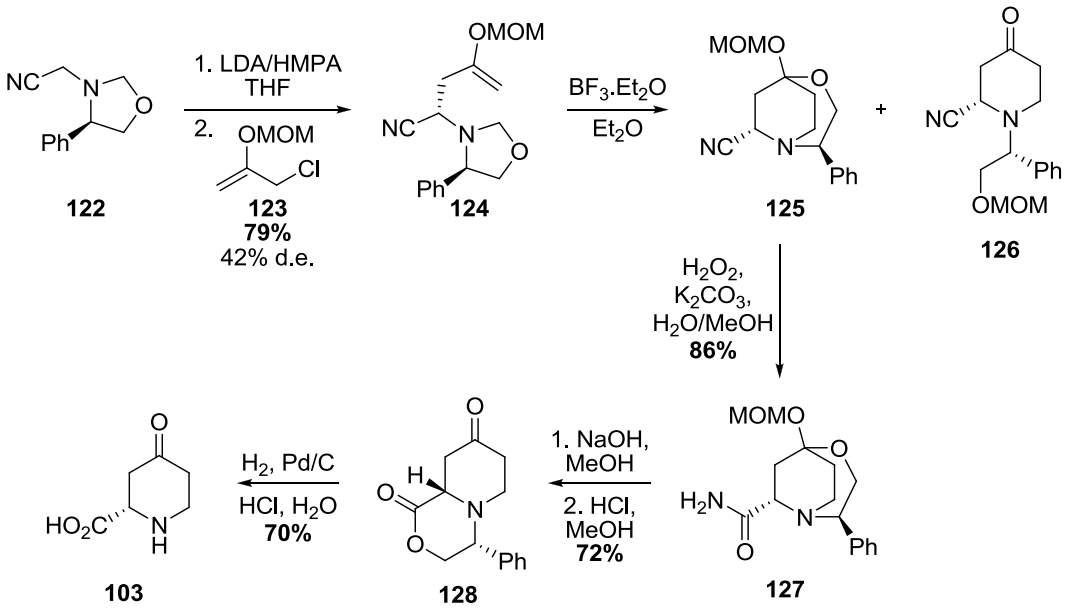
117. Alternatively, conversion of the ketal to dithiane **119** and subsequent reduction with Raney nickel produced pipecolic acid **120** in excellent yield. Finally, deprotection of the esters with sodium hydroxide in methanol gave the parent pipecolic acid derivatives **118** and **121**.



Scheme 1.9 Modification of trifluoromethyl-4-oxopipecolic acid derivative **115** to give pipecolic acid analogues

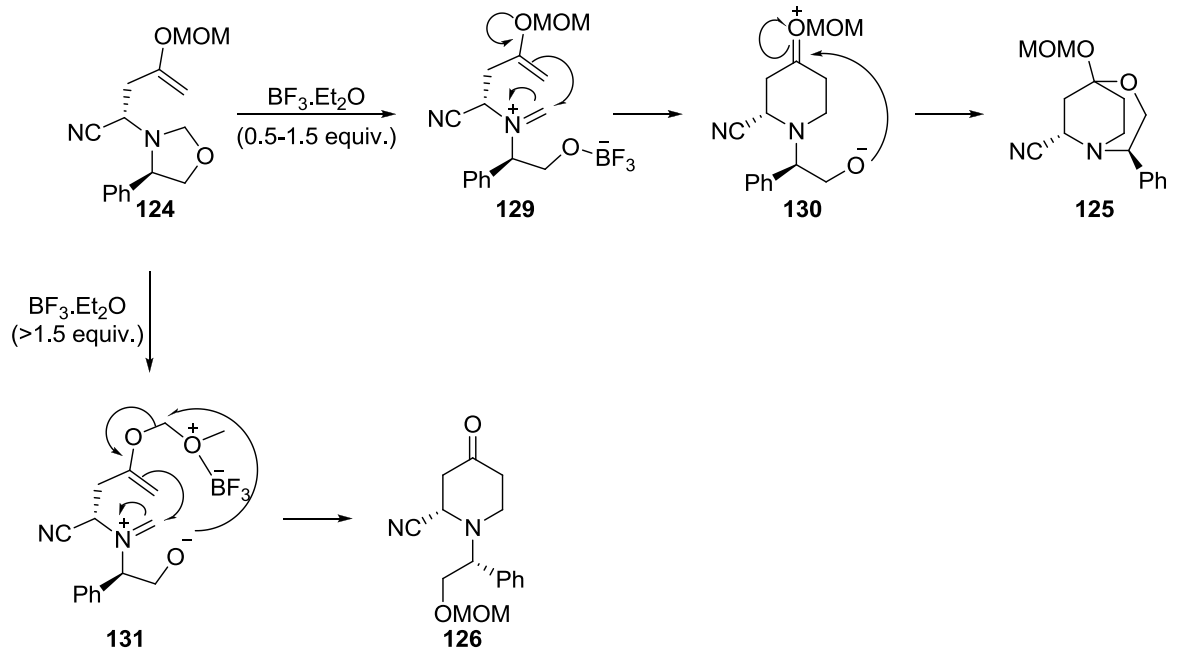
The synthetic route devised by Canet and co-workers enabled the synthesis of 4-oxopipecolic acid in 6 steps from a commercial fluoro-acetal in 27% overall yield. The strategy benefits from high stereoselectivity for the enol ether addition to the oxazolidine to produce the enantiopure β-amino ketone **112**. This reaction dictates the stereochemistry of the 6-substituent of the pipecolic acid derivative. High diastereoselective discrimination is also observed for the intramolecular Mannich reaction to give the *syn*-6-substituted configuration on the heterocyclic core. This approach for the synthesis of substituted pipecolic acids is a versatile route because variation is possible to an extent when other hemiacetals are employed as the starting material.[61]

An intramolecular Mannich-type reaction was also investigated by Aitken and co-workers for the synthesis of 4-oxopipecolic acid.[62] Enantiomerically pure oxazolidine **122** was deprotonated with lithium diisopropylamide (LDA) and subsequent nucleophilic attack on MOM-protected allyl chloride **123** gave intermediate **124** as the major diastereomer (Scheme 1.10). The key cyclisation step took place under Lewis acid catalysed conditions to form the *N*-heterocyclic core with two possible products **125** and **126**.



Scheme 1.10 Intramolecular Mannich-type reaction for the synthesis of 4-oxopipecolic acid

The mechanism for the cyclisation involved boron trifluoride etherate-induced ring opening of the oxazolidine to generate an iminium **129**, followed by spontaneous cyclisation through the enol ether to provide the piperidine nucleus containing an electrophilic centre (Scheme 1.11). The oxyanion **130** can attack the carbonyl from either face to produce the major bicyclic product **125** as a 1:1 mixture of diastereomers at the bridgehead carbon. With excess Lewis acid, coordination to the MOM group takes place and allows abstraction of the protecting group by the oxyanion with concomitant cyclisation to yield piperidone derivative **126**. The yields and ratios of products were dependent on the quantity of boron trifluoride etherate employed (Table 1.1).



Scheme 1.11 Mechanism for the intramolecular Mannich-type addition

Entry	$BF_3.Et_2O$ (equiv.)	Solvent	Yield 125 (%)	Yield 126 (%)
1	0.5	THF	36	12
2	1.5	THF	72	26
3	2.5	THF	38	62
4	1.5	Et_2O	84	10

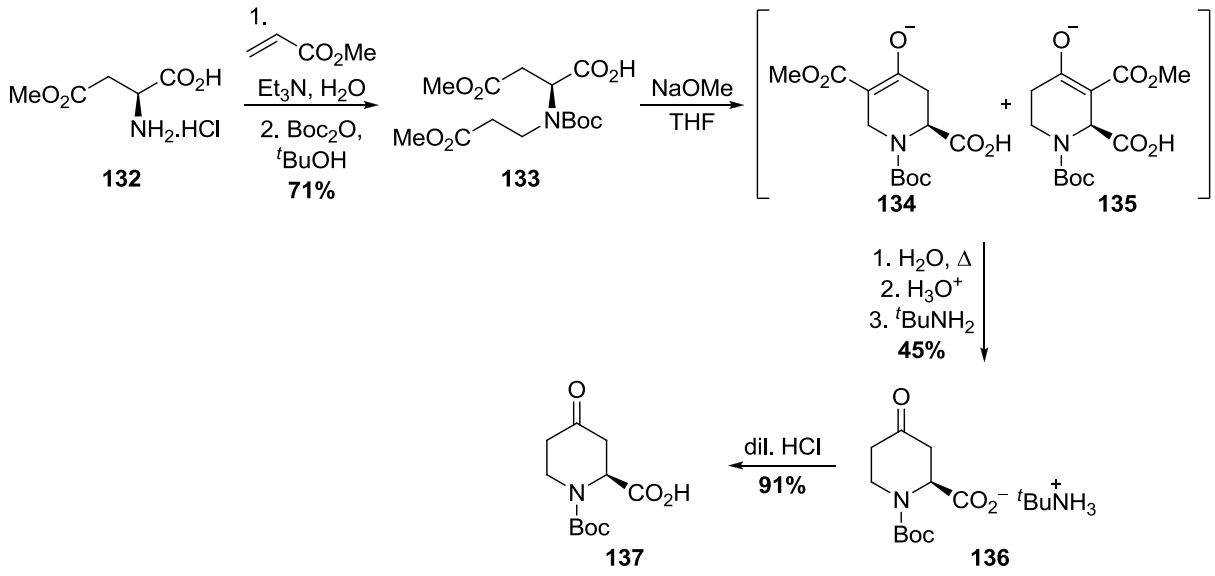
Table 1.1 Intramolecular Mannich-type cyclisation conditions

Completion of the synthesis entailed formation of amide **127**, which was hydrolysed to the corresponding carboxylic acid under basic conditions (Scheme 1.10). Acid-promoted cleavage of the semi-cyclic acetal produced an alcohol which cyclised to form a lactone and simultaneous deprotection of the MOM group yielded intermediate **128**. Finally, hydrogenolysis gave rise to the desired 4-oxopipecolic acid **103**.

This approach produces 4-oxopipecolic acid in seven steps in a respectable 29% overall yield. One limitation of this method is that it would be difficult to place substituents around the heterocyclic core as this may complicate the cyclisation step. This method therefore lacks the versatility to synthesise pipecolic acid derivatives.

An alternative route where the piperidine core is constructed *via* an intramolecular cyclisation is Bousquet and co-worker's synthesis of 4-oxopipecolic acid.[58] They embarked on a programme to target inhibition of HIV protease, where the lead compound, palinavir **109**, contained a *cis*-configured 4-hydroxypipecolic acid motif (Figure 1.17). The aim of the research was to develop an efficient approach to the pipecolic acid core that was amenable on a large scale to produce sufficient quantities for clinical trials.

A Dieckmann condensation was employed as the key step to produce the heterocyclic core using an enantiopure α-amino acid as the starting material. The initial step involved a conjugate addition of L-aspartic acid derivative **132** to methyl acrylate, then Boc-protection of the amine in a one-pot procedure generated diester **133** (Scheme 1.12). Formation of the pipecolic acid core was achieved when intermediate **133** was subjected to standard Dieckmann condensation conditions to produce regioisomers **134** and **135**. Decarboxylation *in situ* under thermal conditions followed by acidification enabled extraction of the crude product. 4-Oxopipecolic acid **136** was isolated as the *tert*-butyl amine salt. Finally, addition of dilute hydrochloric acid yielded the desired 4-oxopipecolic acid **137**.

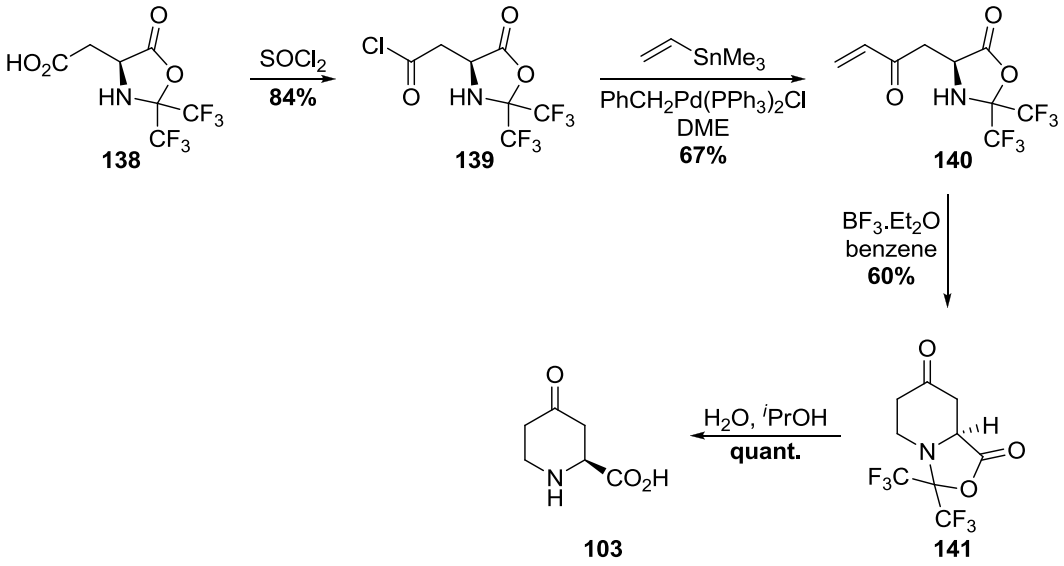


Scheme 1.12 Dieckmann cyclisation to produce Boc-protected 4-oxopipecolic acid

The Dieckmann strategy used by Bousquet and co-workers requires few steps and the yields are reasonable. Also, the stereochemistry of the carboxylic acid is defined by the starting material from the chiral pool and therefore, the enantiopurity of the product is high. The difficulty with

implementing this approach for access to a wider range of pipecolic acid derivatives is that installing substituents in the 5- or 6-position may be problematic. Permutations of methyl acrylate would be necessary for this approach and therefore the aza-conjugate addition reaction may be less efficient with substituted alkenes. Mixtures of diastereomers could also be obtained from the intermolecular conjugate addition of substituted olefins.

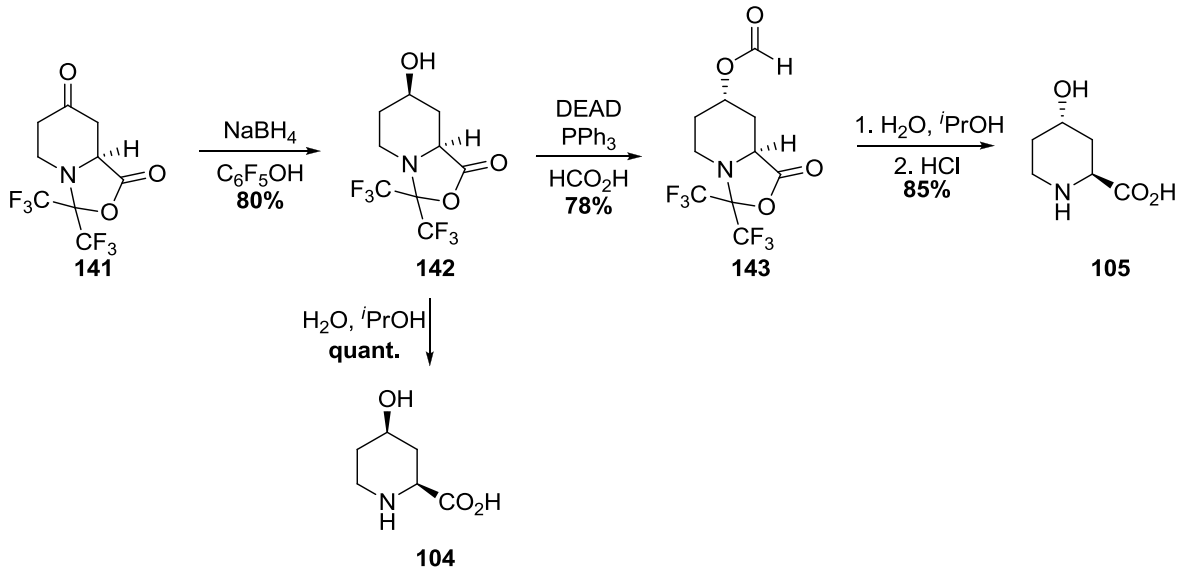
Access to 4-oxo-, *cis*-4-hydroxy- and *trans*-4-hydroxypipecolic acid is possible using Burger and co-worker's route which employs an intramolecular aza-conjugate addition as the key step to construct the heterocycle.[63] L-Aspartic acid was the enantiopure synthetic precursor for the approach, which was reacted with hexafluoroacetone to give protected oxazolidinone **138** (Scheme 1.13). Intermediate **138** was converted to acid chloride **139** and then subjected to standard Stille coupling conditions with vinyltrimethyltin as the corresponding partner to produce unsaturated amino acid derivative **140**. Subsequent Lewis acid-induced 6-*endo*-*trig* conjugate addition generated saturated *N*-heterocycle **141** in 60% yield. Finally deprotection yielded 4-oxopipecolic acid **103** quantitatively.



Scheme 1.13 Conjugate addition reaction for the synthesis of 4-oxopipecolic acid

4-Oxopipecolic acid derivative **141** could also be reduced diastereoselectively using sodium borohydride in the presence of pentafluorophenol to produce alcohol **142** (Scheme 1.14).[63] The fluorine-mediated boron reduction has been shown to reduce cyclohexanones *via* axial attack under the given conditions.[64] The equatorial hydroxyl of **142** can be inverted using a Mitsunobu

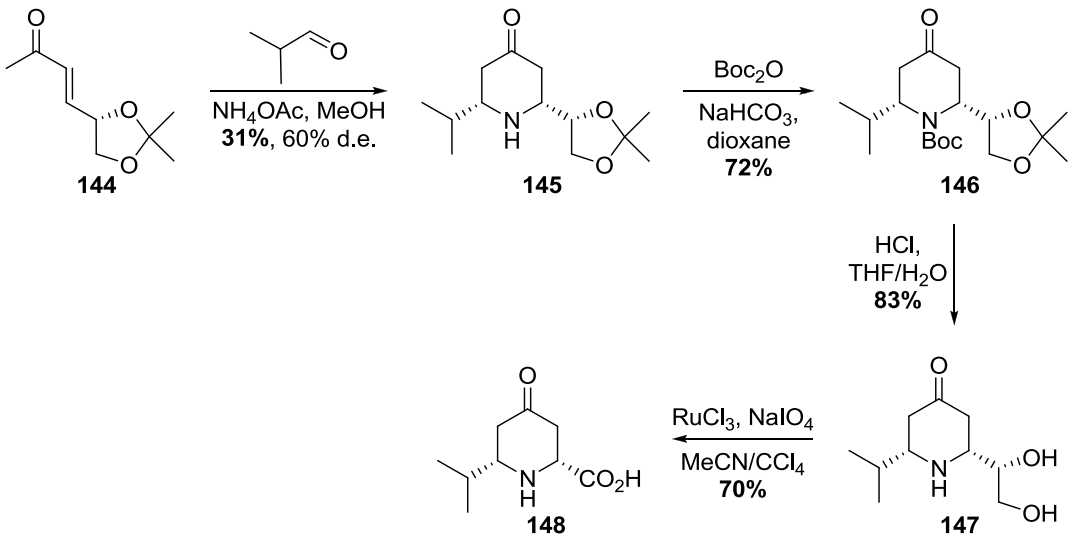
reaction with formic acid to give *trans*-4-hydroxy derivative **143**. Both derivatives were fully deprotected to yield *cis*- and *trans*-4-hydroxypipecolic acids **104** and **105**.



Scheme 1.14 Synthesis of *cis*- and *trans*-configured 4-hydroxypipecolic acids

The scope and limitations of this strategy were explored in an attempt to obtain 6-substituted-4-oxygenated pipecolic acid analogues. Employing a variety of substituted vinylic tributyltin derivatives for the Stille coupling enabled the synthesis of methyl, methyl ester, phenyl and *gem*-dimethyl substituted enones. The intramolecular aza-conjugate addition was attempted on the enone derivatives, however, only the methyl analogue cyclised slowly in 30% yield and therefore, analogous to previous approaches, the method doesn't appear to be flexible enough to synthesise alternative pipecolic acid scaffolds.

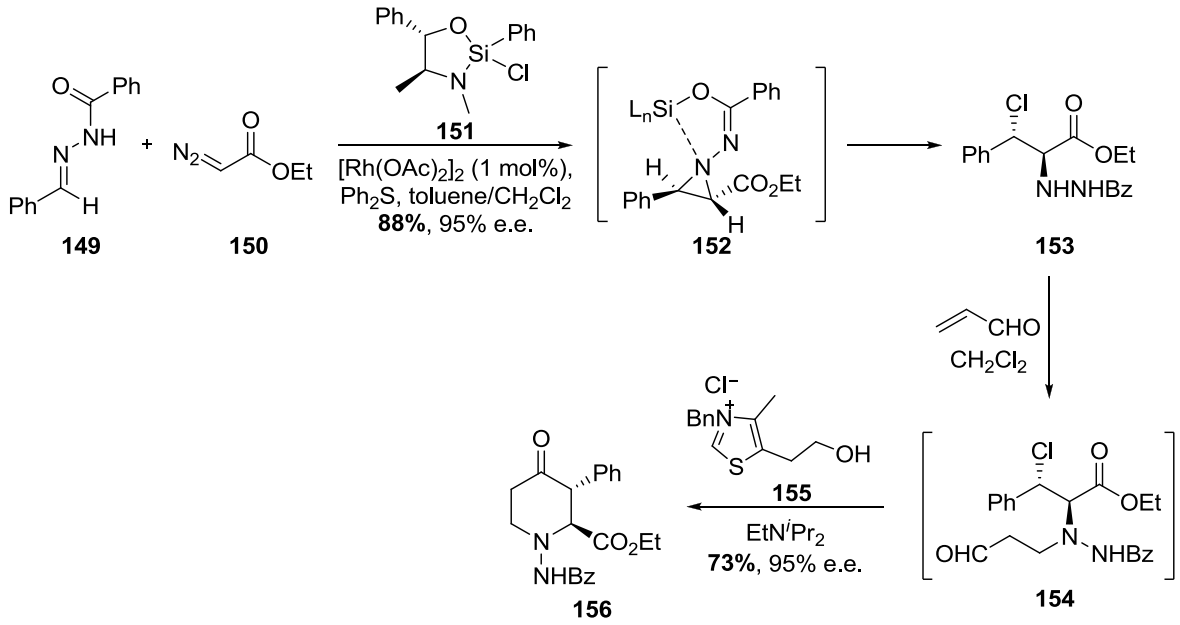
A one-pot, three component intermolecular reaction was investigated by Pätzel and co-workers to form 6-substituted-(2*R*)-4-oxopipecolic acids.[65] Employing a chiral α,β-unsaturated ketone, an aliphatic aldehyde and an amine gave rise to *cis*-2,6-disubstituted piperidones in moderate yields. Enantiomerically pure *E*-enone **144** reacted *via* conjugate addition with the imine of ammonia and *iso*-butyraldehyde formed *in situ* (Scheme 1.15). Concomitant intramolecular Mannich reaction closed the heterocyclic ring to give piperidone **145** with moderate diastereoselectivity. Boc protection of the amine, followed by ketal hydrolysis generated diol **147**. Finally, oxidation of the alcohol to the carboxylic acid produced novel *cis*-(2*R*,6*S*)-6-substituted-4-oxopipecolic acid **148** in 13% overall yield.



Scheme 1.15 Multicomponent method to synthesise 6-substituted-4-oxopipecolic acid

This multicomponent reaction is appealing because in theory, diversity could be easily attained by varying the aldehyde or amine source, of which there are plenty available. The disadvantage is that the yields and diastereoselectivities are modest as a result of competing reactions.

Leighton and co-workers reported a method to synthesise 3-substituted-4-oxopipecolic acid derivatives using a tandem asymmetric aza-Darzens reaction with nucleophilic ring opening *in situ*.[66] A chiral silane-containing Lewis acid was employed to activate both the imine for the aza-Darzens reaction and facilitate subsequent nucleophilic opening of the aziridine. In a one-pot process, a sulfonium ylide was generated from ethyl diazoacetate **150** and diphenylsulfide catalysed by rhodium acetate (Scheme 1.16). The ylide attacks the acylhydrazone **149**, which is complexed with enantiomerically pure silane **151**, followed by elimination of diphenylsulfide to form chiral aziridine **152**. The silane remains complexed to the aziridine. This activates it towards nucleophilic attack by the chloride liberated from the silane and gives rise to a single regioisomer of aminohalide **153** in good yield with excellent enantiomeric excess. To produce the *N*-heterocyclic core, intermediate **153** was reacted with acrolein to give aldehyde **154**. Deprotonation of thiazolium salt **155** forms an *N*-heterocyclic carbene which reacts with the aldehyde moiety to give an enol.[67] Subsequent cyclisation of the enol *via* a nucleophilic substitution reaction with inversion of the stereogenic centre generates 4-oxopipecolic acid analogue **156** in good yield with retention of enantiopurity.



Scheme 1.16 Tandem asymmetric aza-Darzens/ring-opening reaction for the synthesis of 4-oxopipecolic acid derivative **156**

The appeal of this route is the ability to telescope the aza-Darzens reaction and nucleophilic addition to carry out an aminohalogenation reaction, as well as using a one-pot procedure to generate the pipecolic acid. This methodology is fast and efficient and an excellent overall yield of 64% is obtained with high levels of enantioselectivity. This approach is interesting as it also allows entry to unusual linear α-amino acid derivatives. Alternative 3-substituted analogues could be formed by varying the hydrazone.

To summarise, a range of intramolecular cyclisation strategies can be applied for the synthesis of 4-oxopipecolic acid derivatives. In most cases, commercially available or naturally occurring chiral starting materials are employed, however, the use of a chiral ligand also proved to be extremely effective. The disadvantage of the approach is that a number of steps are required to obtain a suitably functionalised precursor for the cyclisation. In contrast, pericyclic chemistry can offer faster access to the desired pipecolic acid core.

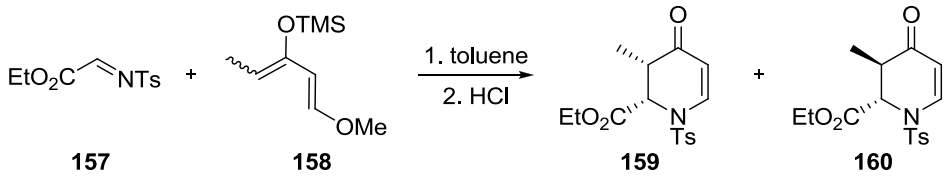
1.3.1.2 Cycloaddition

Pericyclic chemistry is an under-exploited method to produce 4-oxopipecolic acid, however advances within the field reveal that there is significant potential. Utilising cycloaddition reactions

to form the heterocyclic core can be difficult because controlling the relative and absolute stereochemistry is challenging. There are however a limited number of examples that obtain asymmetric induction.

Weinreb and co-workers reported the use of a Diels-Alder reaction for the preparation of a piperidine-containing precursor to the alkaloid natural product, cylindrospermopsin.[68] The tetracyclic molecule is a heptatoxin produced in the cyanobacterium, *Cylindrospermopsin raciborskii*, thought to inhibit cell-reduced glutathione synthesis which leads to hepatoenteritis in humans.[69]

The synthetic strategy to produce the 4-oxopipecolic acid scaffold involved an aza Diels-Alder cycloaddition as the first step. Oxygenated diene **158** was prepared as a 4:1 mixture of *Z*:*E* isomers. Diene **158** was reacted with ethyl glyoxylate-derived *N*-tosyl imine **157** to generate the heterocyclic core. Acidic hydrolysis of the trimethylsilyl (TMS) group *in situ* with concomitant elimination produced unsaturated cycloadducts **159** and **160** (Scheme 1.17).



157 **158** **159** **160**

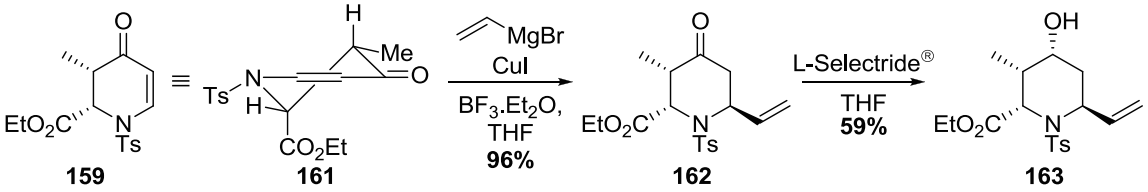
Scheme 1.17 Diels-Alder cycloaddition to form unsaturated pipecolic acid derivatives

Weinreb observed significant variation in the ratios of cycloaddition products obtained depending on the reaction conditions employed (Table 1.2). The optimal conditions utilised zinc chloride as a catalyst to facilitate the reaction to give excellent diastereoselectivity in favour of the *syn*-analogue **159** in 60% yield. Preference for the *syn* diastereomer is rationalised as the Diels-Alder cycloaddition will occur *via* an *endo* transition state with the major *Z*-diene. The variation in the ratios observed is postulated to be the result of *E*/*Z* isomerisation under the reaction conditions.

Entry	Catalyst	Temp. (°C)	Ratio (*syn*:*anti*)	Yield (%)
1	$AlCl_3$	−78	7:1	53
2	$ZnCl_2$	−78	22:1	60
3	-	r.t.	5:1	51

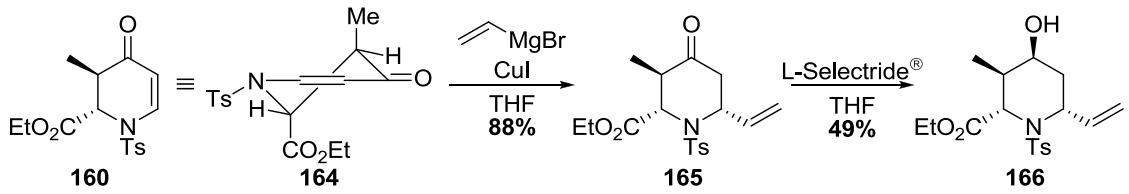
Table 1.2 Diels-Alder conditions

In order to synthesise the saturated *N*-heterocycle, a copper-mediated conjugate addition was investigated. According to ^{1}H NMR spectroscopic analysis of **159**, the heterocycle exists as a half-chair conformation **161** with the ethyl ester axial to avoid steric clash and minimise allylic strain with the *N*-tosyl group (Scheme 1.18). It is well documented that *C*-2 substituents of *N*-acylpiperidines reside axial for this reason.[70,71] Copper-catalysed conjugation addition of vinyl magnesium bromide occurs with an equatorial trajectory to avoid 1,3-diaxial interactions with the ester to produce 3,6-disubstituted-4-oxopipecolic acid derivative **162**. Subsequent reduction of the ketone with L-Selectride® led to formation of 4-hydroxypipecolic acid analogue **163**. This product however did not have the desired stereochemistry for the target molecule.



Scheme 1.18 Further functionalisation of *syn*-derivative **159**

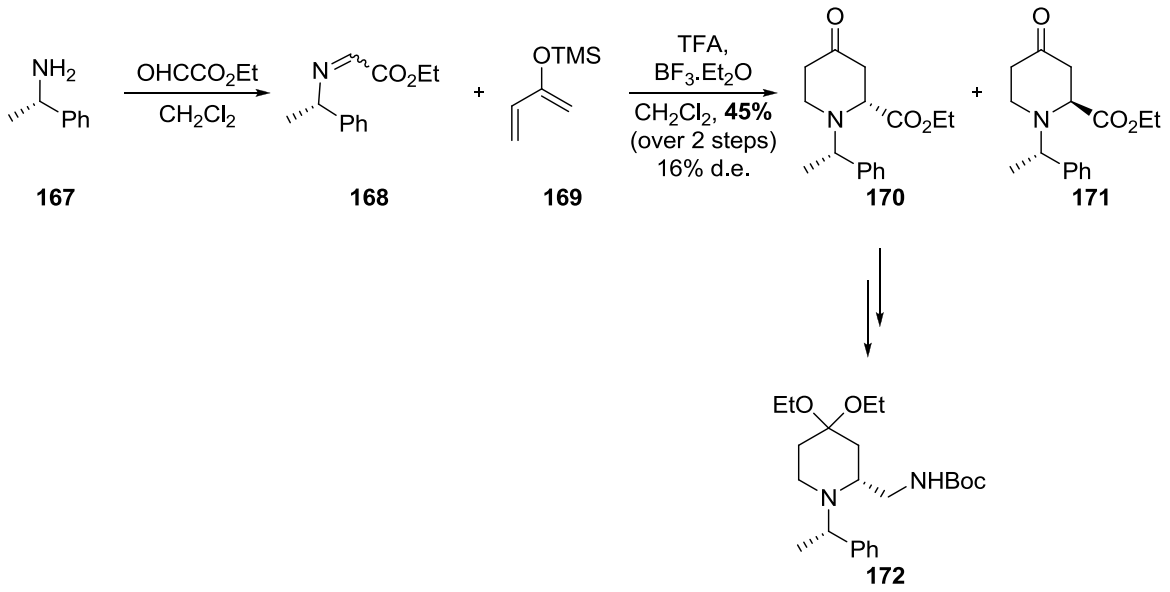
Similarly, the *trans*-cycloaddition product **160** adopts a half-chair conformation **164**, however attack of the vinyl magnesium bromide occurs *via* an axial direction to give 4-oxopipecolic acid **165** (Scheme 1.19). Reduction of the ketone to 4-hydroxy derivative **166** provided the stereochemistry necessary for the synthesis of the natural product. Subsequent modifications allowed the pipecolic acid analogue to be converted to a useful cylindrospermopsin intermediate.



Scheme 1.19 Further functionalisation of *anti*-derivative **160**

Hetero Diels-Alder chemistry is an efficient method to form the piperidine nucleus in one step. A variety of substituents can also be introduced around the heterocyclic core which makes this route attractive. The limitation of this approach is that only relative stereochemistry is established and ideally the route would be asymmetric. The problem could be rectified by using a chiral component for the Diels-Alder reaction as exemplified by the following methods.

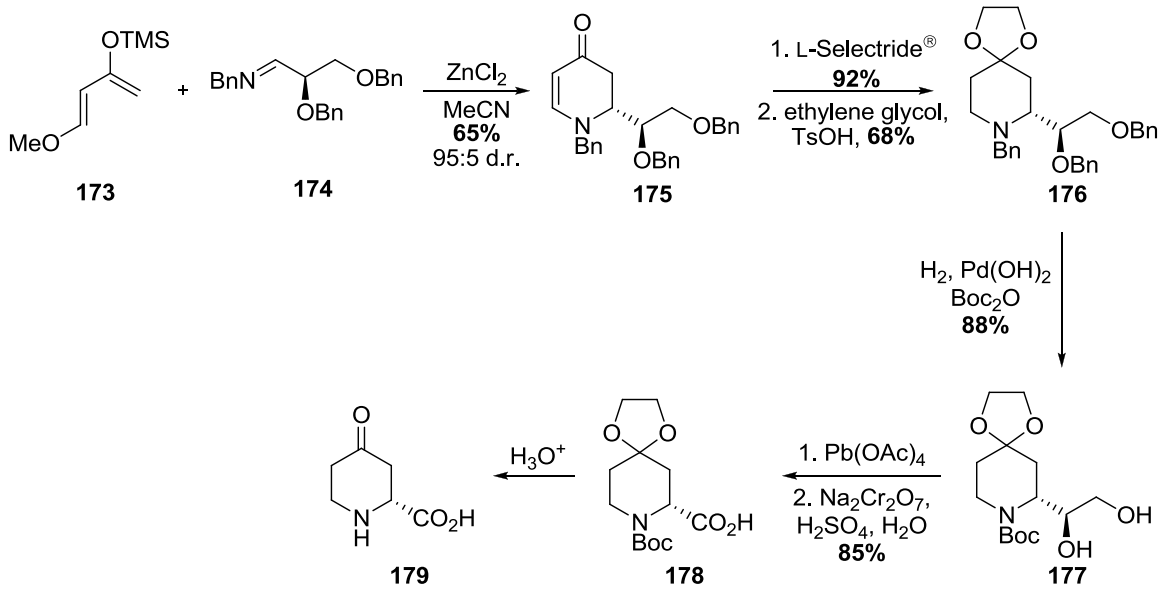
Lau and co-workers have presented a large-scale, asymmetric synthesis of 4-oxopipecolic acid using an aza Diels-Alder cycloaddition with an enantiomerically pure dienophile.[72] During work on a programme to synthesise 2-aminomethyl-4-oxopiperidine for use as a protein tyrosine phosphatase inhibitor, pericyclic chemistry was explored to incorporate the desired functionality of the piperidine ring. Enantiopure *S*-(−)-α-methylbenzylamine **167** was reacted with ethyl glyoxylate to give imine **168** (Scheme 1.20). Addition of diene **169** to the prepared imine **168** along with trifluoroacetic acid (TFA) and boron trifluoride etherate gave 4-oxopipecolic acid **170** as the major diastereomer in a 7:5 ratio. The major stereoisomer produced is the unnatural (2*R*)-pipecolic acid, however, using the opposite enantiomer of the starting material, (*R*)-(+)-α-methylbenzylamine, can give rise to the (2*S*)-configuration. Several steps were required to convert **170** to Lau's desired protected 2-aminomethyl-4-ketalpiperidine **172**.



Scheme 1.20 Asymmetric hetero Diels-Alder cycloaddition for the synthesis of 2-aminomethyl-4-ketalpiperidine **172**

The aza Diels-Alder process is elegant and efficient because the desired heterocycle is produced in two steps *via* a one-pot process. Devising synthetic strategies where multiple reactions are carried out in the one vessel enables less solvent to be used for the reactions and fewer work-ups. Also, fewer purification steps are required which makes tandem reactions environmentally friendly and economically viable for industrial purposes. The limitation of this approach is that the Diels-Alder reaction offers only a 16% diastereomeric excess.

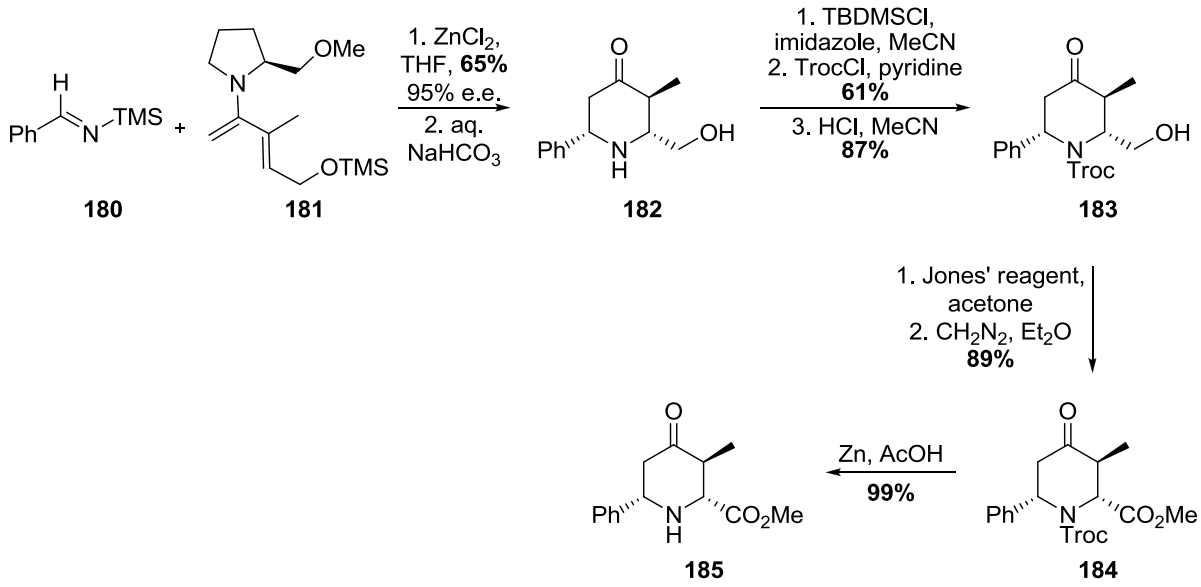
An asymmetric hetero Diels-Alder approach to synthesise 4-oxopipecolic acid was published by Gálvez and co-workers using an enantiomerically pure imine.[73] Danishefsky's diene **173** was reacted with a chiral imine **174** derived from 2,3-dibenzyl-D-glyceraldehyde and benzylamine, catalysed by zinc chloride to produce the piperidone core in moderate yield with excellent diastereoselectivity (Scheme 1.21). To generate the desired product, L-Selectride® was employed to reduce the alkene and then protection of the ketone as a ketal gave intermediate **176**. Hydrogenolysis of the benzyl protecting groups then Boc protection of the nitrogen, followed by oxidation of diol **177** gave carboxylic acid **178**. Finally, removal of the protecting groups under acidic conditions yielded the unnatural enantiomer of 4-oxopipecolic acid **179**.



Scheme 1.21 Asymmetric hetero Diels-Alder cycloaddition for the synthesis of 4-oxopipecolic acid

Gálvez and co-worker's synthetic methodology gives rise to improved yields and excellent stereoselectivity in comparison to Lau's results. The imino Diels-Alder reaction allows rapid access to the desired pipecolic acid motif and has the potential for subsequent modifications to be undertaken. A later paper published by Gálvez suggested the mechanism may occur *via* a tandem Mannich-Michael reaction as opposed to the concerted [4+2]-Diels-Alder approach suggested.[74]

In comparison to the previous syntheses that employ chiral dienophiles to induce facial diastereoselectivity, Barluenga and co-workers have developed an approach using a chiral diene for an asymmetric cycloaddition to produce highly functionalised 4-oxopipecolic acid derivatives.[75] A Lewis acid-catalysed Diels-Alder reaction of chiral diene **181** with an *N*-silylaldimine **180** was carried out (Scheme 1.22). Basic hydrolysis cleaved the nitrogen-silicon bond and the resultant enamine of the chiral auxiliary to form piperidone **182** in excellent enantiomeric excess. Several transformations were carried out to protect selectively the amine with 2,2,2-trichloroethyloxycarbonyl chloride (TrocCl). The protecting group reactions were followed by oxidation of the alcohol to the corresponding carboxylic acid and subsequent esterification gave rise to the pipecolic acid motif **184**. Finally, deprotection of the Troc-protecting group yielded (2*R*,3*S*,6*S*)-4-oxopipecolic acid analogue **185** in 99% yield.



Scheme 1.22 Hetero Diels-Alder cycloaddition using a chiral diene for the synthesis of 3,6-disubstituted-4-oxopipecolic acid **185**

This alternative imino Diels-Alder methodology benefits from simple cleavage of the chiral auxiliary with a mild base. Whereas, previous examples using imines derived from enantiomerically pure α-methylbenzylamine require hydrogenation to remove the benzyl moiety from the amine. This expeditious route also generates the diversely functionalised 4-oxopipecolic acids with high levels of enantiopurity and enables simple variation of the 6-substitutent by employing different aldehyde starting materials.

As illustrated, pericyclic chemistry has emerged as a powerful method to rapidly synthesise 4-oxopipecolic acid derivatives. High levels of enantioselectivity can be achieved when chiral imines or chiral dienes are employed. An opportunity for diversity can also be readily introduced depending on the starting materials used. The asymmetric hetero Diels-Alder strategy may become even more prevalent in the future.

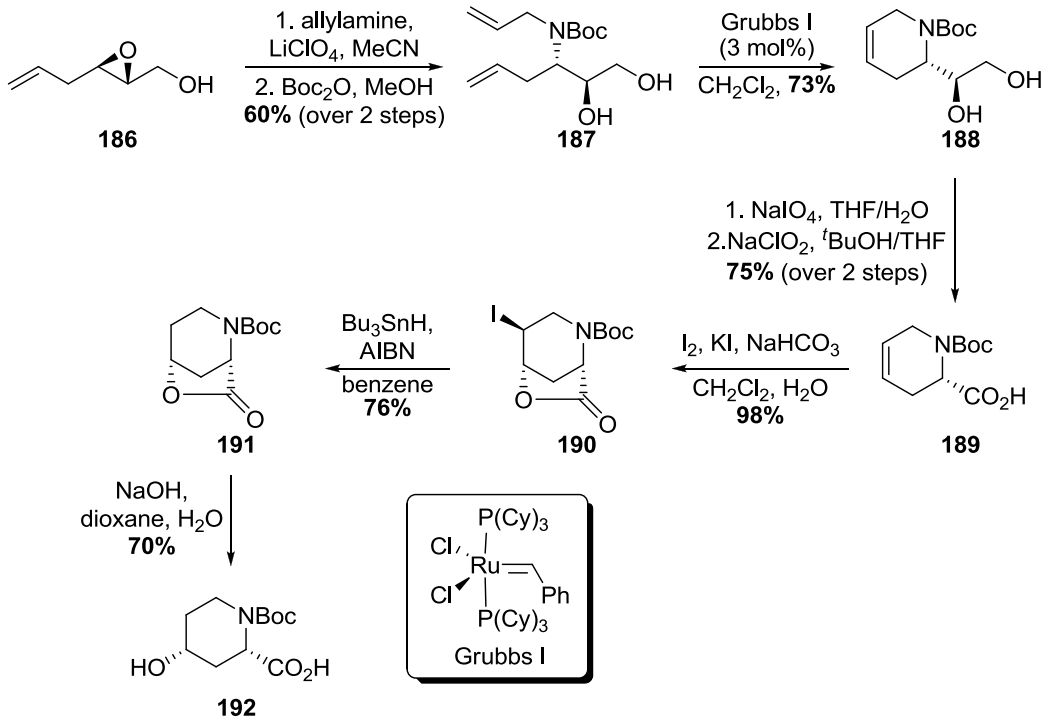
1.3.2 4-Hydroxypipecolic Acid Synthesis

The review of 4-oxopipecolic acid synthesis revealed various methods can be employed to construct the saturated *N*-heterocyclic core. The 4-hydroxy permutation of pipecolic acid has received significant attention because of the biological importance of the motif and its use as a synthetic scaffold and therefore numerous strategies have been devised. There are several examples where the carbonyl of 4-oxopipecolic acid is diastereoselectively reduced to give both (4*R*)- and (4*S*)-hydroxypipecolic acids depending on the reagent used. There are however many syntheses developed that provide the hydroxylated *N*-heterocycle directly.

1.3.2.1 Heterocycle Construction

Analogous to the approaches used to synthesise 4-oxopipecolic acid, intramolecular ring-closing reactions are prevalent to yield 4-hydroxypipecolic acids. More variation of reaction types exists with the hydroxylated analogues.

Riera and co-workers published a route that included ring-closing metathesis (RCM) to generate the *N*-heterocyclic core of 4-hydroxypipecolic acid.[76] This synthesis is one of the few examples where all the stereogenic centres have been constructed *via* asymmetric methods. A Sharpless asymmetric epoxidation of 2,5-hexadien-1-ol was employed to give rise to allylic epoxide **186** in 93% enantiomeric excess. The epoxide was subjected to a regioselective ring-opening with allylamine to give the 3-amino-1,2-diol in a ratio of 10:1, followed by Boc protection to produce **187** (Scheme 1.23). Ring-closing metathesis of diene **187** with Grubbs first generation catalyst gave unsaturated piperidine derivative **188** in good yield. Subsequent two step oxidative cleavage yielded *N*-Boc-(*S*)-baikiain **189**, in 99% enantiomeric excess after recrystallisation. To introduce the hydroxyl substituent, an iodolactonisation, then reduction of the iodide with tributyltin hydride gave bicyclic lactone **191**. Finally, basic hydrolysis produced Boc-protected (2*S*,4*R*)-4-hydroxypipecolic acid **192**.



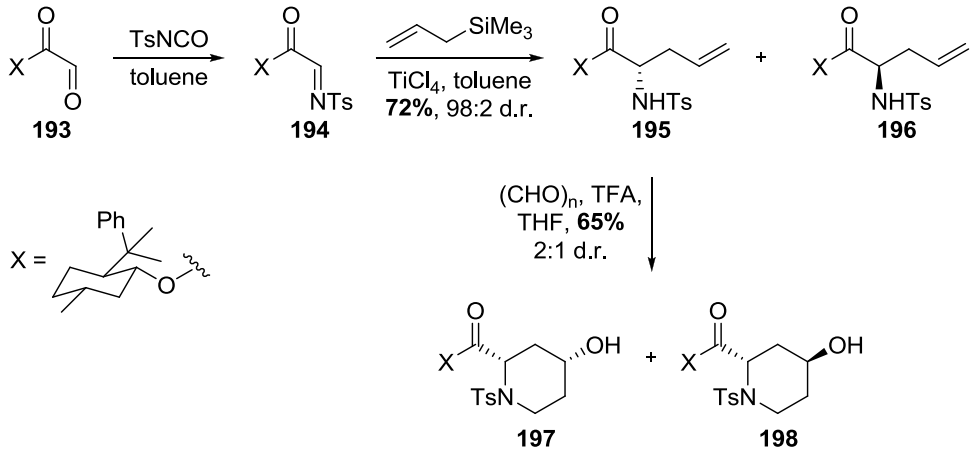
Scheme 1.23 Ring-closing metathesis to form *N*-protected *cis*-4-hydroxypipecolic acid

The route devised by Riera enables the synthesis of *cis*-4-hydroxypipecolic acid **192** in 8 steps from epoxide **186** in 17% overall yield. Using the Sharpless asymmetric epoxidation to dictate the stereochemistry of the starting material would allow both enantiomers of 4-hydroxypipecolic acid to be synthesised. However, only the *cis*-products can be obtained by this method as the iodolactonisation can only occur on the same face as the carboxylic acid substituent.

Alternative methods to synthesise 4-hydroxypipecolic acid using ring-closing metathesis as the key step have also been demonstrated. Hou and co-workers used a chiral auxiliary to establish the stereochemistry of the carboxylate, then Grubbs second generation catalyst to affect the RCM in excellent yield.[77] Whereas, Johnson and co-workers used commercially available vinylglycinol as the starting material, Grubbs (I) for the metathesis and a Prevost reaction to install the hydroxyl substituent.[78]

An alternative method described by Jurczak and co-workers involved an intramolecular ene-iminium cyclisation to close the heterocyclic ring.[79] Asymmetric induction was achieved by using a menthol-derived chiral auxiliary. Enantiomerically pure glyoxylic acid derivative **193** was reacted with *para*-toluenesulfonyl isocyanate to generate imine **194**, which was used *in situ* (Scheme

1.24). An asymmetric 1,2-addition of allyltrimethylsilane to the imine was carried out in the presence of a Lewis acid. α-Aminoketone **195** was obtained in good yield with excellent diastereoselectivity. The high level of diastereoselectivity is postulated to be a result of face-to-face π stacking interactions of the phenyl group of the auxiliary and the imine (Figure 1.18). The allyltrimethylsilane therefore preferentially adds to the *Si*-face.



Scheme 1.24 Ene-iminium cyclisation using a chiral auxiliary to produce 4-hydroxypipecolic acid derivatives

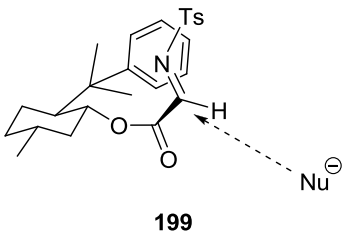
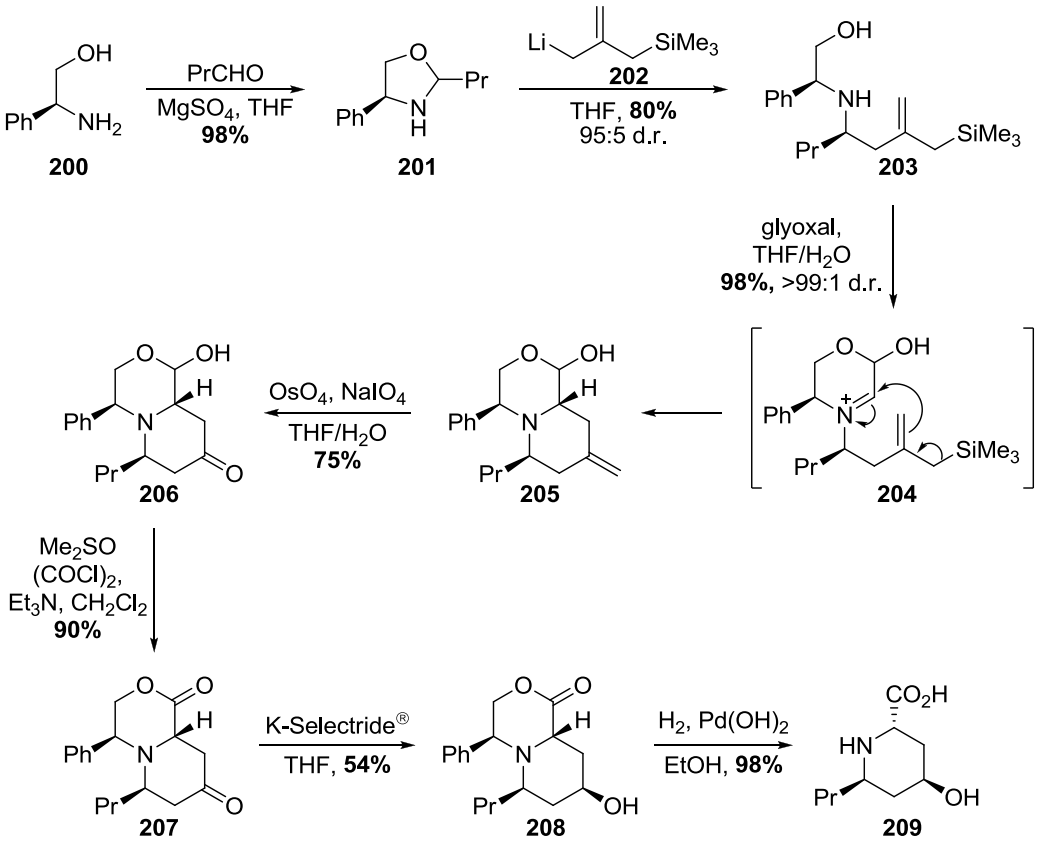


Figure 1.18 Facial discrimination due to face-to-face π stacking interaction

Generation of the 4-hydroxypipecolic acid core entails formation of an iminium ion from homoallylic amine **195** and paraformaldehyde (Scheme 1.24). Subsequent cyclisation of the terminal alkene onto the imine occurs to close the ring and the resultant carbocation can be trapped by a water molecule at the 4-position. A moderate yield for the 4-oxygenated pipecolic acid derivative **197** was obtained, however, the diastereoselectivity was poor. *Anti*-product **197** was obtained as the major stereoisomer in a 2:1 *anti*:*syn* ratio. The chiral auxiliary does not exert long distance steric effects and therefore, fails to influence asymmetric induction.

The ene-iminium cyclisation route to 4-hydroxypipecolic acid presented by Jurczak has several disadvantages. The addition of allyltrimethylsilane occurs highly stereoselectively to create the first stereogenic centre, however incorporation of the hydroxyl substituent occurs with poor diastereoselectivity. The use of a chiral auxiliary is not ideal as additional steps for synthesis and cleavage are necessary, despite Jurczak not demonstrating the removal.

A much improved variation of the ene-iminium cyclisation was published by Kadouri-Puchot and co-workers using a chiral pool starting material.[80] Enantiomerically pure (*S*)-phenylglycinol **200** was converted into oxazolidine **201** by reaction with butyraldehyde (Scheme 1.25). Oxazolidine **201** was reacted with organolithium species **202** to yield β-aminoalcohol **203** with high diastereoselectivity. Oxazolidine **201** exists in equilibrium with the ring-opened imine tautomer with *E*-geometry. In the presence of the organolithium reagent, a highly ordered, chelated transition state results (Figure 1.19). The facial discrimination is rationalised as internal delivery of the nucleophile occurs from the less-hindered *Si* face of the imine.



Scheme 1.25 Ene-iminium cyclisaton to produce 6-substituted-4-hydroxypipecolic acid

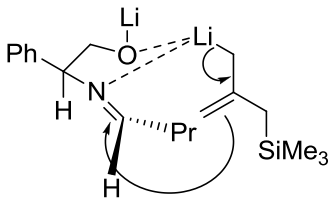


Figure 1.19 Chelated transition state

Reaction of β-aminoalcohol **203** with glyoxal forms an imine which cyclises to give hemi-acetal **204** (Scheme 1.25). The ene-iminium cyclisation then occurs with complete facial discrimination as the phenyl substituent hinders the *Re* face and therefore the concerted process occurs to produce bicyclic intermediate **205**. Completion of the synthesis involves oxidative cleavage of the terminal alkene, followed by Swern oxidation of the hemi-acetal to produce lactone **207**. Diastereoselective reduction of ketone **207** with K-Selectride® installs the 4-hydroxy substituent. Finally, hydrogenolysis yields *trans*-6-substituted-4-hydroxypipecolic acid **208** in almost quantitative yield. A 27% overall yield is achieved in seven steps.

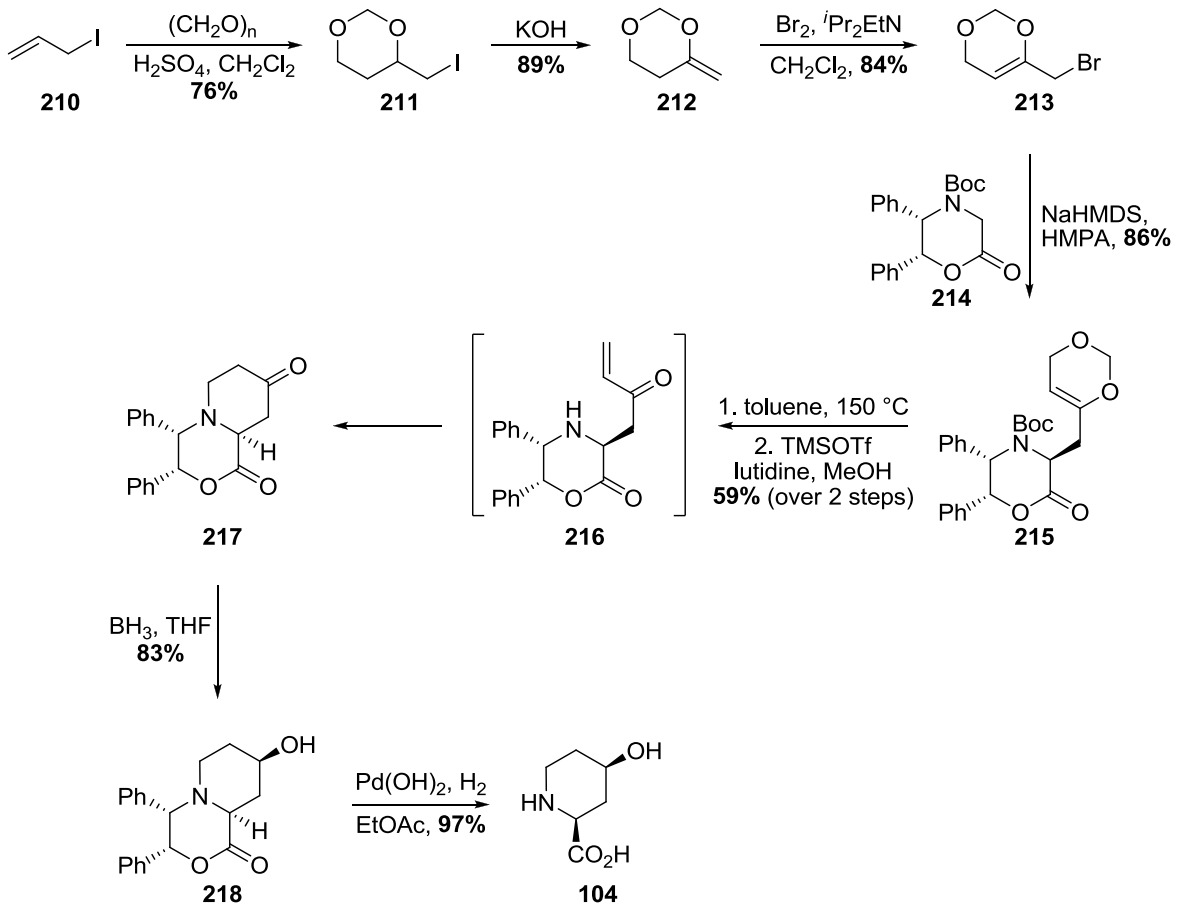
The diastereoselectivity of Kadouri-Puchot's approach for the ene-iminium cyclisation and prior steps are significantly improved in comparison to Jurczak's attempt. The presence of the phenyl stereogenic centre on the rigid cyclic iminium intermediate **204** facilitates the smooth conversion of the tethered alkene during the cyclisation. Using a highly selective, bulky reducing agent to provide the 4-hydroxyl centre also led to good facial selectivity.

Several other approaches have been published which involve an ene-iminium cyclisation,[54,57,81,82] however they suffer from similar difficulties as Jurczak's synthesis and generally provide a 1:1 ratio of (4*R*)- to (4*S*)-hydroxypipecolic acid diastereomers.

An unusual strategy for heterocycle synthesis was developed by Funk and co-workers.[83] The synthesis centres around a bromomethyl vinyl ketone equivalent **213** that possesses two sites of electrophilic character, however the sensitive enone functional group is conveniently masked until required. Once the enone is revealed, an intramolecular conjugate addition reaction closes the *N*-heterocyclic ring.

The bromomethyl vinyl ketone equivalent **213** was synthesised in three steps from allyl iodide **210** (Scheme 1.26). A Prins reaction with allyl iodide **210** and paraformaldehyde followed by elimination under reduced pressure produced methylene-1,3-dioxane **212**. Bromination of **212** in

the presence of base generated bromomethyl vinyl ketone equivalent **213** in 57% yield over the three steps. Williams' lactone **214**[84] was alkylated stereoselectively with allylic bromide **213** to produce enol ether **215**. The enone moiety was then unveiled under thermal conditions *via* fragmentation and the Boc protecting group was removed to yield intermediate **216**. A concomitant 6-*endo-trig* conjugate addition reaction occurred to generate the pipecolic acid core **217**. Stereoselective reduction of the ketone installed the 4-hydroxy substituent as a single diastereomer and then hydrogenolysis liberated the carboxylic acid side-chain to give the natural stereoisomer, (2*S*,4*R*)-4-hydroxypipecolic acid **104** in excellent yield.

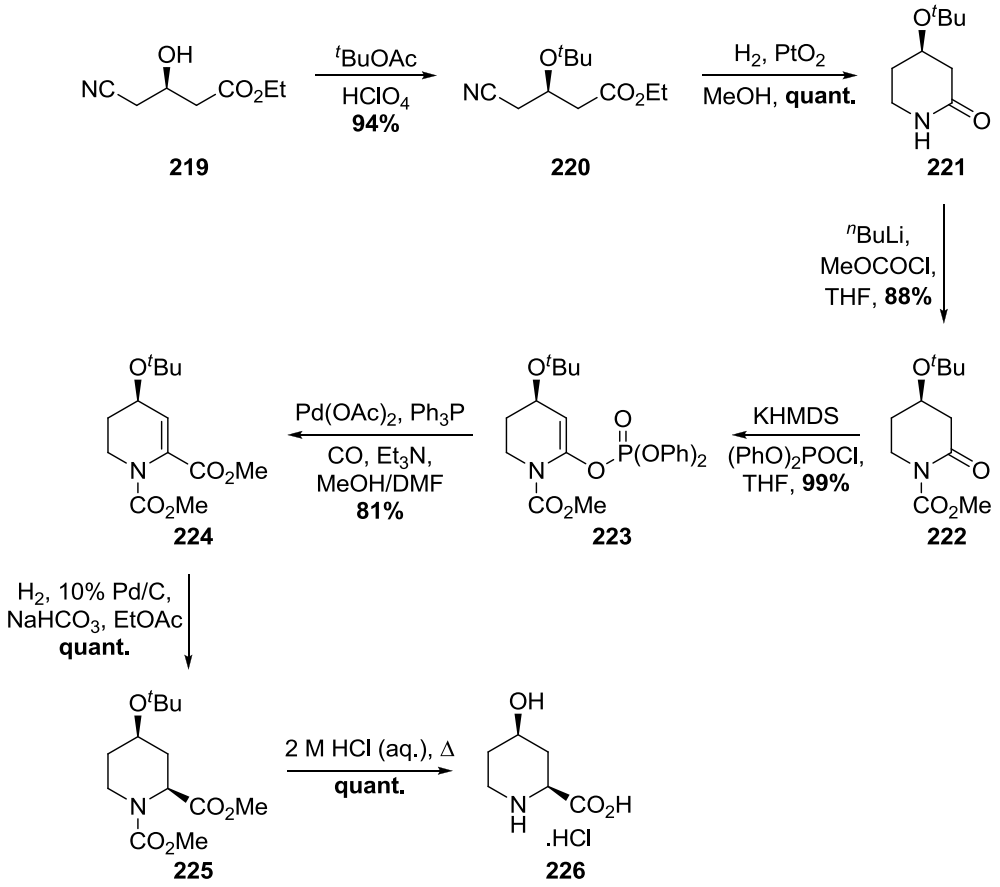


Scheme 1.26 Intramolecular conjugate addition reaction for the synthesis of 4-hydroxypipecolic acid

Funk's approach enables the synthesis of 4-hydroxypipecolic acid in eight steps with good to excellent yields. The communication does not present the diastereoselectivity of the alkylation step and therefore cannot be compared to other approaches. Assuming the alkylation step is highly selective as a result of the chiral lactone, the opposite enantiomer of 4-hydroxypipecolic

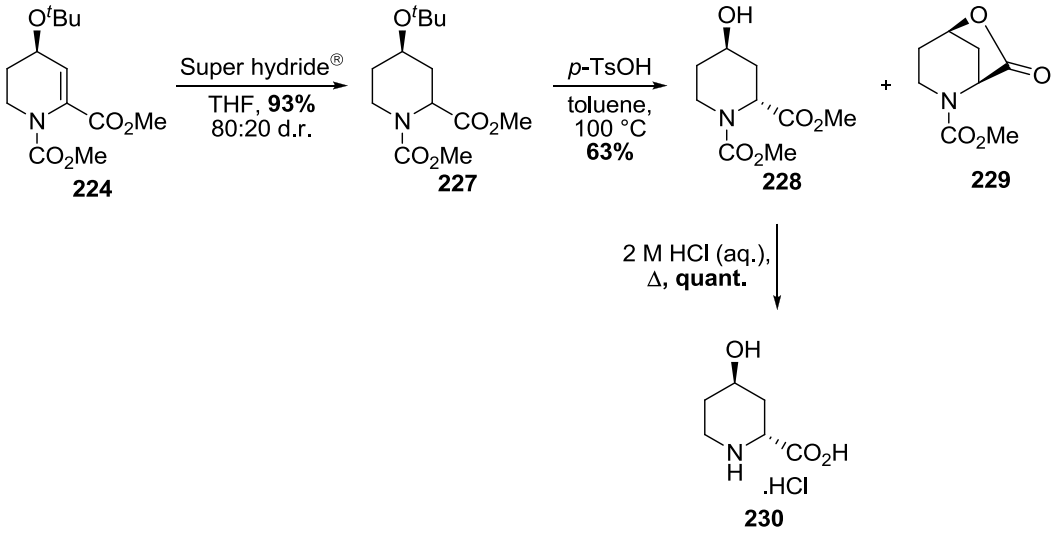
acid could, in theory be formed with use of the opposite configuration of the William's lactone. Funk's method however lacks the ability to incorporate variation to the heterocyclic template.

An alternative approach using an intramolecular lactamisation devised by Occhiato and co-workers enabled the synthesis of both (2*S*,4*R*)- and (2*R*,4*R*)-4-hydroxypipecolic acids.[85] Commercially available ethyl (*R*)-4-cyano-3-hydroxybutanoate **219** was employed as the starting material. The hydroxyl substituent was protected as *tert*-butyl ether **220**, which served as a protecting group and due to the steric bulk allowed facial discrimination during a later reduction step (Scheme 1.27). The cyano group was reduced to an amine, which underwent an intramolecular lactamisation to generate piperidone **221**. Protection of the nitrogen with methyl chloroformate gave intermediate **222**. Treatment of piperidone **222** with potassium hexamethyldisilazide produced an enolate that was trapped with diphenylchlorophosphate to yield stable vinyl phosphonate **223**. Vinyl phosphonate **223** is employed as a more stable alternative to the vinyl triflate used in Occhiato's preliminary communication.[86] The enolate equivalent **223** was subjected to palladium-catalysed carbonylation conditions in the presence of methanol to yield vinyl methyl ester **224**. Stereoselective reduction of the alkene occurs from the *Re* face, as a result of the bulky *tert*-butyl ether hindering the top face of the heterocycle. *Syn*-4-hydroxypipecolic acid **225** is formed in excellent yield and with a high diastereomeric ratio of 19:1 *syn*:*anti*. Acid-mediated deprotection generated the free amino acid **226**.



Scheme 1.27 Lactamisation approach to generate 4-hydroxypipecolic acid

Occhiato's route is stereodivergent at the reduction stage of the vinyl methyl ester **224**. To synthesise the opposite configuration of the carboxylic acid, a conjugate reduction with Super hydride® was carried out to give the *trans*-isomer as the major product in 80:20 d.r. (Scheme 1.28). To overcome problems with separation of the diastereomers, the mixture of pipecolic acids **227** was treated with *para*-toluenesulfonic acid. This induced deprotection of the hydroxyl substituents and initiated formation of bicyclic lactone **229** from only the *syn*-diastereomer. The desired *trans*-product **228** was readily isolated and deprotected to yield (2*R*,4*R*)-4-hydroxypipecolic acid **230** quantitatively.



Scheme 1.28 Conjugate reduction to yield unnatural (2*R*,4*R*)-4-hydroxypipecolic acid

The lactamisation route enables access to (2*S*,4*R*)-4-hydroxypipecolic acid in 7 steps in a high 66% overall yield. The stereodivergent route could potentially allow synthesis of all four stereoisomers of 4-hydroxpipecolic acid if ethyl (*S*)-cyano-3-hydroxybutanoate was employed as the starting material. It may also be feasible to functionalise the vinylic methyl ester **224** with nucleophiles to create a new stereocentre in the C-3 position making this approach highly versatile.

The lactamisation approach has also proved successful for Davis and co-workers with an expeditious entry to 4-hydroxypipecolic acids.[87] A chiral sulfoxide auxiliary was employed for asymmetric induction to synthesise the lactam precursor. Guichard and co-workers also published a similar route *via* lactamisation of an L-aspartic acid derivative for formation of the *N*-heterocycle.[88]

Other techniques used to close the heterocyclic ring of 4-hydroxypipecolic acid include a reductive amination approach used by Haddad and co-workers.[89] Low yields were obtained for the heterocycle construction as a result of chemoselectivity issues. Nucleophilic substitution reactions are also commonly employed for the ring closing reaction as exemplified by the research groups of Lesma[90] and Varela.[91,92]

A wide range of reactions have been utilised to close the heterocyclic ring of 4-hydroxypipecolic acid. Using enantiomerically pure starting materials or a chiral auxiliary appears to be the most

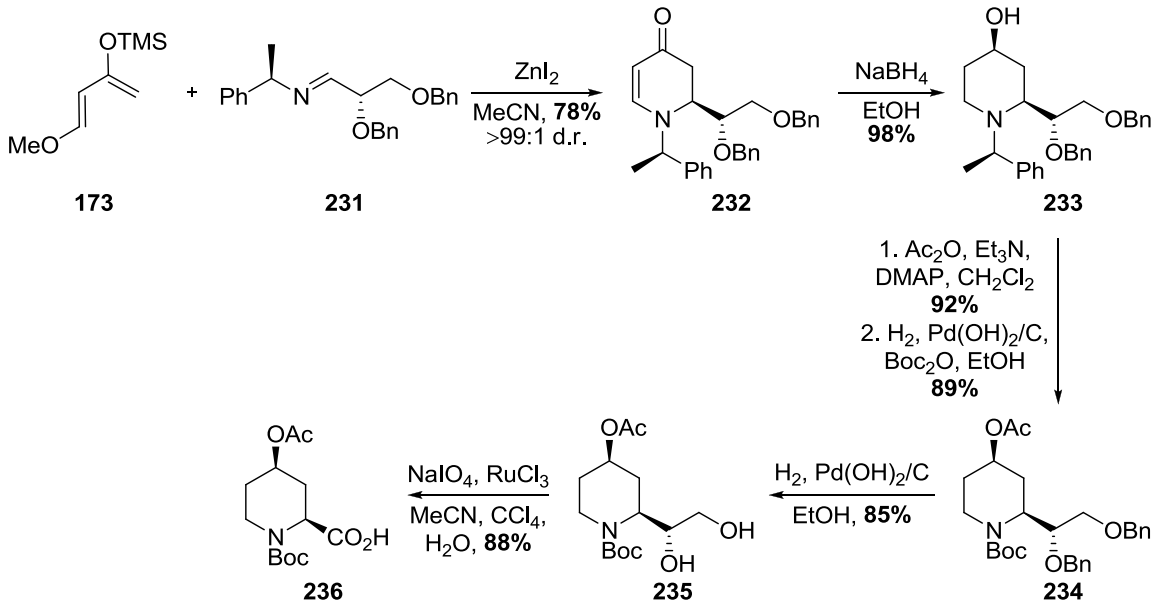
common method to obtain asymmetry, however asymmetric catalysis has also been successfully employed.

1.3.2.2 Cycloaddition

A variety of pericyclic reactions have been explored for the synthesis of 4-hydroxypipecolic acid. Analogous to the cycloaddition chemistry utilised to form 4-oxopipecolic acids, the significant challenge is to exert control over the regio- and stereochemistry during the reaction.

A minor adaption to Gálvez and co-worker's previously published route to 4-oxopipecolic acid[74] has proved successful for direct access to 4-hydroxypipecolic acid using a hetero Diels-Alder strategy.[93] The aim of the synthesis was to use the previously established methodology to synthesise palinavir **109** from (2*S*,4*R*)-4-hydroxypipecolic acid. In the earlier route, protected (*R*)-glyceraldehyde yielded (2*R*)-pipecolic acid (Scheme 1.21). In this incidence, protected (*S*)-glyceraldehyde was employed as the chiral imine and was anticipated to give the opposite enantiomer.

(*S*)-2,3-Di-*O*-benzylglyceraldehyde was synthesised in six steps from L-mannonic γ-lactone in 44% overall yield and reacted with (*R*)-α-methylbenzylamine to produce chiral imine **231** (Scheme 1.29). A Lewis acid catalysed hetero Diels-Alder reaction of imine **231** with Danishefsky's diene **173** produced unsaturated (2*S*)-piperidone **232** with complete diastereoselectivity. Concurrent reduction of the enamine and the ketone moiety with sodium borohydride gave a single diastereomer with the desired (4*R*)-4-hydroxy stereochemistry. Acetylation of the hydroxyl and selective hydrogenation of the *N*-benzyl group in the presence of Boc anhydride yielded intermediate **234**. Hydrogenation of both *O*-benzyl protecting groups followed by oxidative cleavage gave (2*S*,4*R*)-4-hydroxypipecolic acid **236**. Further steps were required to convert pipecolic acid **236** into a suitably functionalised key intermediate for the synthesis of palinavir.

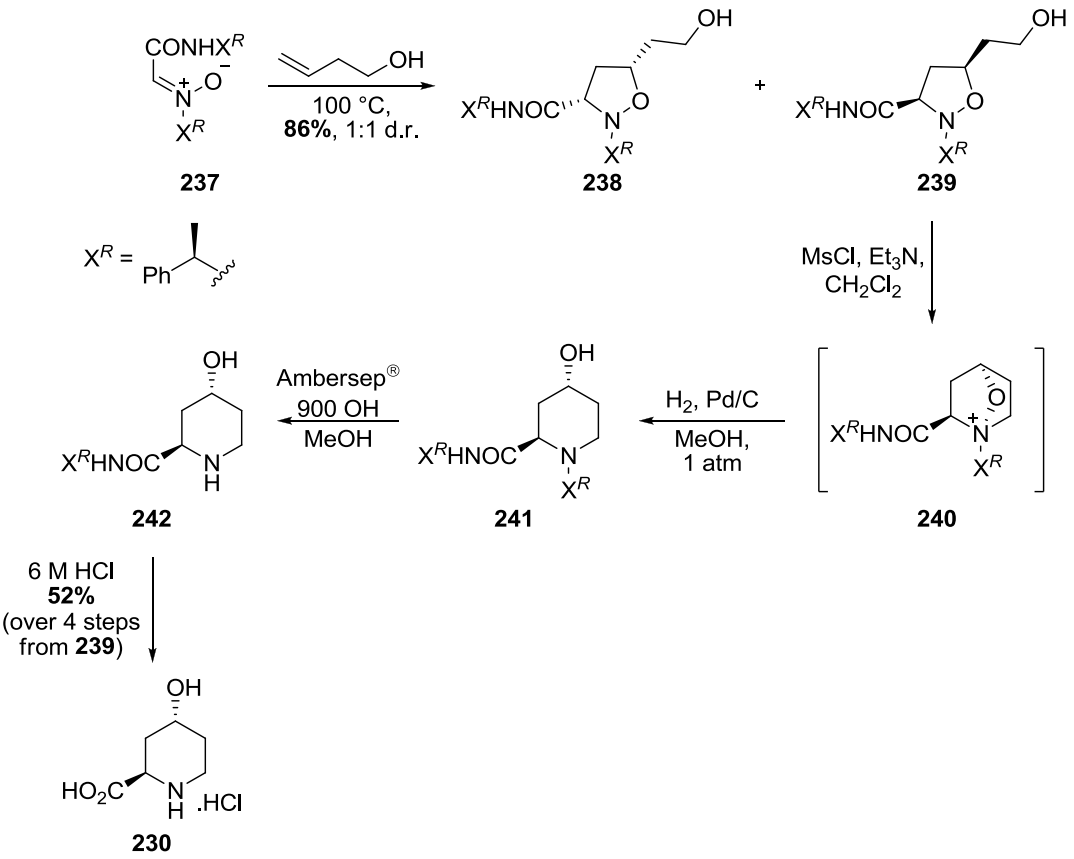


Scheme 1.29 Hetero Diels-Alder cycloaddition to generate (2*S*,4*R*)-4-hydroxypipecolic acid derivative **236**

This method demonstrated by Gálvez and co-workers is highly efficient. The key hetero Diels-Alder reaction and subsequent reduction are completely stereoselective and high yielding. Access to both (2*S*)- and (2*R*)-carboxylic acid substituents is possible using either (*S*)- or (*R*)-configurations of starting material respectively. Gálvez has also shown that the opposite sterochemistry of the hydroxyl group can be obtained with L-Selectride®. The negative point of this approach is the seven linear steps required to make the starting imine **231**.

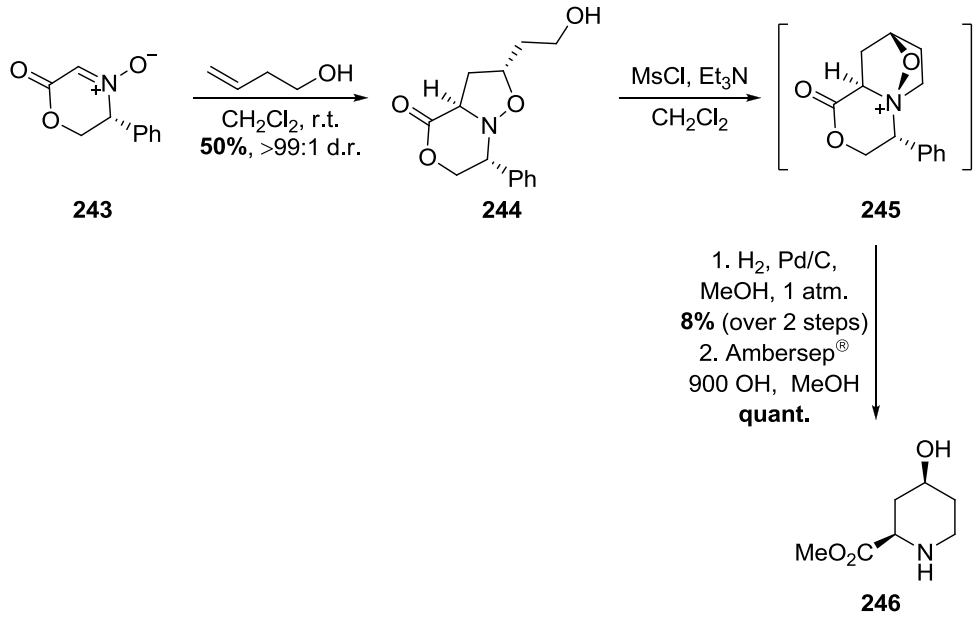
1,3-Dipolar cycloaddition reactions have also been effective for the synthesis of 4-hydroxypipecolic acid. Cordero and co-workers published a route to both *cis*- and *trans*-4-hydroxypipecolic acid using a nitrone-containing chiral auxiliary as the 1,3-dipole.[94] Thermally stable *Z*-*C*-aminocarbonyl nitrone **237** possessing a chiral auxiliary was reacted with butenol to produce an equimolar mixture of diastereomeric isoxazolidines **238** and **239** (Scheme 1.30). An *exo*-type transition state gives rise to the relative *syn*-configuration, however the conformationally labile *N*-chiral auxiliary of the acyclic nitrone does not induce diastereofacial discrimination. The diastereomeric mixture was separated, then isoxazolidine **239** was mesylated and subsequent nucleophilic substitution yielded the bicyclic *N*-heterocycle **240**. Catalytic hydrogenation opened the isoxazolidinium ring to reveal the 4-hydroxy substituent of intermediate **241**. Removal of the chiral auxiliary attached to nitrogen by hydrogenation followed by amide hydrolysis generated (2*R*,4*R*)-4-hydroxpipecolic acid **230** in five steps in an overall 52%

yield from **239**. The same synthetic route was employed using isoxazolidine **238** to produce the opposite enantiomer, (2*S*,4*S*)-4-hydroxypipecolic acid in 54% overall yield from **238**.



Scheme 1.30 1,3-Dipolar cycloaddition to produce *trans*-4-hydroxypipecolic acid **230**

The use of a cyclic *E*-*C*-carboxy nitrone **243** enabled the synthesis of *cis*-4-hydroxypipecolic acid **246**.[94] In this example, the rigid nitrone produces only one cycloadduct from the 1,3-dipolar cycloaddition. Nitrone **243** was reacted with butenol to give bicyclic intermediate **244** as a single diastereomer (Scheme 1.31). An *exo*-type addition to the less hindered *Re* face, opposite to the phenyl substituent, allows excellent diastereofacial discrimination. Mesylation followed by hydrogenolysis as before generated (2*R*,4*S*)-4-hydroxypipecolic acid **246** in four steps in 4% overall yield. The poor yield during the mesylation and subsequent intramolecular cyclisation is attributed to the high degree of ring strain of tricyclic intermediate **245**.



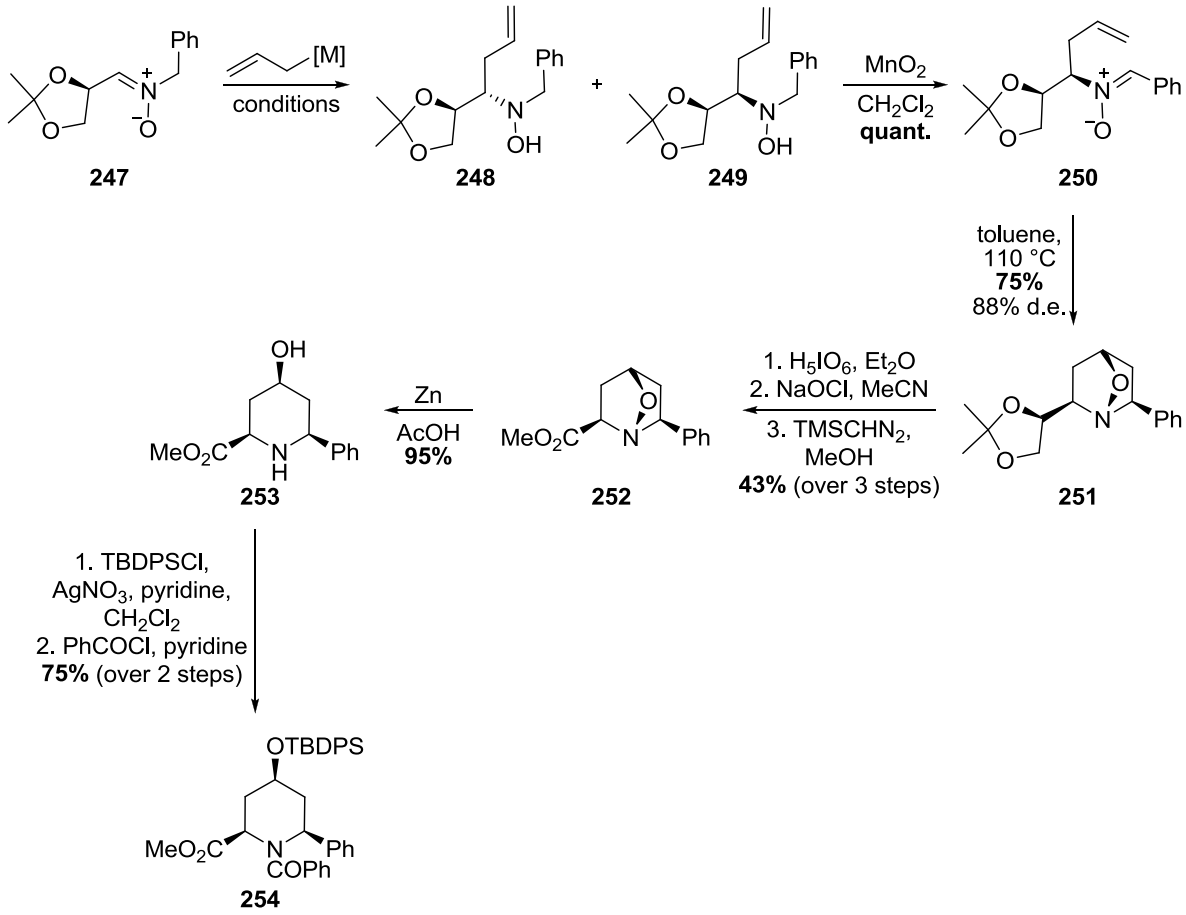
Scheme 1.31 1,3-Dipolar cycloaddition to generate *cis*-4-hydroxypipecolic acid derivative **246**

The efficacy of Cordero and co-worker's strategy is compromised by the lack of facial control during the 1,3-dipolar cycloaddition of acyclic nitrones to alkenes. This problem was overcome with the use of rigid cyclic nitrones, however the cyclic nature of the auxiliary hindered subsequent synthetic steps.

A 1,3-dipolar cycloaddition strategy was also published by Merino and co-workers, however they employed an intramolecular cyclisation.[95] This approach provides significantly enhanced facial selectivity in comparison to the previous route. Access to highly desirable *syn*-6-substituted 4-hydroxypipecolic acid analogues was feasible using this method.

Enantiopure nitrone **247**, derived from protected D-glyceraldehyde, was subjected to allylation conditions to yield either the *anti*- **248** or *syn*-product **249** depending on the Lewis acid employed (Scheme 1.32, Table 1.3). The selectivity was efficiently tuned to give the *syn*-diastereomer with zinc bromide and the *anti*-diastereomer using boron trifluoride in excellent yields. The *syn*-product **249** was oxidised with manganese dioxide to produce *Z*-nitrone **250** quantitatively. The nitrone containing the tethered alkene was subjected to thermal cycloaddition conditions to produce cycloadduct **251** as the major diastereomer *via* an *endo*-type transition state. The dioxolane of bicyclic intermediate **251** was oxidatively cleaved to give an aldehyde, then oxidised to a carboxylic acid and then esterified to produce fused 2,6-disubstituted piperidine **252**. Zinc-promoted reduction of the *N–O* bond generated the 4-hydroxypipecolic acid skeleton **253** in good

yield. Conversion of substituted pipecolic acid into orthogonally protected product **254** in 2 steps yielded the *N*-heterocycle in nine steps in 23% overall yield.

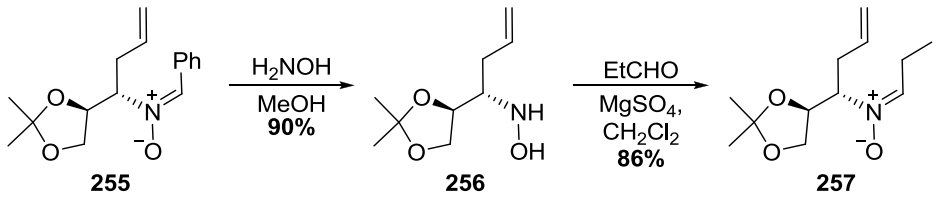


Scheme 1.32 1,3-Dipolar cycloaddition to generate 6-substituted-4-hydroxypipecolic acid derivative **254**

Entry	Metal	Lewis Acid	Solvent	Temp. (°C)	Time (h)	Ratio (*anti*:*syn*)	Yield (%)
1	Li	$ZnBr_2$	Et_2O	−80	1	10:90	75
2	MgBr	$ZnBr_2$	Et_2O	−50	8	5:>95	100
3	$SnBu_3$	$BF_3.Et_2O$	CH_2Cl_2	25	72	95:≤5	90
4	MgBr	$BF_3.Et_2O$	THF	−50	10	5:95	90

Table 1.3 Conditions for the allylation of nitrone **247**

Using the *anti*-product **248**, Merino and co-workers demonstrated that the opposite enantiomer (2*S*,4*R*,6*R*)-4-hydroxypipecolic acid could also be synthesised.[95] They also showed that other substituents could potentially be introduced into the 6-position by transhydroximation. Nitrone **255** was converted into hydroxylamine **256**, which was reacted with propionaldehyde to yield nitrone **257** (Scheme 1.33). Cyclisation of nitrone **257** would allow the incorporation of an ethyl substituent into the 6-position of pipecolic acid. In theory, a wide range of aldehydes could be condensed in the same way to allow access to various 6-substituted-4-hydroxypipecolic acid analogues.



Scheme 1.33 Transhydroximation to yield *C*-ethyl-*N*-alkenyl nitrone **257**

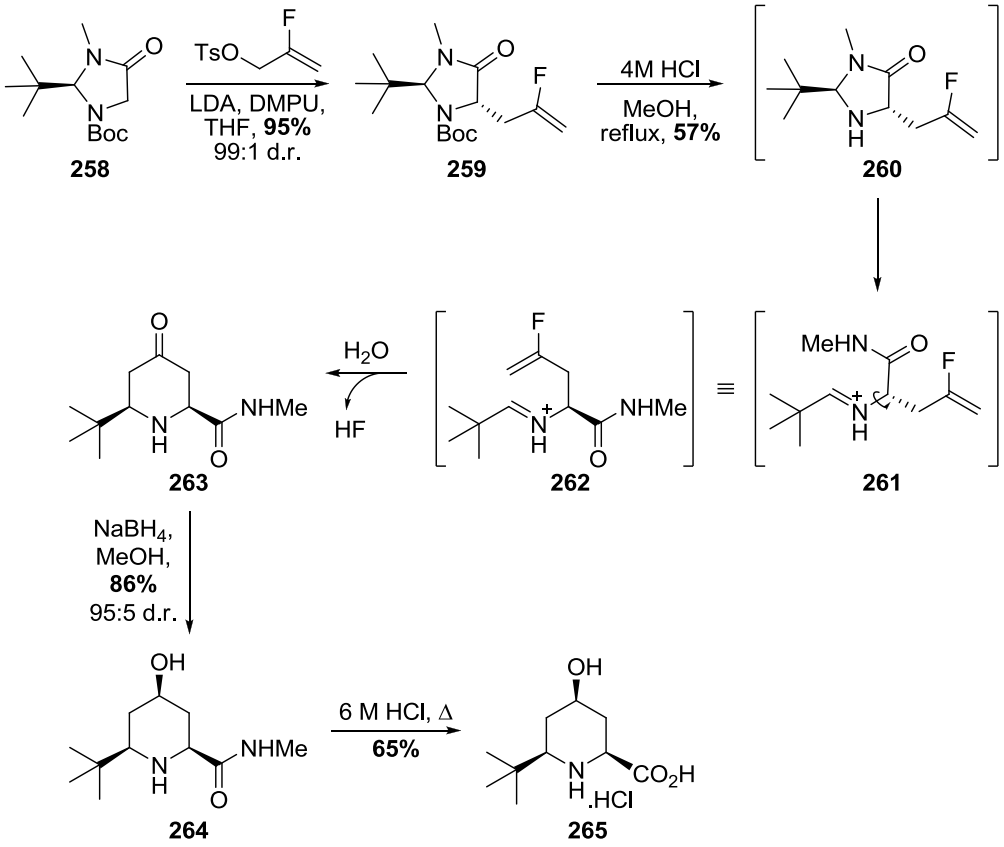
The use of pericyclic chemistry is less popular because of issues with establishing relative and absolute stereochemistry of substituents. However, several elegant and highly diastereoselective approaches have been developed. Undoubtedly, further advances in this expanding field will increase the importance in the future.

1.3.2.3 Ring Expansion / Rearrangement

Rearrangement and ring expansion reactions are much less common for the synthesis of *N*-heterocycles, however they can provide a novel entry to desirable structures with high levels of asymmetric induction.

A cascade involving a rearrangement reaction was employed by Haufe and co-workers to synthesise a 6-substituted-4-hydroxypipecolic acid derivative following observation of a reaction by-product.[96] Seebach's chiral Boc-protected imidazolidinone **258** was alkylated asymmetrically with 2-fluoroallyltosylate in good yield with excellent diastereoselectivity to produce vinylfluoro intermediate **259** (Scheme 1.34). Functionalised imidazolidinone **259** was heated under reflux in hydrochloric acid, which induced a reaction cascade. Acid-promoted cleavage of the Boc protecting group with concomitant opening of the imidazolidinone ring produces iminium **261**.

Rotation of the vinylfluoro group enables an ene-iminium cyclisation to occur followed by hydration and elimination of hydrogen fluoride to generate the *N*-heterocyclic ring **263**. *Syn*-6-substituted-4-oxopipecolic acid derivative **263** was produced as a single diastereomer due to the *tert*-butyl group which adopts an energetically favourable equatorial position during the cyclisation. Reduction of the ketone occurred with an axial trajectory to yield the (4*R*)-4-hydroxy diastereomer **264** with excellent stereocontrol. Finally, acidic hydrolysis of the amide yielded 6-substituted-4-hydroxypipecolic acid **265** in 30% overall yield in 4 steps.



Scheme 1.34 Rearrangement of a vinylfluoro imidazolidinone to yield 6-substituted-4-hydroxypipecolic acid **265**

Interestingly, only vinylfluoro imidazolidinone **259** will undergo the rearrangement reaction. Equivalent vinylbromo and vinylchloro compounds fail to yield the desired pipecolic acid product. This is rationalised by the unique resonance and inductive effects caused by fluorine.

The rearrangement reaction illustrated by Haufe and co-workers provides excellent asymmetric induction throughout the synthetic scheme. The *tert*-butyl group serves as a highly efficient

equatorial locking-group to provide high levels of diastereoselectivity. An attempt was made to simulate the ene-iminium cyclisation by reacting a selection of aldehydes with an open-chain analogue of vinylfluoro intermediate **259**. Reaction with pivaldehyde gave 4-oxopipecolic acid derivative **263** in 73% yield, however enolisable aldehydes or benzaldehydes did not produce the desired product. This may indicate a limitation of this approach as incorporation of different substituents into the 6-position might not be possible.

1.4 Summary

The importance of the piperidine motif has been illustrated by the numerous synthetic, biological and medicinal applications. A survey of recent literature for the synthesis of piperidine derivatives revealed multiple methods to yield chiral *N*-heterocycles.

Chiral substituted piperidines are most commonly synthesised *via* intramolecular ring-closing reactions such as metathesis, reductive amination and nucleophilic substitution reactions. Construction of the saturated *N*-heterocycle by cycloaddition has been demonstrated and can be highly efficient. Rearrangement reactions to generate six-membered rings are present in the literature, however are usually employed in specific cases rather than applicable for general syntheses. Extensive research has been carried out in the field of pyridine reduction, however stereochemistry can be difficult to control and therefore the synthetic utility is limited. Numerous other synthetic methodologies also exist which haven't been mentioned. Many of the general methods to synthesise piperidines have been used to construct the heterocycle of pipecolic acid analogues.

The synthesis of 4-oxopipecolic acid derivatives is commonly carried out using classical chemistry such as the Dieckmann reaction and conjugate additions. In most cases examined, asymmetry is established using the chiral pool as a source of starting materials. Several examples using pericyclic chemistry have been demonstrated and this appears to provide rapid entry to the desired 4-oxopipecolic acid scaffold. The on-going challenge is to control regio- and stereochemistry efficiently.

4-Hydroxypipecolic acid is one of the most studied members of the pipecolic acid family. A range of transformations have been utilised to synthesise this important motif including ring-closing metathesis, intramolecular lactonisation and nucleophilic substitution. Synthetic strategies devised containing intramolecular conjugate addition reactions are frequent. Pericyclic chemistry

such as hetero Diels-Alder reactions and 1,3-dipolar cycloadditions have also successfully yielded the desired framework.

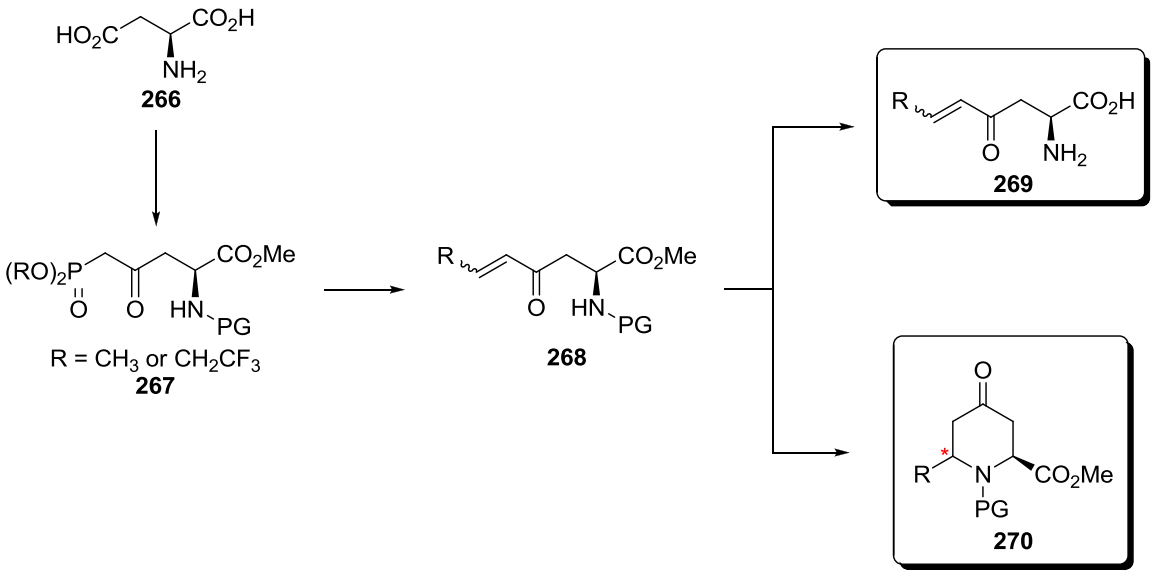
Despite the numerous synthetic strategies developed to date, a great deal of interest in these molecules remains and therefore the challenge to provide a fast, efficient and varied route to these important compounds is still active.

1.5 Proposed Methodology to Synthesise 4-Oxygenated Pipecolic Acid Derivatives

There were two primary aims of this Ph.D. research programme to be investigated. The first objective was to develop a fast and efficient method to synthesise a novel class of unnatural, linear α-amino acids containing an enone **268**. The second endeavour was to employ the enone-containing α-amino acids **268** as precursors for an intramolecular cyclisation to produce highly desirable 4-oxygenated pipecolic acid derivatives **270**.

The strategy devised takes advantage of the chiral pool by employing L-aspartic acid **266** as the enantiomerically pure starting material. The proposed approach was to transform L-aspartic acid **266** into β-ketophosphonate ester **267** capable of undergoing a stereoselective olefination reaction to install the enone alkene with defined *E*- or *Z*-geometry (Scheme 1.35). Deprotection of enone **268** to the corresponding parent α-amino acid **269** was also desirable. This unusual class of amino acid derivative may have several important uses as a result of the highly conjugated, electrophilic acceptor functionality coupled with the amino acid moiety.

Following the development of an expeditious route to the unnatural α-amino acids, the intention was to use a protected version of the enone **268** and investigate a diastereoselective 6-*endo*-*trig* cyclisation to yield 6-substituted-4-oxopipecolic acid analogues **270**. As mentioned previously, 4-oxygenated pipecolic acid congeners possess many interesting biological properties which make them attractive targets in organic synthesis. They can also serve as valuable synthetic scaffolds. The 2,6-substitution pattern around the heterocyclic core is significant because of the many natural products and synthetic derivatives of pipecolic acid that contain this motif.[69,97,98]



Scheme 1.35 Proposed route to unnatural α-amino acids and 4-oxopipecolic acid derivatives

The research programme strives to provide an alternative route to these important molecular building blocks. The proposed strategy to substituted pipecolic acid will enable diversity to be readily achieved by varying the R group of the enone. These highly functionalised saturated *N*-heterocyclic structures contain several functional groups that can easily be transformed *via* a variety of chemical interconversions to provide a versatile synthetic scaffold.

2 Novel Enone-Containing α-Amino Acids

2.1 Introduction

The synthesis of unnatural α-amino acids is a well-established field that continues to gain popularity and relevance with recent developments in the biosciences and fine-chemical industry. Advances in genetic technologies[99] and proteomics have led to innovation with regard to producing novel α-amino acids and corresponding congeners.

Non-proteinogenic α-amino acids play an integral role in numerous aspects of chemistry, biology and medicine. In modern organic synthesis, they have found applications as organocatalysts and as ligands for asymmetric induction.[100] They can also serve as optically active synthetic scaffolds. Pioneering research in the field of peptidomimetics requires the incorporation of unnatural amino acid analogues. Peptide surrogates with enhanced metabolic stability have been designed to have analogous therapeutic effects as the endogenous peptide[101] and therefore, this technology could potentially lead to the identification of biological enzyme or receptor targets for drug molecules. Modified α-amino acids have also been shown to act directly as therapeutic agents.[102]

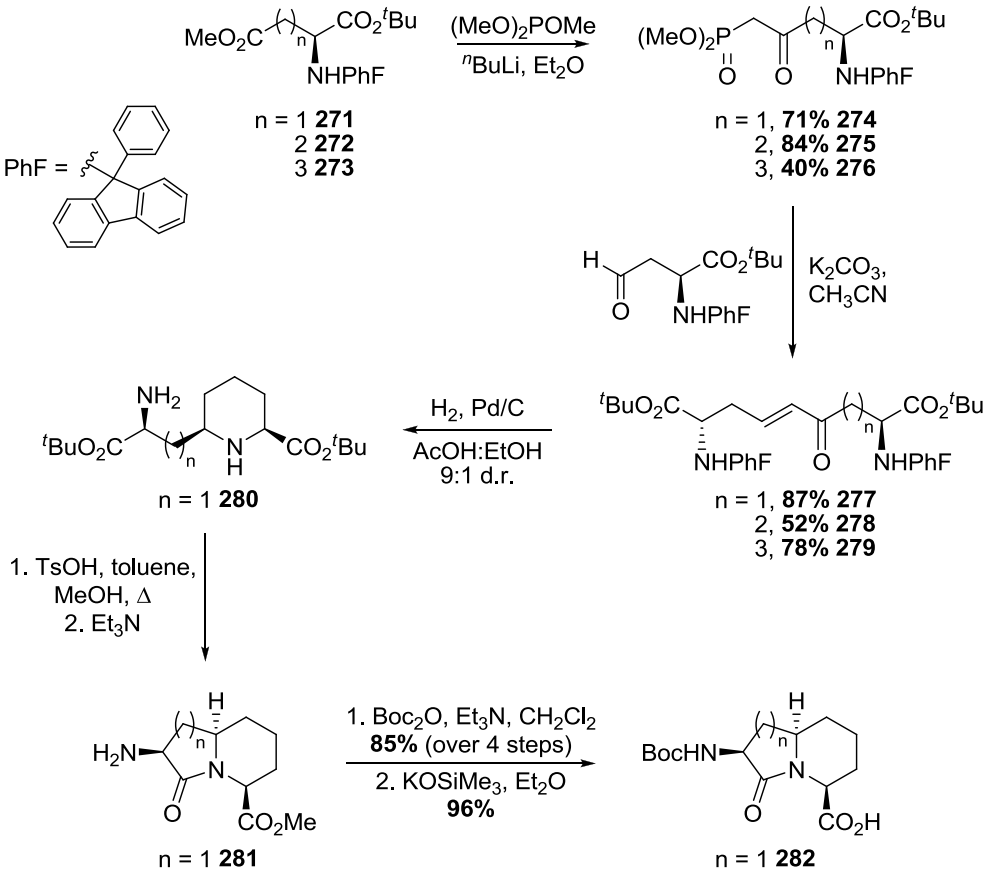
Although an array of unnatural amino acid analogues exists for a variety of different functions, novel α-amino acids that comprise an enone motif are relatively scarce in the literature. There are however a limited number of examples that possess the intriguing α,β-unsaturated ketone moiety.[63,103,104]

2.2 Previous Syntheses of Enone-Containing α-Amino Acids

A range of unsaturated α-amino acids were synthesised by Lubell and Gosselin with the intention to use the enones as substrates to produce azabicyclo[X.Y.0]alkane amino acids.[103] These bicyclic structures have been shown to act as conformationally restricted dipeptide surrogates that restrain the backbone and side-chain geometry of native proteins.[101]

The synthetic strategy devised by Lubell made use of naturally occurring α-aminodicarboxylates; aspartate, glutamate and α-aminoadipate, as chiral starting materials. These were converted to suitable substrates for a Horner-Wadsworth-Emmons (HWE) reaction in order to incorporate the enone portion of the α-amino acids.

Protection of the carboxylic acid moieties as esters and amine protection with a 9-(9-phenylfluorenyl) group generated intermediates **271**-**273**. The protected amino acids were converted to β-ketophosphonate esters using the anion of dimethyl methylphosphonate to produce the HWE precursors **274**-**276** in 40–84% yield (Scheme 2.1). Installation of the α,β-unsaturated ketone using a HWE olefination with an amino acid-derived aldehyde produced the enone-containing diamino acids **277**-**279** in moderate to good yield. Completion of the synthesis involved a further 5 steps to generate the azabicyclo[X.Y.0]alkane amino acid **282** for use as a conformationally restricted dipeptide surrogate.



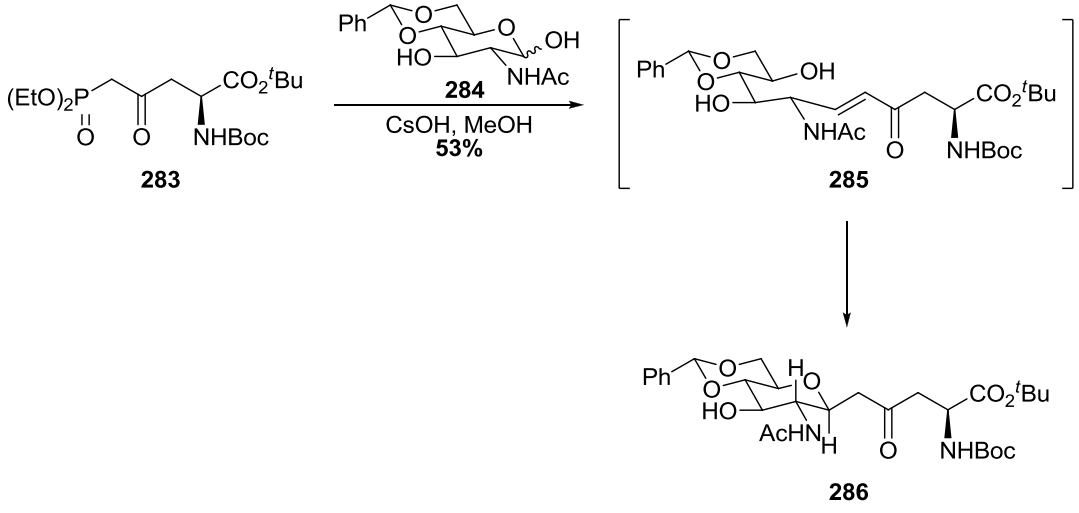
Scheme 2.1 Lubell's synthesis of peptiodomimetic **282**

Lubell's eloquent synthesis provides a versatile route to access a range of β-ketophosphonate esters by varying the α-amino acid starting material. This enables the synthesis of enone-containing α-amino acids that differ by the number of carbon atoms connecting the enone carbonyl to the amino acid moiety. Choice of a connective double bond forming methodology, such as the HWE reaction, provides further scope for variation because there is a wealth of

aldehydes available for use as the corresponding HWE partner and therefore, highly diverse structures can be designed.

Enone-containing α-amino acids have also been used as synthetic intermediates in carbohydrate chemistry as exemplified by Davis and co-worker's synthesis of a *C*-linked glycoamino acid.[105] Replacement of the naturally occurring carbon–nitrogen or carbon–oxygen glycosidic bond of glycoproteins with a carbon–carbon bond enables *C*-glycoside analogues to be resistant to chemical and enzymatic cleavage and therefore, these analogues may function as potential enzyme inhibitors.[106]

Davis' synthesis involved a tandem HWE olefination/oxo-conjugate addition to produce the unsaturated amino acid as an intermediate that was not isolated. The route involved generation of a β-ketophosphonate ester **283** from L-aspartic acid.[107] HWE reaction of phosphonate ester **283** with hemi-acetal **284** gave the *C*-glycoside analogue **286** (Scheme 2.2). The reaction proceeded through an enone-functionalised α-amino acid intermediate **285**, which underwent subsequent intramolecular oxo-conjugate addition to give the target molecule in moderate yield.

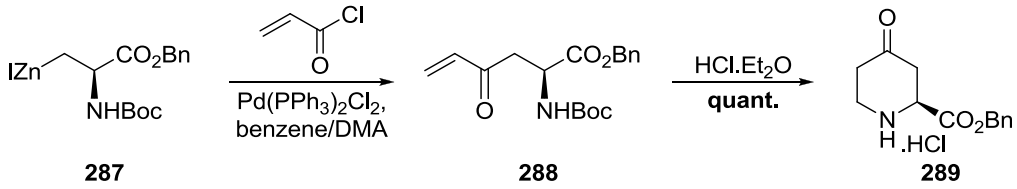


Scheme 2.2 *C*-linked glycoamino acid synthesis *via* a tandem HWE/conjugate addition reaction

Although the synthesis of enone-containing amino acids was not the objective of Davis' work, this scheme illustrates the potential to use unsaturated amino acids as scaffolds for further modification to generate synthetically useful molecules. The limitations of this strategy are the moderate yield and the lack of significant variation to the template.

Jackson and co-workers published a short route to synthesise enantiomerically pure 4-oxopipecolic acid by means of an intramolecular cyclisation of an α-amino acid containing a terminal enone.[104] In contrast to the previous approaches that used a connective double bond forming strategy, Jackson employed a palladium-catalysed coupling reaction to install the alkene.

The stereogenic centre of the product arises from the L-serine-derived organozinc reagent **287**.[108] Palladium-mediated coupling of organozincate **287** with acryloyl chloride generated the terminal enone **288** directly (Scheme 2.3). Exposing the enone-containing α-amino acid to anhydrous, acidic conditions promoted the 6-*endo*-*trig* cyclisation to give rise to 4-oxopipecolic acid benzyl ester **289** in quantitative yield.



287 **288** **289**

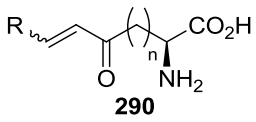
Scheme 2.3 4-Oxopipecolic acid derivative synthesis *via* a terminal enone α-amino acid

Jackson's expeditious route is beneficial as it produces enone-containing α-amino acids in one step from the organozincate, however the drawback of this coupling method is the limited sources of vinylic acid chlorides to produce useful variation. Jackson indicates that 3-bromopropionyl chloride can be employed in the coupling process to yield the terminal alkene **288**, however is less efficient than acryloyl chloride. Also the use of a metal catalyst may be undesirable if the targets are to be used for biological purposes due to trace metal residues.

A brief synopsis of previously synthesised enone-functionalised α-amino acids has been presented. In all cases illustrated, naturally occurring α-amino acids have been selected as the synthetic start point because they are readily available and have the advantage that the α-stereogenic centre is already present and therefore the process offers high atom economy. It is also evident that the most versatile strategies employ a connective alkene bond forming approach to allow maximum structural diversity. The previously synthesised enones have predominantly served as synthetic intermediates, however there are several potential uses that could be explored with enone-containing α-amino acids.

2.3 Potential of Novel Enone-Containing α-Amino Acids

A novel class of α-amino acid-derived enones of the form **290** (Figure 2.1) may have numerous potential functions. The possible uses of previously synthesised enone-containing α-amino acids of this type have yet to be fully explored, as they have primarily been employed as synthetic intermediates. A crucial factor that has also hindered the application of these structures is that the enones have not been deprotected and liberated as the parent α-amino acids.



290

R = aryl or alkyl
n = 1,2,3

Figure 2.1 Generic enone-containing α-amino acid structure

It is feasible that α-amino acids of the type **290** may function as irreversible enzyme inhibitors in certain eukaryotic or prokaryotic cells. The amino acid portion will act as the recognition motif to allow the substrate to be transported across cell membranes *via* embedded amino acid transporter proteins.[109] It is proposed that once transported into a cell, the presence of the highly reactive enone functionality of the α-amino acid could react with nucleophilic residues of amino acid side-chains within active or allosteric sites of enzymes. This would result in covalent bonding to the enzyme, and therefore irreversibly decrease enzymatic activity.

Another area of interest for exploration is the synthesis of short biologically active peptides. The field of small bioactive peptides is expansive due to the multiple functions these molecules exhibit. They have found applications as antibiotics, anti-fungal and anti-cancer agents, as well as other biological applications.[110] Development of orthogonally protected enone-containing α-amino acids would enable efficient amide coupling to produce novel short peptides which may possess biological activity.

Incorporation of an unsaturated R group to the amino acid would generate an extensively conjugated system. Highly conjugated molecules are significant because they can have photoluminescent properties. Consequently, it is possible that novel conjugated enone-containing α-amino acids may behave as fluorophores, and therefore could be employed as fluorescent biological probes.

A fast and efficient route is required to enable exploration of these interesting, novel structures with ample potential. To employ the enone-containing α-amino acids in biological systems, they must be synthesised with high levels of enantiopurity. Ideally, the synthetic strategy will allow diverse structures to be produced from a common intermediate.

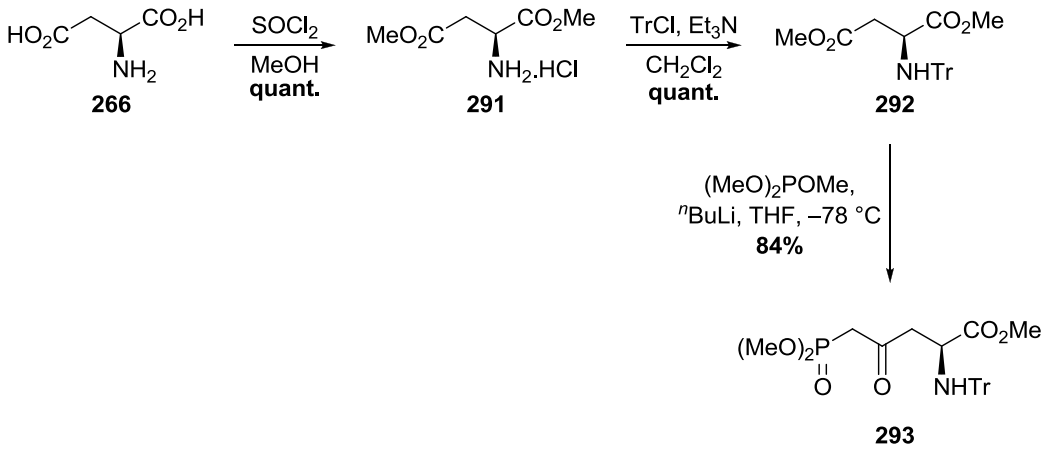
2.4 Synthesis of Novel Enone-Containing α-Amino Acids

The strategy devised for the synthesis of novel enone-functionalised α-amino acids was to employ naturally occurring L-aspartic acid as the enantiomerically pure starting material. This allows for excellent atom economy, as the amino acid moiety is already present and the correct configuration of the α-stereogenic centre is set. Amino acids are also readily available and inexpensive, which makes them attractive starting materials. A connective double bond approach was preferential to incorporate variation into the structures from an advanced intermediate, which would enable libraries of compounds to be easily synthesised.

2.4.1 *E*-Configured Enone-Functionalised α-Amino Acids

A rapid and highly efficient four-step synthesis was developed utilising the Horner-Wadsworth-Emmons reaction as the crucial double bond forming step to yield the novel enone-containing α-amino acid derivatives (Scheme 2.4). The strategy devised was to synthesise amino acid-derived β-ketophosphonate ester **293** as the key intermediate.

L-Aspartic acid **266** was converted to the dimethyl ester hydrochloride salt **291** in quantitative yield.[111] Subsequent protection of the amino group with the bulky trityl protecting group gave **292** quantitatively. Formation of the β-ketophosphonate ester **293** was achieved by reacting the lithium anion of dimethyl methylphosphonate with the less-hindered β-methyl ester of intermediate **292**.[107] The steric bulk of the trityl protecting group enabled regioselective discrimination and therefore, led to a highly selective and high yielding reaction to generate the Horner-Wadsworth-Emmons substrate in 84% yield.

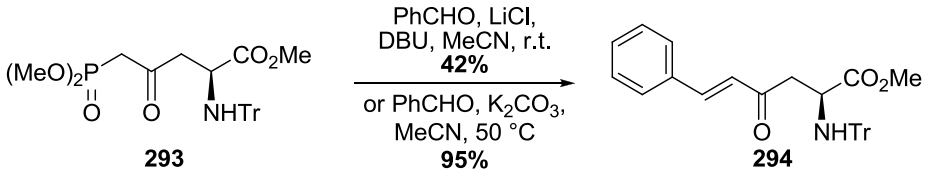


Scheme 2.4 Synthetic route to amino acid-derived β-ketophosphonate ester **293**

Following the synthesis of intermediate **293**, formation of the alkene was investigated using a Horner-Wadsworth-Emmons reaction to generate the enone. The HWE reaction is a well-established and reliable method for the formation of alkenes. It was developed in 1958 by Horner[112] and popularised by Wadsworth and Emmons[113] in 1961. Analogous to the Wittig reaction, the HWE reaction can generate both *E*- and *Z*-alkenes, however the advantage of the HWE reaction in comparison to the Wittig reaction is the formation of water-soluble by-products that enable simpler purification.

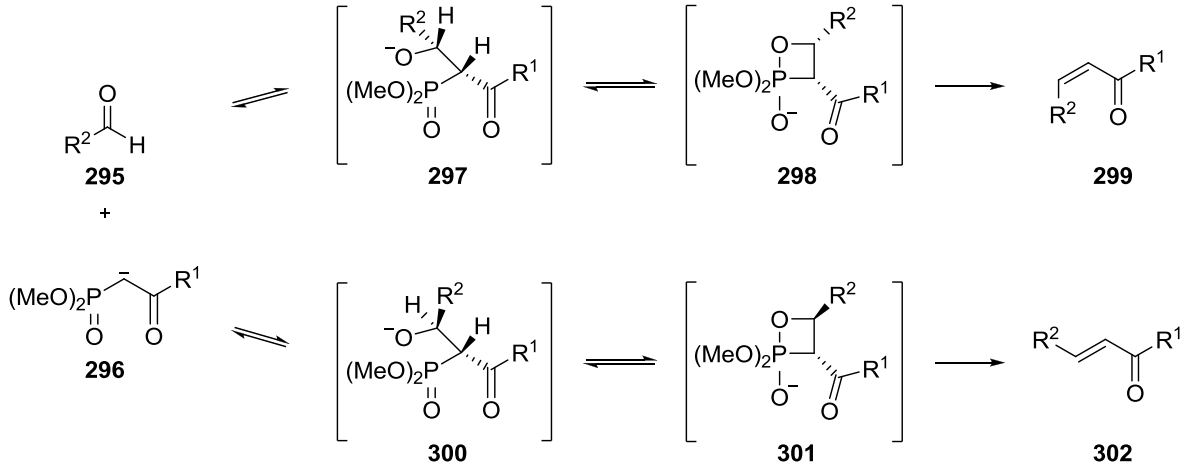
The HWE reaction of β-ketophosphonate ester **293** with benzaldehyde was initially attempted using Masamune-Roush conditions to give enone **294**.[114] Lithium chloride was employed as an additive to lower the pKa of the protons between the carbonyl and the phosphonate ester, and therefore the neutral organic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), could carry out the deprotonation at room temperature. Reaction of β-ketophosphonate **293** with benzaldehyde under the mild conditions gave a moderate 42% yield with complete *E*-selectivity (Scheme 2.5).

In an attempt to optimise the HWE reaction, alternative conditions developed by Lubell using the inorganic base, potassium carbonate, in acetonitrile at 50 °C were explored (Scheme 2.5).[115] Under these conditions, the desired enone-functionalised α-amino acid **294** was produced in an excellent 95% yield with complete *E*-selectivity.



Scheme 2.5 Horner-Wadsworth-Emmons reaction

The geometry of the alkene was confirmed as the *E*-isomer by ^{1}H NMR spectroscopy, as a vicinal coupling constant of 16.2 Hz was observed. The selectivity of the HWE reaction arises from the initial carbon-carbon bond forming step and the reversibility of intermediates. Stepwise attack of phosphoryl-stabilised carbanion **296** on aldehyde **295** generates interchangeable oxyanions **297** and **300** (Scheme 2.6).[116] The more stable *trans*-intermediate **300** can then decompose *via* a transient four-centred oxaphosphonate **301** to allow the thermodynamic product **302** to be generated.



Scheme 2.6 Horner-Wadsworth-Emmons mechanism

With the optimised route to synthesise novel enone-containing α-amino acids in place, the scope of the HWE reaction was explored. A variety of aldehydes were employed to generate a diverse library of analogues (Figure 2.2).

A wide range of side-chains could be incorporated to give a selection of enone-containing α-amino acids. α,β-Unsaturated ketones with *para*-substituted aryl halide motifs **303**-**305** were synthesised in good to excellent yield. An enone with an *ortho*-substituted aryl bromide side-chain **306** was also produced in good yield. The electron-withdrawing effect of the halide enabled

a rapid reaction rate and high yield. These substrates were of interest as they have the potential to be further modified *via* cross-coupling reactions.

Alternative substitution patterns around the aromatic ring were also possible. *Meta*-substituted vinylic analogue **307** was synthesised in moderate yield. Elaboration using a Heck cross-coupling reaction could be envisaged to further functionalise the unsaturated α-amino acid. A surprisingly moderate yield was obtained for *meta*-nitrophenyl derivative **308**. A fast rate of reaction had been anticipated due to the electron-withdrawing capability of the nitro group, however this was not observed. It should be noted that the reaction was not optimised and therefore, recrystallisation of the aldehyde would possibly give an improved yield.

Electron rich aldehydes were suitable for the HWE reaction to give *para*-methoxyphenyl **309** and 3,4-dimethoxyphenyl **310** analogues. Despite the low yield when veratraldehyde was employed, there doesn't appear to be a correlation with the decrease in reactivity with electron rich aldehydes, as a moderate 66% yield was obtained for the 4-methoxyphenyl derivative. Instead, the quality and stability of the aldehyde employed appears to be the determining factor for the yield.

The HWE reaction is not limited to aromatic aldehydes, as several non-conjugated alkyl variants have been synthesised including methyl **311**, *iso*-butyl **312**, *tert*-butyl **313** and phenethyl **314** derivatives. The *tert*-butyl analogue **313** demonstrated the limitation of the reaction, as the sterically demanding pivalaldehyde required a significantly higher reaction temperature (82 °C) and longer reaction time. However, even under the harsh conditions, a poor yield of 11% was the maximum obtained.

Heteroaromatic groups can be attached to the enone-containing α-amino acids. For example furan **315**, 5-bromofuran **316**, thiophene **317** and pyridine **318** moieties were incorporated in moderate to good yield. Addition of privileged structures such as heteroaryl groups is significant as these motifs commonly feature in pharmaceutical products because of recognition within the human body. Inclusion of these side-chains may therefore increase the potential to use the enone-containing α-amino acids as therapeutic agents.

Synthesis of highly conjugated structures was also possible using this approach to produce naphthalene **319** and diene **320** derivatives. The extensive conjugation of these analogues may give rise to luminescent properties and therefore they may be useful as biological probes.

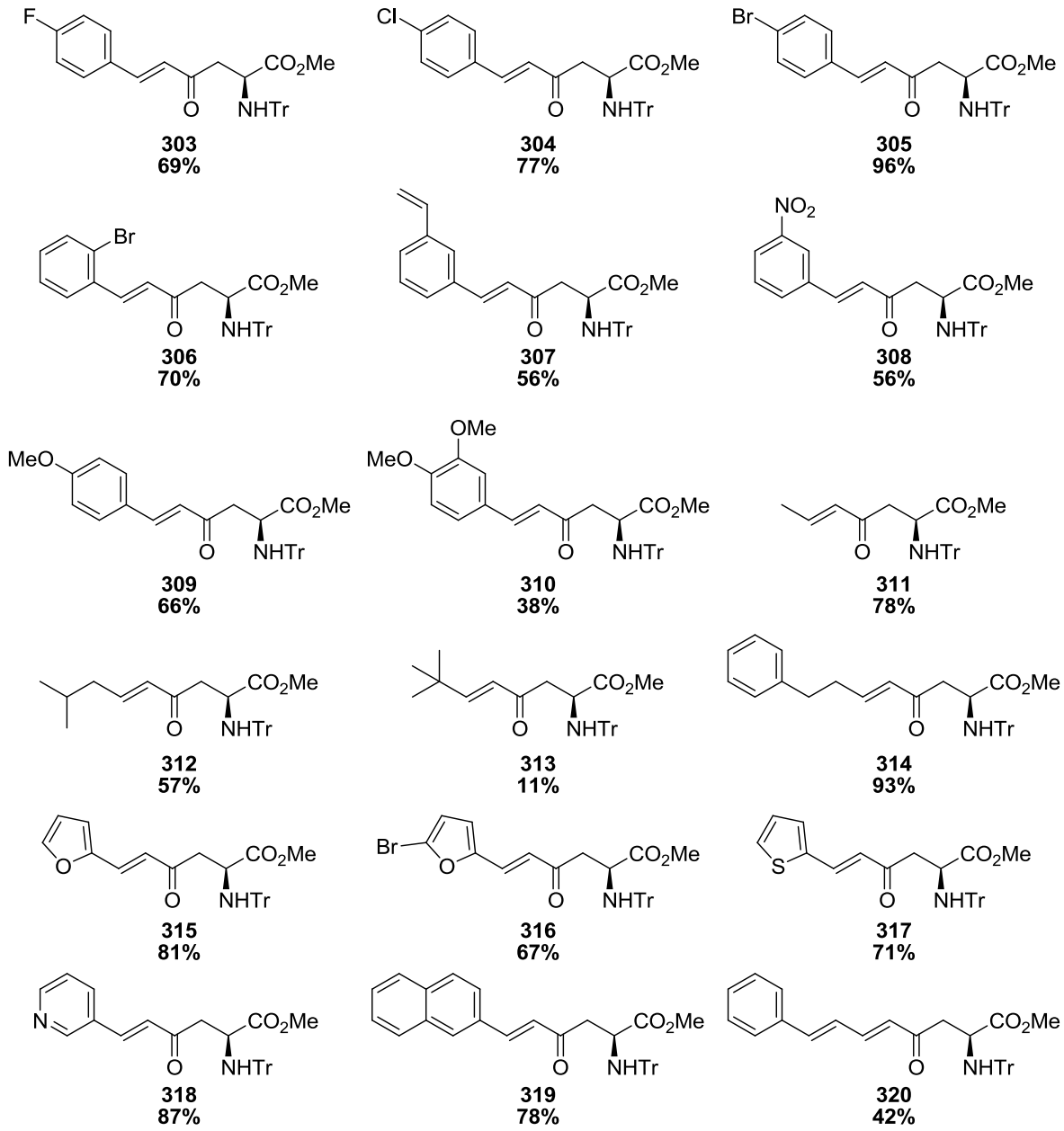


Figure 2.2 Enone-functionalised α-amino acid analogues

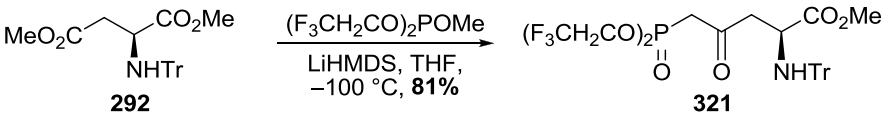
Overall, nineteen examples of novel enone-functionalised α-amino acids were produced. The small library illustrates that both electron rich and deficient aldehydes are applicable for the HWE reaction, as well as, aromatic and non-aromatic substrates. The four step synthetic route

developed allows rapid access to a range of enones using robust chemistry to give reliably high yields and complete *E*-selectivity.

2.4.2 *Z*-Configured Enone-Functionalised α-Amino Acids

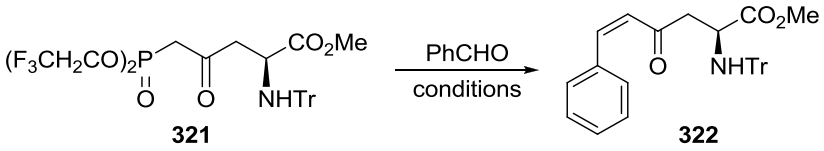
Following the success of the HWE route to produce *E*-alkenes, it was desirable to gain access to the corresponding *Z*-configured enone-derived α-amino acids. We anticipated that a minor modification to the existing route would enable *Z*-enones to be prepared, whilst retaining the benefits of the original synthetic scheme. Application of the Still-Gennari modification of the HWE reaction was explored to permit a connective double bond forming approach to be used. This would enable diverse analogues to be synthesised from a common intermediate.

Enantiomerically pure L-aspartic acid **266** was converted to the dimethyl ester and the amine was subsequently protected with a trityl group as previously described. *N*-Trityl protected intermediate **292** was then converted to bis(2,2,2-trifluoroethyl) phosphonate ester **321** using commercially available bis(2,2,2-trifluoroethyl) methylphosphonate in 81% yield (Scheme 2.7).[117] Synthesis of phosphonate ester **321** required a lower reaction temperature of −100 °C in comparison with the −78 °C reaction temperature required to produce phosphonate ester **293**. The anion of bis(2,2,2-trifluoroethyl) methylphosphonate is destabilised due to the inductive effect of the two trifluoroethyl groups and therefore is short-lived. A lower temperature lengthened the lifespan of the anion and therefore enabled the reaction to occur. Previous syntheses of bis(2,2,2-trifluoroethyl) phosphonate esters[117] generally employ acid chlorides as the coupling partner, however we have demonstrated that less reactive methyl esters can be successfully employed to gain access in high yields. The dual-purpose, bulky trityl protecting group proved equally as efficient to shield the hindered ester from attack of the bis(2,2,2-trifluoroethyl) methylphosphonate anion to give a clean, high yielding reaction.



Scheme 2.7 Synthesis of bis(2,2,2-trifluoroethyl) phosphonate ester **321**

The Still-Gennari olefination with bis(2,2,2-trifluoroethyl) phosphonate ester **321** and benzaldehyde was then investigated (Scheme 2.8). Strongly dissociating conditions to favour rapid elimination are required for the Still-Gennari modification to limit equilibration of intermediates and therefore facilitate *Z*-alkene formation.[118] The two trifluoroethyl groups disfavour resonance stabilisation of the carbanion and therefore the initial addition reaction is irreverisible and rapid elimination occurs to give the *Z*-alkene. Low temperatures were employed to ensure the reaction was under kinetic control. However, a rapid rate of reaction was still possible at reduced temperatures because the bis(2,2,2-trifluoroethyl) phosphonate ester anion is a very powerful nucleophile.



Scheme 2.8 Still-Gennari reaction

Initial exploration using sodium hydride, with and without 15-crown-5, proved unsuccessful (Table 2.1).[117] Using potassium hexamethyldisilazide (KHMDS) and 18-crown-6 at −78 °C gave a good yield of 76% with 10:3 *Z*/*E*-selectivity.[118] When potassium carbonate and 18-crown-6 were utilised, *Z*-enone **322** was produced in an excellent 91% yield with 8:1 *Z*/*E*-selectivity.[118] Changing the base and solvent employed led to a more selective reaction and an increase in temperature accounts for the improved yield.

Entry	Base	Ionophore	Solvent	Temperature	*E*/*Z* ratio[a]	Yield (%)[b]
1	NaH	none	THF	0 °C	-	-
2	NaH	15-crown-5	THF	0 °C	-	-
3	KHMDS	18-crown-6	THF	−78 °C	3:10	76
4	K_2CO_3	18-crown-6	toluene	−20 °C	1:8	91

[a]Determined by ^{1}H NMR spectroscopy [b]Overall isolated yield of both *E*- and *Z*-isomers

Table 2.1 Still-Gennari reaction conditions

The *Z*-geometric isomer was confirmed by ^{1}H NMR spectroscopy with a vicinal alkene coupling constant of 12.8 Hz detected. According to Karplus, the coupling constant of *cis*-configured alkenes can range from approximately 6–12 Hz.[119] The observed coupling constant resides at the top end of this scale and therefore we concluded that the desired *Z*-enone had been formed.

With conditions in place for reliable *Z*-selective alkene formation, a small library of *Z*-configured enone-containing α-amino acids were synthesised. Analogous to the *E*-enones, it was possible to produce a diverse selection of *Z*-enones (Figure 2.3).

In addition to phenyl derivative **322**, both electron-deficient *para*-bromophenyl **323** and electron-rich *para*-methoxyphenyl **324** analogues could be generated in 78% and 70% yield, respectively. Non-conjugated aliphatic examples were also feasible, however lower selectivities were observed. This is possibly due to the reduced electrophilicity of the alkyl aldehydes, which retards the rate of condensation and therefore elimination.

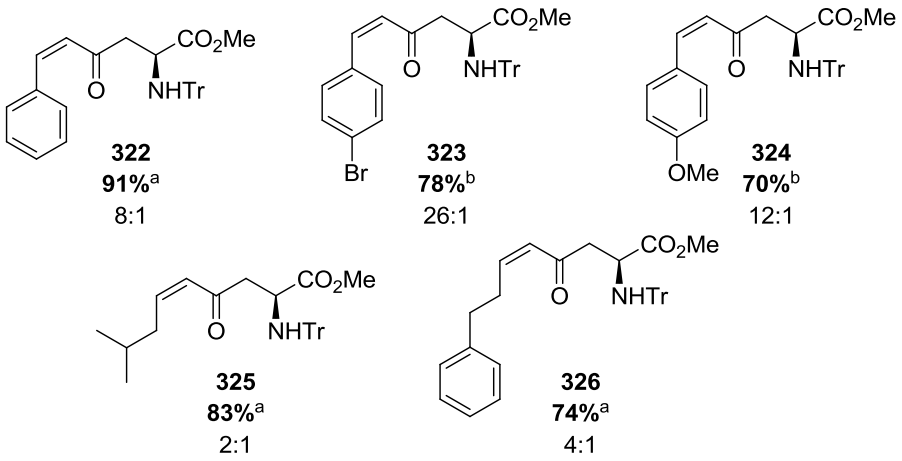


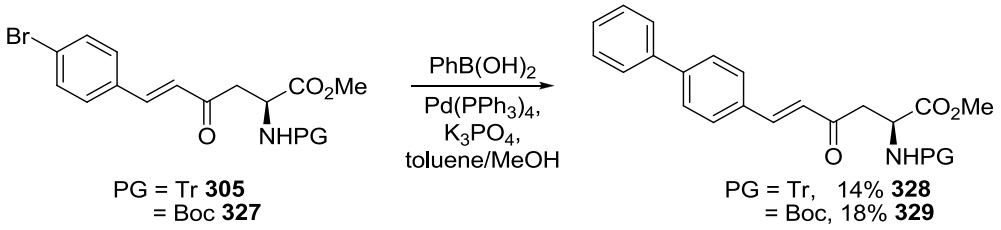
Figure 2.3 *Z*-configured enone-containing α-amino acids [a]Represents the overall isolated yield of both *E*- and *Z*-enone [b]Represents the isolated yield of *Z*-enone

For the *Z*-configured enone-containing α-amino acids, a small selection of five examples were generated in moderate to good yield. The *E*/*Z*-isomers could be separated readily by column chromatography on silica to give pure samples of the *Z*-configured enones. The Still-Gennari method proved fairly reliable for the formation of *Z*-alkenes with high levels of geometric selectivity for the aromatic analogues, although to a lesser extent with non-conjugated derivatives. A minor modification to the original route allowed the novel amino acids to be produced in only four synthetic steps, all of which gave excellent yields. The efficient route to generate bis(2,2,2-trifluoroethyl) phosphonate ester **321** enabled a divergent synthesis from a common intermediate.

2.5 Further Elaboration of Novel Enone-Functionalised α-Amino Acids

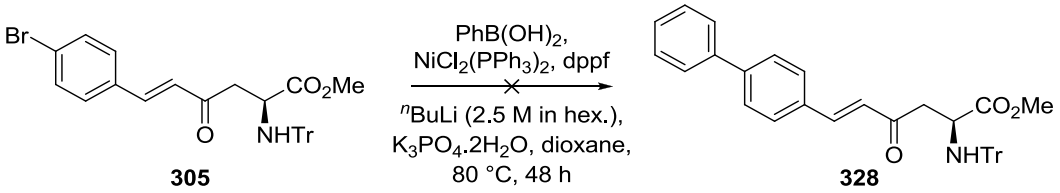
The possibility to further functionalise the halide-containing HWE products was alluded to previously, and therefore elaboration *via* a Suzuki-Miyaura cross-coupling was investigated to produce a biaryl system. The presence of a biaryl side-chain is a desirable feature for certain therapeutic small molecules, as favourable interactions can occur within a hydrophobic pocket of a biological receptor.

Initially, the trityl-protected *para*-bromophenyl analogue **305** was employed as the model substrate for the aryl halide coupling partner. The α-amino acid was subjected to standard Suzuki-Miyaura cross-coupling conditions using phenylboronic acid as the corresponding coupling partner, tetrakis(triphenylphosphine)palladium to catalyse the reaction and potassium phosphate tribasic as the base.[120] A base is required to activate the boronic acid as a quaternised boronate complex to facilitate the transmetallation step of the catalytic cycle.[121] First attempts under thermal conditions in DMF at 80 °C after 24 hours did not afford any product. Changing to a co-solvent system of toluene and methanol gave an isolated yield of 14% of the biaryl product **328** (Scheme 2.9). Switching the bulky trityl protecting group to a Boc-protecting group did not affect the reaction outcome and gave an equally poor yield of 18% (see Scheme 2.15 for details of the synthesis of **327**).



Scheme 2.9 Suzuki-Miyaura cross-coupling with 4-bromophenyl derivatives

One possible explanation for the poor yield may be the presence of the enone system. Coordination of palladium to the α,β-unsaturated moiety could cause degradation of the substrate and therefore result in complex reaction mixtures. Removal of palladium from the catalytic cycle may also attribute to the low yields of the cross-coupled product. There are limited examples of Suzuki-Miyaura cross-coupling reactions in the presence of enone-systems, however one case has proven successful utilising nickel as the catalyst.[122] Attempts were made to carry out the cross-coupling using the nickel-catalysed reaction conditions with trityl protected 4-bromophenyl enone **305**, however no biaryl product was obtained (Scheme 2.10).

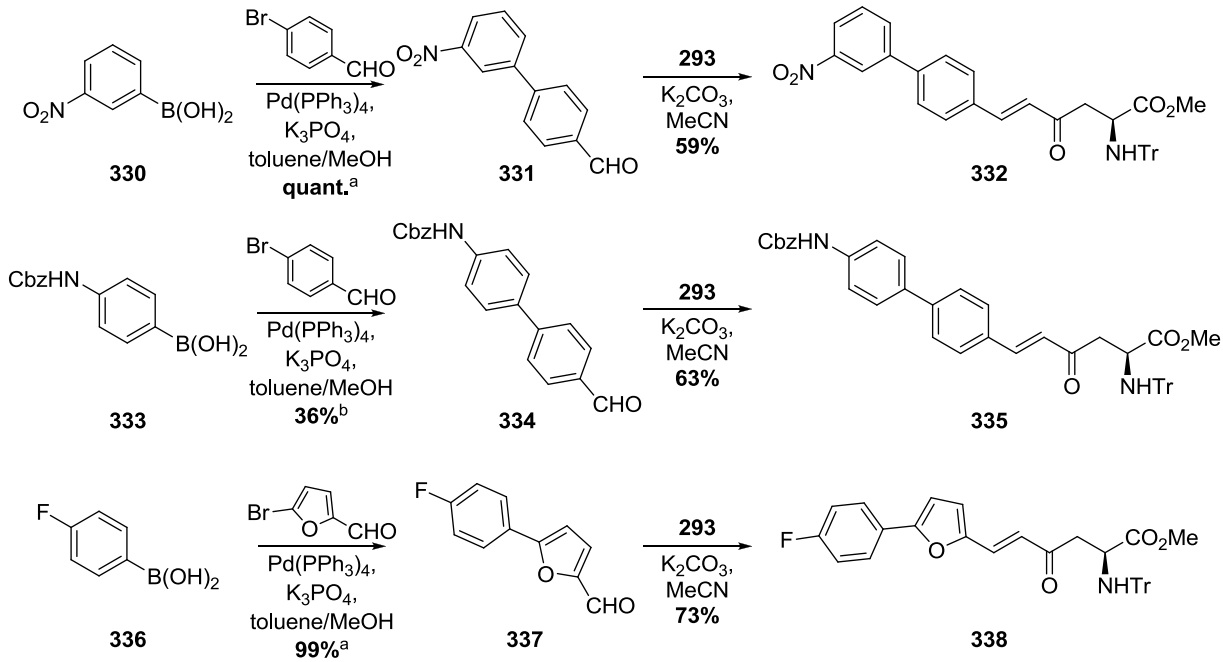


Scheme 2.10 Attempted nickel-catalysed Suzuki-Miyaura cross-coupling reaction

Direct functionalisation of the *para*-bromophenyl enone-containing α-amino acid analogues *via* a Suzuki-Miyaura cross-coupling reaction proved to be capricious and therefore an alternative approach was sought.

The proposed methodology was to reverse the coupling order, whereby the Suzuki-Miyaura reaction was carried out using a bromo-substituted aryl aldehyde prior to the HWE reaction with β-ketophosphonate ester **293**. *Para*-bromobenzaldehyde was coupled to 3-nitrophenylboronic acid **330** and 4-(benzyloxycarbonylamino)phenylboronic acid **333** to give biaryl products **331** and **334**, respectively (Scheme 2.11). 2-Bromofuraldehyde was coupled to 4-fluorophenylboronic acid **336** to generate the hetero-biaryl system **337**. Following synthesis of the three biaryl aldehydes, the HWE reaction using conditions previously described with β-ketophosphonate ester **293**

enabled access to novel enone-containing α-amino acid derivatives **332**, **335** and **338** in moderate to good yields.



Scheme 2.11 Suzuki-Miyaura cross-coupling prior to HWE reaction [a]Represents crude yield of product [b]Represents isolated yield of product

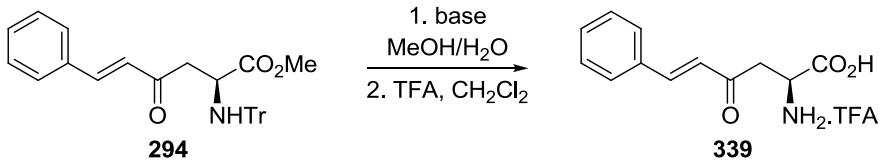
The ability to gain access to interesting biaryl derivatives has been exemplified using Suzuki-Miyaura cross-coupling of a boronic acid to a halo-substituted aryl aldehyde, followed by HWE reaction with the β-ketophosphonate ester **293**. With the methodology in place, a variety of novel enone-containing α-amino acids with biaryl side-chains could be readily synthesised.

2.6 Deprotection to Parent α-Amino Acids

A crucial component of the research programme was to deprotect the novel enone-functionalised amino acids to generate the parent amino acid structures. In general, an unprotected amino acid motif would be required to employ the enone substrates for potential biological purposes as this would enable recognition. Although, there are a few examples of protected enone-containing α-amino acids in the literature, the amino acid motif has not previously been liberated. Consequently, an efficient approach was sought to fully deprotect the novel enone-derived α-amino acids.

2.6.1 Deprotection of *E*-Configured Enones

The initial strategy to obtain the parent α-amino acids was to firstly hydrolyse the methyl ester, then remove the trityl protecting group with trifluoroacetic acid to give the amino acids as TFA salts. Generation of the TFA salt of the amine was critical because the presence of the nucleophilic amine and electrophilic conjugate acceptor may lead to unwanted reactions such as cyclisation or polymerisation. Masking the amine as a salt was anticipated to circumvent side reactions at this stage. Phenyl derivative **294** was employed as the model substrate to explore the deprotection (Scheme 2.12).



Scheme 2.12 Proposed deprotection of enone-containing α-amino acid **294**

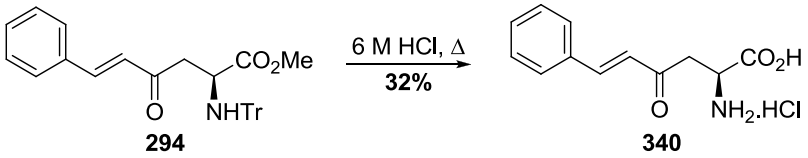
Initial investigations to cleave the ester employed conventional, basic hydrolytic conditions. Sodium and lithium hydroxide were used at both room and elevated temperatures, however these conditions gave rise to complex reaction mixtures and no carboxylic acid product could be identified or isolated (Table 2.2). The strongly basic conditions degraded the enone-substrates. Whereas, using milder cesium carbonate conditions only returned starting material, presumably due to the bulky trityl protecting group which is known to hinder α-ester hydrolysis.[123]

Entry	Base	Conditions	Outcome
1	NaOH	65 °C, 24 h	complex mixture
2	LiOH	r.t., 48 h	complex mixture
3	Cs_2CO_3	60 °C, 48 h	complex mixture
4	Cs_2CO_3	r.t., 48 h	S.M.

Table 2.2 Basic conditions for attempted hydrolytic ester cleavage

Failure to obtain the carboxylic acid under basic conditions promoted investigation using acid to cleave the protecting groups. An attempt to simultaneously hydrolyse the ester and remove the trityl protecting group was explored using hydrochloric acid under reflux (Scheme 2.13). The hydrochloride salt of the parent amino acid could be obtained, however isolation of the product

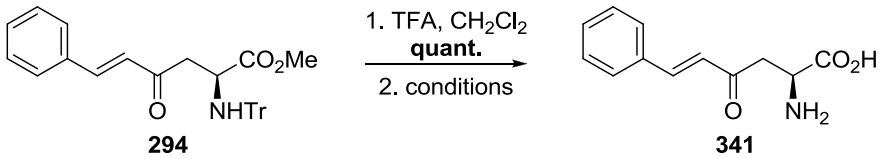
proved challenging and a maximum yield of 32% was obtained. The extremely polar nature of the amino acid salt made purification difficult, resulting in a low isolated yield. Harsh reaction conditions may cause decomposition or promote unwanted side-reactions which would also lead to a diminished yield.



294 **340**

Scheme 2.13 Acid-promoted deprotection to yield parent α-amino acid **340**

An alternative approach was investigated where the order of deprotection was reversed (Scheme 2.14). The bulky trityl protecting group that had previously hindered ester hydrolysis was firstly removed using TFA to give the TFA salt of the amine in quantitative yield. A range of mild hydrolytic conditions were then explored to generate the carboxylic acid.



294 **341**

Scheme 2.14 Attempted reversal of the order of deprotection

Inorganic bases such as lithium hydroxide and cesium carbonate gave complex reaction mixtures when reacted with the TFA salt (Table 2.3, entries 1 and 2). Under acidic conditions, a low 28% yield of the hydrochloride salt **340** was isolated (entry 3). Hydrolysis of the ester with trimethylsilyl iodide (TMSI) was also attempted, however starting material was returned at ambient temperature and complex mixtures were observed at higher temperatures (entries 4 and 5).[124] The final endeavour *via* this approach was to explore enzymatic cleavage of the ester using both lipase and α-chymotrypsin[125] under buffered conditions (entries 6 and 7). Both enzymes yielded complex reaction mixtures and no product could be identified.

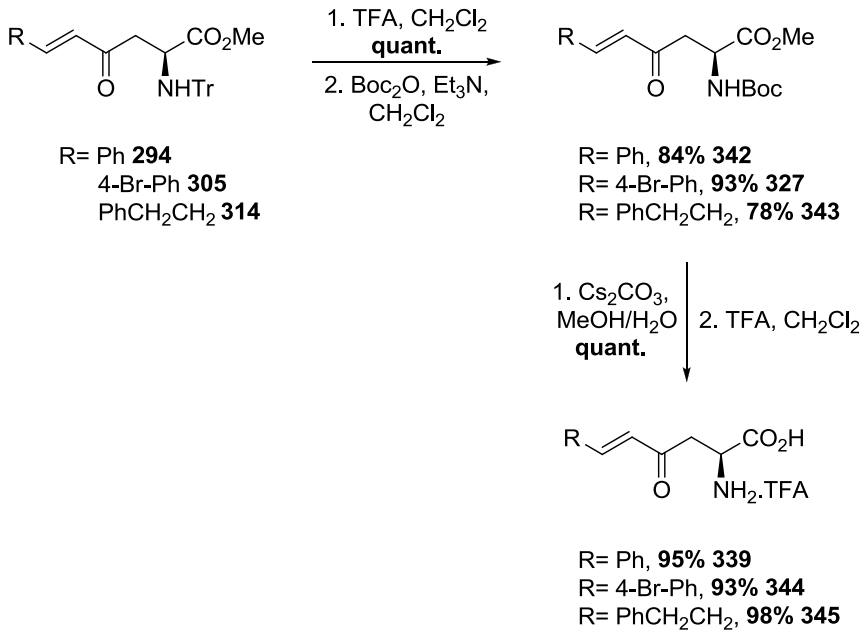
Entry	Reagents	Conditions	Outcome
1	LiOH	r.t., 24 h	complex mixture
2	Cs_2CO_3	r.t., 24 h	complex mixture
3	HCl	reflux, 24 h	**28%**
4	TMSI	r.t., 48 h	S.M.
5	TMSI	reflux, 7 h	complex mixture
6	lipase	r.t., 24 h	complex mixture
7	α-chymotrypsin	r.t., 24 h	complex mixture

Table 2.3 Conditions for attempted ester hydrolysis

In order to overcome the problems previously described, a mild two-stage approach was investigated to generate the parent enone-functionalised α-amino acids. The previous research suggested that the bulky trityl protecting group was too sterically encumbered to allow nucleophilic hydrolysis, whereas, in the absence of amine protection, the enone substrate appeared to be overly sensitive to various hydrolytic conditions.

The successful approach adopted was firstly to remove the bulky trityl protecting group of phenyl derivative **294** with TFA to give the TFA salt in quantitative yield (Scheme 2.15). Subsequent protection of the amine with a less-sterically demanding Boc-protecting group enabled access to a stable, orthogonally protected intermediate **342** in good yield. The Boc-protected intermediate could then be readily hydrolysed under mild basic conditions, employing cesium carbonate to quantitatively synthesise the carboxylic acid. Finally, removal of the Boc-group with TFA produced the target parent α-amino acid **339** in high isolated yield and high purity.

Development of the general two-stage deprotection strategy, where the amine protecting groups are exchanged, allowed access to a selection of unsaturated parent α-amino acid derivatives. The 4-bromophenyl **305** and phenethyl **314** analogues were subjected to the conditions as previously described to give the orthogonally protected Boc-intermediates **327** and **343** in excellent yields. Hydrolysis under basic conditions, followed by TFA-facilitated removal of the Boc-group generated the parent α-amino acids **344** and **345** in excellent yields.

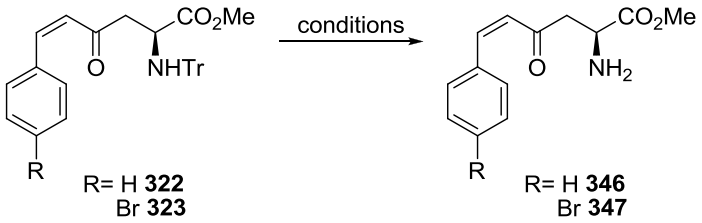


Scheme 2.15 Two-stage deprotection of enone-functionalised α-amino acids

2.6.2 Deprotection of *Z*-Configured Enones

The deprotection of *Z*-configured enone-containing α-amino acids was also desirable for subsequent modifications to the structures. It was anticipated that deprotection of *Z*-enones would occur in the same manner as the *E*-enones. Initial exploration sought to employ the two-stage synthetic strategy as previously described.

Phenyl derivative **322** and 4-bromophenyl derivative **323** were utilised as model substrates for initial removal of the trityl protecting group using TFA (Scheme 2.16, Table 2.4). However, in the presence of the strong acid, the deprotected compound isomerised to give a 1:1 ratio of *E*/*Z* isomers. It is feasible that protonation of the enone carbonyl induces enol formation and therefore allows free rotation around the double bond which results in the geometric scrambling. The reaction was also attempted on *para*-bromophenyl derivative **323** with mild citric acid, however a crude mixture of unknown products was attained. Stoichiometric quantities of Lewis acids; magnesium and zinc bromide were employed with a view to circumvent isomerisation.[126,127] Unfortunately, a mixture of 1:1 *E*/*Z*-isomers of deprotected product was produced as before.



Scheme 2.16 Trityl deprotection of *Z*-enones **322** and **323**

Entry	R	Reagents	Conditions	*E*/*Z* Ratio	Yield (%)
1	H	TFA, CH_2Cl_2	r.t., 2 h	1:1	78
2	Br	citric acid, MeCN/H_2O	r.t., 24 h	-	-
3	Br	$MgBr_2$, CH_2Cl_2	r.t., 3 h	1:1	quant.
4	Br	$ZnBr_2$, CH_2Cl_2	r.t., 3 h	1:1	quant.

Table 2.4 Deprotection conditions for *Z*-enones **322** and **323**

Preliminary investigations for trityl removal with the *Z*-enones proved unsuccessful. General methods utilise either acidic or Lewis acid conditions, under which enol formation is promoted. To overcome this problem, further investigation would be required into an alternative protecting group that could be removed under milder or non-acidic conditions. One possible protecting group that could be employed is the relatively stable triphenylsilyl group. This should offer comparable selectivity as the trityl group for the synthesis of the phosphonate esters and be stable under basic conditions, whilst enabling removal with a fluoride source.

For the first time, *E*-configured enone-containing α-amino acids have been formed as the parent amino acid structures **339**, **344** and **345**. The ability to deprotect the novel α-amino acids under mild reaction conditions to yield an orthogonally protected intermediate increases the number of potential applications of this methodology. For example, Boc-protected carboxylic acid intermediates could be employed for the synthesis of short peptides. Obtaining the desired amino acid products in high yields and high chemical purity is synthetically beneficial, however high optical purity is also required if the compounds are to be employed for biological purposes.

2.7 Stereochemical Evaluation

An important aspect of the synthetic route devised to gain access to the novel enones requires that the conditions employed do not cause epimerisation of the α-stereogenic centre. High enantiomeric excess is necessary to use the novel enones within biological systems.

Determination of the enantiopurity of the enone-containing α-amino acids was carried out by analytical chiral high performance liquid chromatography (HPLC). Boc-protected phenyl derivative **342** was selected as the substrate for HPLC analysis. The L-aspartic acid starting material employed in the asymmetric synthesis was purchased from Sigma-Aldrich and specifies an enantiomeric excess of greater than 96%. The corresponding racemic Boc-protected phenyl derivative **348** was synthesised from D/L-aspartic acid in order to identify the two enantiomers for comparison with the enantiomerically pure form.

Both racemic and enantiomerically pure analogues were analysed by chiral HPLC using an OD-H column with hexane/*iso*-propanol (90:10) as the solvent system at a flow rate of 1 mL min^{-1}. Chiral HPLC of the racemic substrate shows a clear separation of enantiomers (Figure 2.4a). Under the given conditions, the D-enantiomer has a retention time of 18.3 minutes and the L-enantiomer peaks at 21.6 minutes. When compared to the chiral material, the L-enantiomer is evident at 21.4 minutes (Figure 2.4b), however the D-enantiomer is not observed and therefore, the enantiomeric excess is calculated at greater than 99%.

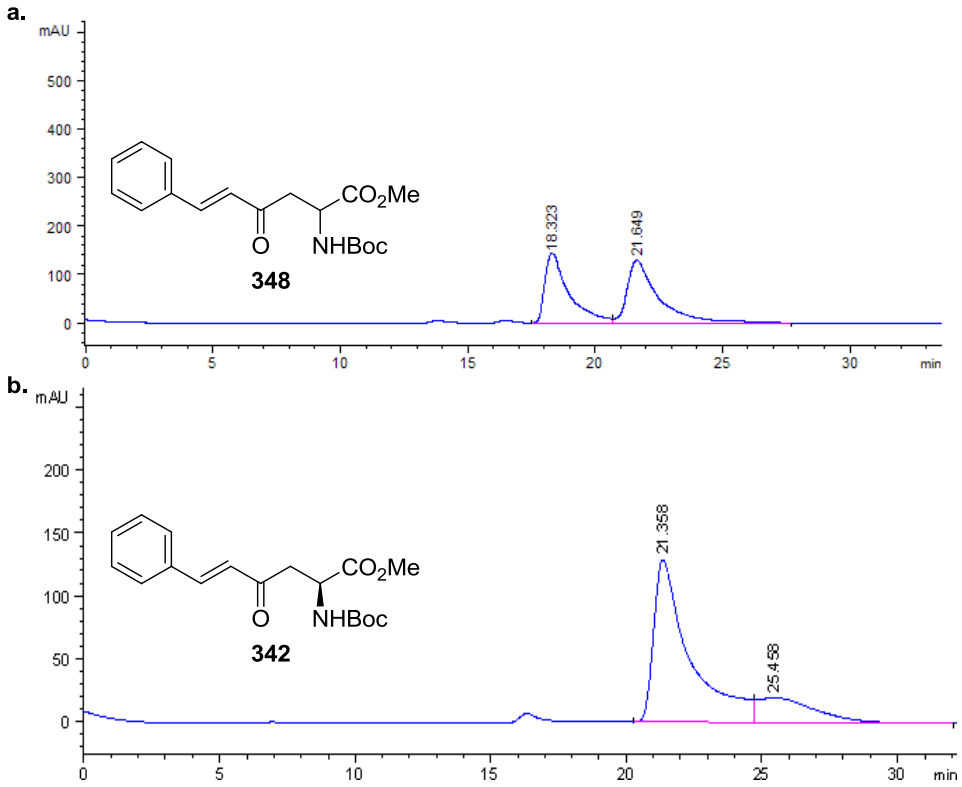


Figure 2.4 a. Chiral HPLC of racemic Boc-protected phenyl derivative **348** b. Chiral HPLC of enantiopure Boc-protected phenyl derivative **342**

Confirmation that the stereochemical integrity of the α-centre has been retained throughout the synthetic route has been proven using chiral HPLC. Successful optimisation of the synthetic strategy and stereochemical evaluation of the approach to generate chiral enone-containing α-amino acids has been carried out and therefore the utility of the synthetic methodology was then explored with a potential application.

2.8 Application of Enone-Functionalised α-Amino Acids

With an established route for the fast and efficient synthesis of novel enone-containing α-amino acids in place, an application was sought to highlight the potential use of these interesting structures. During the research, it was apparent that certain analogues of the enones emitted light in the visible region of the electromagnetic spectrum. We hypothesised that a highly conjugated enone-containing α-amino acid derivative may possess photoluminescent properties and therefore, could be employed as a fluorescent biological probe.

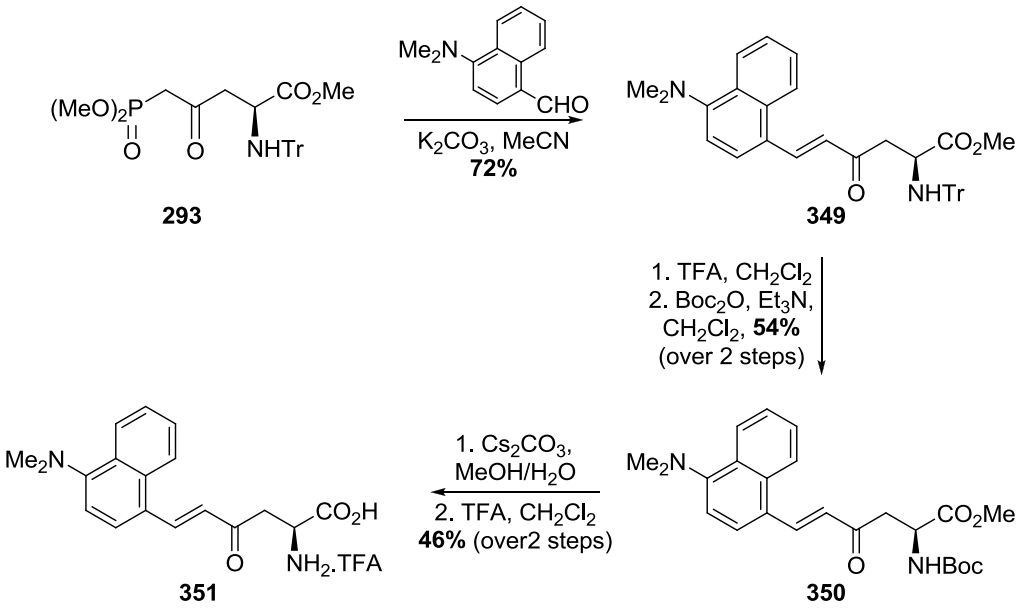
2.8.1 Fluorescent Labelling

Imaging living cells is an important, yet challenging area of cellular biology. The ability to visualise intracellular components such as nucleic acids, peptides and metabolites is crucial to further our understanding of the nature and dynamics of cellular events.[128] Labelling is one of the most common bioanalytical techniques to evaluate biological processes, in particular using radioactive and fluorescent approaches.

The use of fluorescent tags has increased in recent years due to the technical improvements in fluorescent instrumentation and the synthesis of novel fluorophores.[129] Fluorescent markers can be produced by using semi-conductor nanocrystals,[130] green fluorescent protein[131] or organic molecules.[129] Historically, using the former two methods has been challenging and therefore, using fluorescent organic compounds can be more straight-forward.

2.8.2 Synthesis of a Novel α-Amino Acid Fluorophore

Synthesis of a potential α-amino acid fluorophore was carried out using the previously developed route. This entailed a HWE reaction with β-ketophosphonate **293** and commercially available 4-*N*,*N*-dimethylamino-1-naphthaldehyde to generate enone **349** in 72% yield (Scheme 2.17). The novel highly conjugated analogue was subsequently deprotected using the mild two-stage deprotection procedure to give parent α-amino acid **351** as the TFA salt.



Scheme 2.17 Synthesis of novel α-amino acid fluorophore **351**

The highly conjugated *N*,*N*-dimethylaminonaphthyl side-chain was selected because it is analogous to the commonly employed dansyl fluorescent tag. Incorporation of the substituted naphthyl group adjacent to the enone generated an extensively conjugated system of overlapping p-orbitals. Highly conjugated molecules have a smaller energy gap between the HOMO and LUMO than their non-conjugated counterpart and therefore can absorb longer wavelengths of light. Depending on the maximum absorbance, relaxation to the electronic ground state can occur with emission of photons of lower energy leading to photoluminescence. It is therefore possible that highly conjugated enone-containing α-amino acids may function as fluorophores.

To test the hypothesis, the fluorescent output of the compound was measured in a variety of common solvents using a fluorescent spectrometer. Initially, the ultra-violet (UV) absorption of α-amino acid **351** was determined. The compound was then irradiated at the absorption wavelength and the fluorescent emission was measured qualitatively. Strong fluorescent emission was detected in organic solvents such as dimethyl sulfoxide (DMSO), methanol, ethyl acetate and toluene, however, lower fluorescence was observed in aqueous solution (Figure 2.5). A shift in emission maxima was observed depending on the polarity of the solvent. The wavelength of fluorescent emission ranged from 506 nm to 552 nm depending on the solvent employed (Table 2.5).

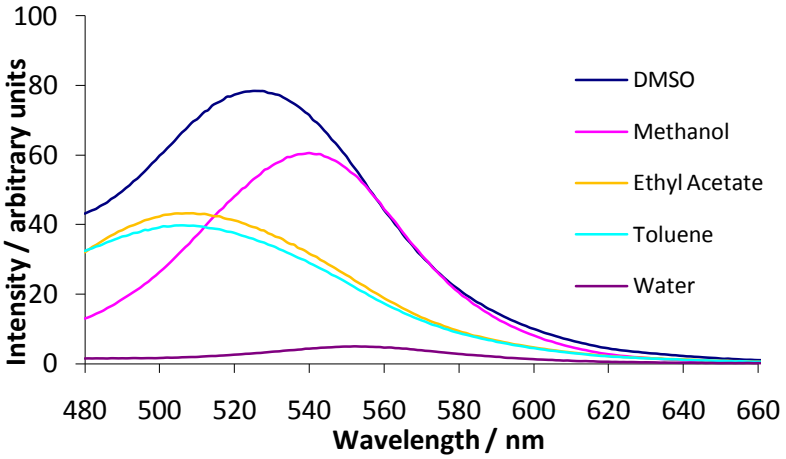


Figure 2.5 Fluorescent emission spectra for *N*,*N*-dimethylaminonaphthyl analogue **351**

Entry	Solvent	Concentration (mol L^{-1})	λ_{abs} (nm)	$\lambda_{Em.}$ (nm)
1	DMSO	9×10^{-6}	390	525
2	Methanol	9×10^{-6}	390	540
3	EtOAc	9×10^{-6}	390	509
4	Toluene	9×10^{-6}	390	506
5	Water	9×10^{-6}	390	552

Table 2.5 Absorption and emission measurements of novel α-amino acid fluorophore **351**

The excitation and emission properties of this unnatural analogue differ significantly from fluorescent proteinogenic amino acids. Naturally occurring fluorescent amino acid residues; tryptophan and tyrosine, absorb UV light at 278 and 274 nm and fluoresce at 352 and 303 nm respectively, in ethanol.[132] If the novel α-amino acid analogue were to be incorporated into a peptide as a fluorescent biomarker, detection of fluorescence could be distinguished from native amino acids because of the significant difference in spectroscopic properties.

2.9 Summary

A rapid and efficient synthetic route has been devised to synthesise novel enone-containing α-amino acids from a common, advanced intermediate. Using the methodology, a library of *E*-configured enones was produced to demonstrate the versatility of the HWE reaction. A smaller selection of *Z*-enones showed the possibility to synthesise efficiently *Z*-enones containing an aromatic side-chain using the Still-Gennari reaction. The non-aromatic *Z*-analogues exhibited comparable yields, but inferior *Z*-selectivity.

Initial attempts to modify *para*-halide substituted enone-containing α-amino acids directly *via* cross-coupling reactions were unsuccessful. However, an alternative approach was adopted that allowed access to biaryl structures.

For the first time, enone-functionalised amino acids were deprotected to give the parent α-amino acids. This was an important element of the research as future applications of the compounds may necessitate either orthogonal protection or the free amino acid.

A potential application of the novel enones has also been illustrated. Development of a highly conjugated α-amino acid fluorophore was carried out and the excitation and fluorescent emission of the compound was measured in a range of common organic solvents.

Alongside the possible modifications and uses that have been presented, there are several avenues yet to be explored in relation to the enone-functionalised α-amino acids. Investigations to use the novel compounds as synthetic scaffolds to produce alternative structures is desirable.

3 Chiral 6-Substituted-4-Oxygenated Pipecolic Acid Derivatives

3.1 Introduction

Chiral *N*-heterocycles are one of the most important structural motifs in chemical, biological and medicinal research. Piperidine has been the focus of extensive investigations due to the wealth of properties and functional roles possessed by molecules containing the heterocycle. Modifications to the piperidine scaffold have also provoked interest with synthetic chemists. As exemplified previously, 4-oxygenated pipecolic acid derivatives have emerged as significant bioactive molecules and valuable synthetic scaffolds.

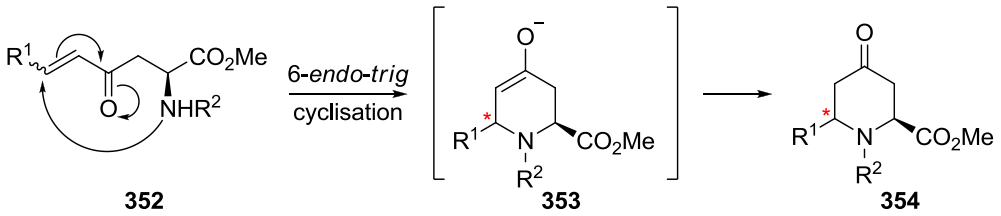
4-Oxo- and 4-hydroxypipecolic acid have been identified in several naturally occurring secondary metabolites which possess potent therapeutic properties. 4-Oxygenated pipecolic acid derivatives are also components of many active pharmaceutical products and therefore are highly sought after targets in organic synthesis. In particular, chiral pipecolic acid scaffolds are required in the pharmaceutical industry for specificity within the body. Natural products and medicinal agents can display a range of substitution patterns around the saturated *N*-heterocyclic core depending on the function of the molecule. A screen of the literature reveals the 2,4,6-substitution pattern of pipecolic acid as significant and abundant. Substituted pipecolic acid derivatives can include a wide variety of functional groups and side-chains on the heterocycle suited to their purpose.

Substantial effort has been invested in the synthesis of chiral 4-oxygenated pipecolic acid derivatives. Reports of general synthetic strategies, as well as specific syntheses towards the heterocyclic core continue to advance the field. A successful synthesis is fast, efficient and stereocontrolled. The ability to incorporate diversity at a late stage in the route is also desirable. Many different strategies exist for construction of the *N*-heterocyclic product, however an approach that satisfies all the specifications remains a challenge. Despite the numerous synthetic strategies developed to date, a great deal of interest in these molecules remains and therefore the challenge to provide an efficient and varied route to these important compounds is still active.

3.2 Synthesis of 4-Oxopipecolic Acid Derivatives *via* an Intramolecular Conjugate Addition

The functional significance of enantiopure 4-oxopipecolic acids makes them attractive synthetic targets. At present, there are many methods to obtain 4-oxopipecolic acid, however most strategies suffer from disadvantages. An efficient synthetic strategy would be highly beneficial and therefore the second objective of the research programme was to devise a rapid and sterocontrolled approach to obtain these important molecular scaffolds.

Following the development of an efficient methodology to synthesise novel enone-containing α-amino acids, the aim was to convert the linear α-amino acids into the corresponding cycloadduct possessing the desired pipecolic acid motif. The strategy proposed was to take advantage of the electrophilic nature of α,β-unsaturated ketone **352** and initiate an intramolecular conjugate addition reaction using the α-amine as the internal nucleophile (Scheme 3.1). A diastereoselective cyclisation will generate highly functionalised 6-substituted-4-oxopipecolic acid analogues **354**. The cyclisation reaction is formally classified as a 6-*endo-trig* cyclisation and is favoured according to Baldwin's guidelines.[133] The prospective route allows variation to the pipecolic acid template because the R^1 substituent can include a range of alkyl or aryl groups.



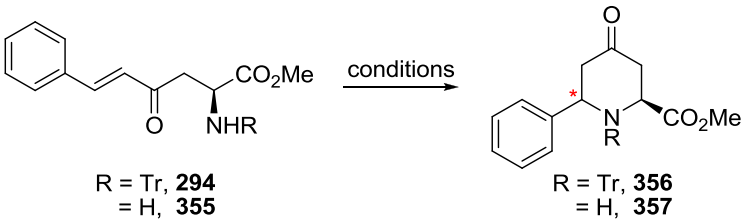
352 **353** **354**

Scheme 3.1 Proposed intramolecular conjugate addition reaction to form 4-oxopipecolic acid derivatives

A small selection of novel enone-containing α-amino acids were utilised during the research in an attempt to attain the desired 4-oxopipecolic acids. Various reaction conditions were explored to promote the diastereoselective intramolecular conjugate addition.

3.2.1 Model Substrate 1 – Phenyl Derivative

Novel *E*-configured enone-containing α-amino acid with a phenyl side-chain was used for the preliminary investigation into a diastereoselective 6-*endo-trig* cyclisation to yield the 4-oxopipecolic acid motif (Scheme 3.2). The initial research employed the model substrate in the *N*-trityl protected form **294**, as well as the free base **355**. A variety of acids, Lewis acids and bases were investigated to facilitate the conjugate addition.



Scheme 3.2 6-*Endo-trig* cyclisation using phenyl derivatives **294** and **355**

Literature precedent existed for simultaneous protecting group cleavage and cyclisation of a terminal enone-functionalised α-amino acid under acidic conditions.[108,134] Using the previously reported conditions, trityl protected enone **294** was exposed to anhydrous ethereal hydrochloric acid (Table 3.1, entry 1), which resulted in removal of the protecting group, however the cyclised product was not observed. The HCl salt of the linear α-amino acid was produced and therefore there is no nucleophilic reacting centre to carry out the intramolecular cyclisation.

Basic conditions were then explored to deprotonate the amine, which would increase nucleophilicity and therefore induce the intramolecular cyclisation. Although it was anticipated that a bulky protecting group would hinder the cyclisation reaction, trityl protected enone **294** was treated with sodium hydride in an attempt to promote cyclisation (entry 2). A complex mixture resulted and no product was identified. The reaction was then attempted in the absence of the protecting group. The 6-*endo-trig* cyclisation was investigated using free amine **355** with strong bases (entries 3–5). Highly polar, complex mixtures resulted and no traces of the cycloadduct were observed by ^{1}H NMR spectroscopy. It is possible that following deprotonation, polymerisation may occur resulting in the complex spectra. Formation of diketopiperazines is also feasible from the α-amino acids and may account for the complicated reaction composition. Weak base also did not instigate the reaction (entry 6).

An alternative approach was explored using a Lewis acid to activate the enone by increasing the electrophilicity of the system and therefore facilitate 1,4-conjugate addition. Oxophilic Lewis acids; boron trifluoride and cerium(III) chloride[135] were employed (entries 7–9), however at room temperature and under reflux, complex mixtures were obtained and no product was identified.

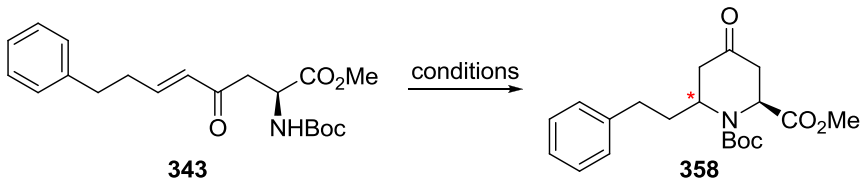
Entry	R	Reagent	Solvent	Conditions	Outcome
1	Tr	$HCl.Et_2O$	-	r.t., 48 h	Tr removed
2	Tr	NaH	THF	r.t., 72 h	complex mixture
3	H	$^{n}BuLi$	THF	−78 °C → r.t., 24 h	complex mixture
4	H	LiHMDS	THF	reflux, 24 h	complex mixture
5	H	DBU	MeOH	r.t., 24 h	complex mixture
6	H	Na_2CO_3	CH_2Cl_2	r.t., 48 h	S.M.
7	H	$BF_3.Et_2O$	CH_2Cl_2	r.t., 24 h	complex mixture
8	H	$BF_3.Et_2O$	toluene	reflux, 24 h	complex mixture
9	H	$CeCl_3.7H_2O$	MeCN	r.t., 48 h	complex mixture

Table 3.1 Conditions for the attempted intramolecular cyclisation

The initial research proved unsuccessful as the trityl protected enone generated no product when exposed to acidic or basic conditions. Similarly, 4-oxopipecolic acid was not formed in the absence of the protecting group. When the free amine of the enone-containing α-amino acid was employed, complex, highly polar mixtures resulted. This made isolation and identification of side-products difficult and therefore the postulated problems associated with the reaction were unconfirmed. To gain an insight into the reaction pathway, it was proposed that the nitrogen should be protected to decrease the polarity of the resultant mixtures. It was also suggested that the close proximity of the aromatic ring may hinder the intramolecular nucleophilic addition and therefore the enone-containing α-amino acid with a phenethyl side-chain **343** was used as the model substrate.

3.2.2 Model Substrate 2 – Phenethyl derivative

Boc-protected enone-functionalised α-amino acid **343** was investigated for the diastereoselective conjugate addition reaction (Scheme 3.3). It was anticipated that the phenethyl derivative, with the aromatic ring further from the reacting centre, would enable a facile reaction. A Boc group was selected to protect the nitrogen and decrease the polarity of the compound to enable the reaction progress to be monitored. An array of bases and Lewis acids were explored to initiate the cyclisation.



343 **358**

Scheme 3.3 Intramolecular cyclisation of Boc-protected phenethyl derivative **343**

Basic reaction conditions were investigated with Boc-protected enone **343** (Table 3.2, entries 1–5). Precedent existed for an exocyclic aza-Michael ring closure of a linear *N*-Boc protected α,β-unsaturated ketone using sodium hydride.[136] Using the reported conditions at room temperature returned starting material, however increasing the temperature gave complex mixtures of compounds. An alternative strong base, lithium bis(trimethylsilyl)amide, was used, however a complex mixture resulted. The reaction was also explored using a weak base, potassium carbonate, heated under reflux and heated under microwave irradiation, however no product was formed.

There is literature precedent for intermolecular 1,4-addition of carbamates to simple α,β-unsaturated ketones using Lewis acids.[137,138] Carbamates are weakly nucleophilic and only certain Lewis acids have proven suitable for the conjugate addition. Bismuth nitrate and gold(I) chloride have been employed for conjugate addition of carbamates to simple enone systems, however did not promote the intramolecular reaction with the Boc-protected enone-functionalised α-amino acid **343** (entries 6 and 7).

Entry	Reagent	Solvent	Conditions	Outcome
1	NaH	THF	r.t., 24 h	S.M.
2	NaH	THF	reflux, 3 h	complex mixture
3	LiHMDS	THF	reflux, 1 h	complex mixture
4	K_2CO_3	MeCN	reflux, 48 h	S.M.
5	K_2CO_3	MeCN	MW, 100 °C, 30 min	S.M.
6	$Bi(NO_3)_3$	CH_2Cl_2	r.t., 72 h	S.M.
7	AuCl	THF	60 °C, 48 h	S.M.

Table 3.2 Attempted intramolecular conjugate addition reaction conditions

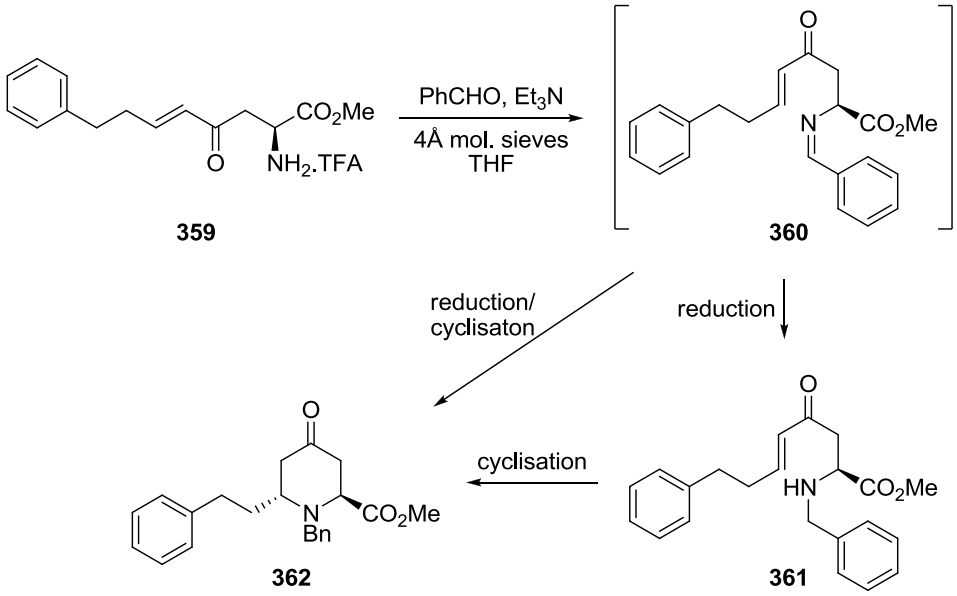
Aside from the reaction of enone **343** with strong bases at high temperatures, basic conditions and Lewis acid catalysis returned starting material and there was no evidence of cyclisation. We concluded that the *N*-carbamate was not sufficiently nucleophilic to attack the enone system of the unnatural amino acid. The lone pair of the carbamate is delocalised, which makes it weakly basic. It was evident that an alternative strategy was required to tune the amine nucleophilicity to make it suitable for a controlled conjugate addition. The proposed approach involved incorporation of a protecting group that would increase the nucleophilicity of the nitrogen to allow the 6-*endo*-*trig* reaction to take place, yet enable the reaction mixtures to be easily handled.

3.3 One-Pot Reductive Amination/Intramolecular Cyclisation for the Synthesis of 4-Oxopipecolic Acid Derivatives

An alternative strategy was devised to incorporate a protecting group that would increase the nucleophilicity of the amine of the amino acid and therefore facilitate the intramolecular conjugate addition. An *N*-benzyl protecting group was selected due to the inductive electron donating capability of the benzyl group towards the nitrogen. This increases the electron density on the nitrogen and increases the energy of the lone pair, which makes the nitrogen more basic. Selective mono-alkylation of the nitrogen atom was required to enable the conjugate addition to occur. A reductive amination reaction was proposed to avoid common issues with over alkylation of nitrogen using standard alkyl halides.

Phenethyl derivative **359** was used as the test substrate for the investigation. The strategy devised was to generate an imine using the TFA salt of enone **359** followed by reduction to yield the desired *N*-benzyl protecting group (Scheme 3.4). Benzaldehyde was reacted with enone **359** in the

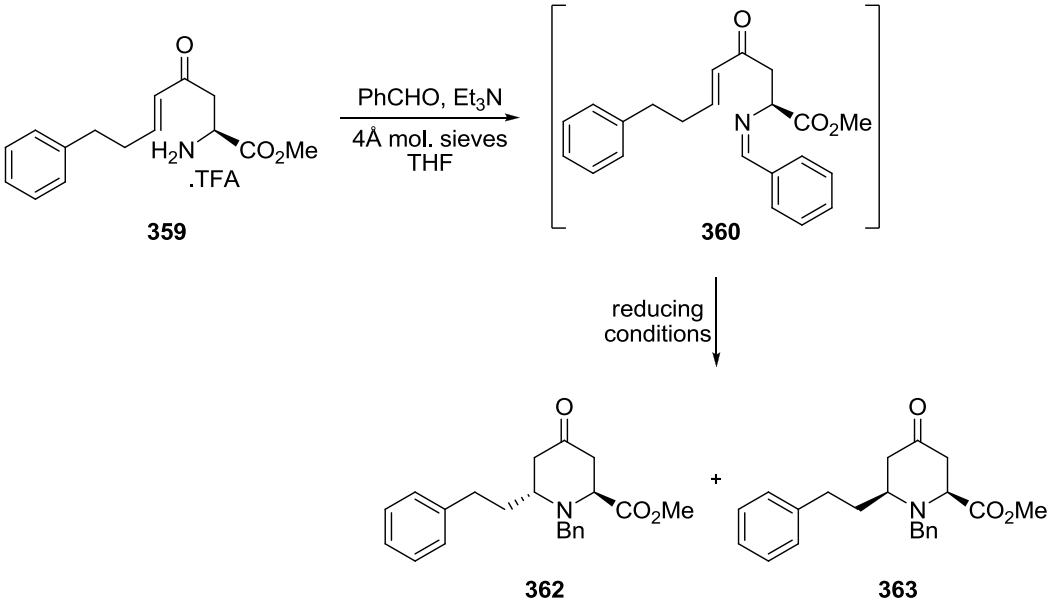
presence of 4Å molecular sieves to remove the resultant water and drive the equilibrium in favour of formation of imine **360**. It was anticipated that reduction of imine **360** would give linear benzyl protected α-amino acid **361** and subsequent cyclisation would yield the desired cycloadduct **362**. The caveat with this route is that a chemoselective reduction of the imine is required in the presence of the enone moiety. Exploration of mild reductive conditions to allow a selective reaction was carried out.



Scheme 3.4 Reductive amination/6-*endo*-*trig* cyclisation strategy for the synthesis of 4-oxopipecolic acid derivatives

Following imine formation, reductive conditions were explored in an attempt to obtain a chemoselective process (Table 3.3). Preliminary investigations employed the mild reducing agent, triethylsilane, in the presence of acid or a Lewis acid to increase the electrophilicity of imine **360** and allow reduction to take place (entries 1 and 2). These reductive conditions returned the starting imine with no trace of product. Reduction of the imine using trichlorosilane[139] and DMF as a Lewis base gave rise to interesting results (entry 3). Following aqueous work-up, the linear *N*-benzyl-*N*-silyl-protected α-amino acid was observed by ^{1}H NMR spectroscopy. Subsequent column chromatography on silica resulted in the desired 4-oxopipecolic acid **362** in 25% yield with a 2:1 ratio of diastereomers. The *anti*-diastereomer is obtained as the major product (*vide infra*). Reduction using trichlorosilane occurs with simultaneous formation of a trichlorosilane–nitrogen bond. Cleavage of the *N–Si* bond with the slightly acidic silica gel initiated the intramolecular 6-*endo*-*trig* cyclisation. As the yield of 4-oxopipecolic acid **362** was low, alternative reducing agents were explored in an attempt to optimise the reaction.

Conventional reductive amination conditions using borohydride reducing agents were then investigated (entries 4–7). After 48 hours at room temperature, reduction of imine **360** with sodium triacetoxyborohydride led directly to formation of cyclic pipecolic acid **362** in 45% yield. There was no evidence of the linear *N*-benzyl-protected α-amino acid **361**. Changing the reducing agent to sodium cyanoborohydride resulted in a dramatic increase in the reaction rate. The yield of product also increased to 53%, however the same diastereoselectivity was achieved with both hydride reducing agents at room temperature (entries 4 and 5). In an attempt to improve the stereoselectivity, the reaction was carried out at lower temperatures with sodium cyanoborohydride, however the diastereomeric ratio remained the same but reaction rate decreased and the yields declined (entries 6 and 7).



Scheme 3.5 Reductive amination/cyclisation strategy to generate 4-oxopipecolic acid derivatives

Entry	Reductant	Conditions	Temp. (°C)	Time (h)	Yield (%)[a]	d.r. (*anti*:*syn*)[b]
1	Et_3SiH	TFA, CH_2Cl_2	r.t.	24	S.M.	-
2	Et_3SiH	Zn, CH_2Cl_2	r.t.	24	S.M.	-
3	Cl_3SiH	DMF, CH_2Cl_2	0	24	25	2:1
4	$NaB(OAc)_3H$	THF	r.t.	48	45	2:1
5	$NaBH_3CN$	MeOH	r.t.	1	53	2:1
6	$NaBH_3CN$	MeOH	0	15	47	2:1
7	$NaBH_3CN$	MeOH	−20	24	30	2:1

[a]Represents overall isolated yield for both diastereomers. [b]Determined by ^{1}H NMR spectroscopy.

Table 3.3 Reductive amination conditions

The reductive amination/cyclisation sequence has three reactions occurring in a one-pot process and therefore a yield of 53% is acceptable, yet several factors limit the reaction yield. Imine formation is not quantitative, however the major problem is the issue of chemoselectivity. A search of the literature did not uncover a reducing agent that would selectively reduce the imine without a degree of 1,4-reduction of the enone system. The sodium cyanoborohydride conditions were therefore deemed optimal for this approach.

The one-pot reductive amination/cyclisation strategy developed allows rapid access to the highly desirable 6-substituted-4-oxopipecolic acids. Despite the moderate diastereoselective discrimination with the phenethyl analogue, the reaction was attempted with a variety of enone-containing α-amino acids to probe the scope of the reaction. A small library of functionalised 4-oxopipecolic acids were synthesised using this one-pot approach (Figure 3.1).

Enone-functionalised α-amino acids with an aromatic ring directly attached to the enone moiety were investigated to form the corresponding pipecolic acid cycloadducts. It was postulated that the direct attachment of the side-chain to the reacting centre of the enone may lead to an improvement in diastereoselectivity. Enone-functionalised phenyl derivative was cyclised according to the one-pot reductive amination/cyclisation strategy to give 4-oxopipecolic acid **364** in a modest 37% yield. Also, electron rich *para*-methoxyphenyl **365** and electron deficient *para*-bromophenyl **366** derivatives were produced in moderate yield with improved stereoselectivity in

comparison to phenethyl analogue **362**. The *para*-bromophenyl **366** analogue is interesting because it could be further functionalised *via* cross-coupling reactions to yield a diverse array of structures containing the pipecolic acid core.

Alkyl substituted enone-containing α-amino acids were subjected to the cyclisation conditions to generate *iso*-butyl **367** and methyl **368** substituted derivatives in good yields and with good stereoselectivity. Significantly sterically hindered examples of enone-containing α-amino acids could also be cyclised using this approach, as naphthyl **369** and biphenyl **370** derivatives were synthesised in modest yields and with reasonable stereoselectivity.

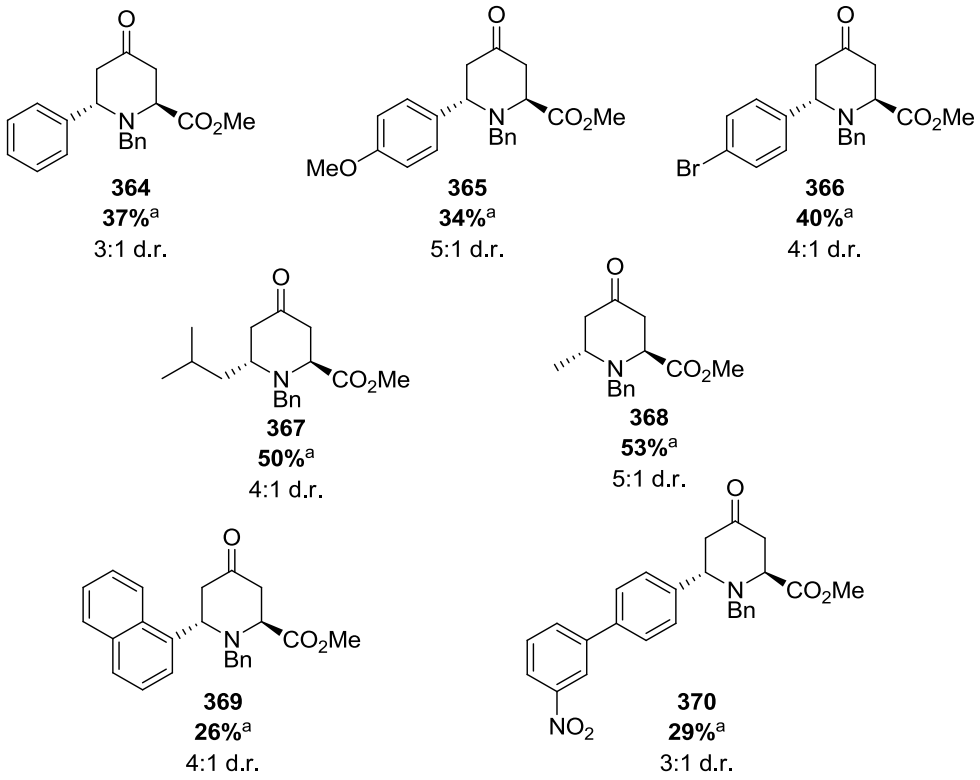


Figure 3.1 Small library of 4-oxopipecolic acid derivatives [a]Represents overall isolated yield for both diastereomers

Analysis of the results indicates that the cyclisation does not appear to follow a definite pattern of reactivity. Within the small library of 4-oxopipecolic acid derivatives, the alkyl analogues **362**, **367** and **368** are produced in the highest yields. Possibly the lack of conjugation is beneficial for the cyclisation reaction. In relation to stereocontrol, the *iso*-butyl **367** and methyl **368** derivatives are generated with good diastereoselective discrimination, however phenethyl derivative **362** is formed with the lowest diastereomeric ratio. It was expected that a bulkier side-chain would give

rise to high stereocontrol, yet the methyl analogue exhibits one of the highest diastereoselectivities.

Aromatic analogues **364**-**366** appear to exhibit a trend in reactivity in terms of electronics. Bromophenyl derivative **366** was anticipated to be the most reactive because the electron-withdrawing effect of the halide would increase the electrophilicity of the enone system and therefore lead to a high yielding reaction. The electron-donating methoxy substituent was expected to be the least reactive in the series, with the phenyl derivative inbetween the two extremes. This is observed experimentally, however the difference in yield is minor. Methoxy derivative **365** is formed with the highest diastereomeric ratio in the series of aromatic analogues. The reason for this outcome is unclear at present, however, the stereoelectronic subtleties of this reductive amination/cyclisation reaction mechanism have yet to be investigated.

With the sterically demanding naphthyl **369** and biphenyl **370** analogues, lower yields were expected as the cyclic transition state would be more strained. As a consequence of the steric hindrance, it was postulated that these substrates would be highly diastereoselective, however they were no more selective than the previously described examples.

Comparison of the most sterically hindered analogues, **369** and **370**, with the least sterically hindered 4-oxopipecolic acid methyl derivative **368**, reveals that atypical results are obtained. Complex stereoelectronic factors govern the cyclisation reaction to give rise to the observed outcome in terms of reactivity and steric bias and therefore further investigation is required.

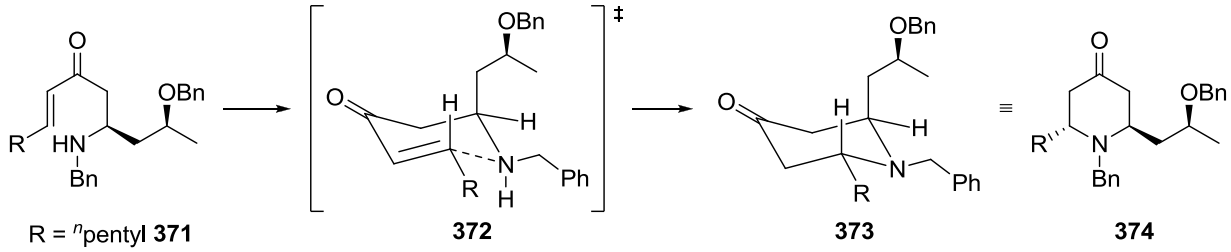
To summarise, eight examples of 6-substituted-4-oxopipecolic acids were synthesised rapidly *via* the one-pot reductive amination/cyclisation strategy. The analogues were produced in moderate yields over the three step process and moderate diastereoselectivity. The diastereomers can be readily separated by column chromatography to yield diastereomerically pure samples of the major *anti*-4-oxopipecolic acid products.

3.3.1 Rationale for the Observed Stereochemical Outcome of the Intramolecular Cyclisation

Following compilation of the results from the 4-oxopipecolic acid synthesis, we aimed to provide an explanation for the observed stereochemical outcome. Analysis of the table of results for the cyclisation of imine **360** *via* reduction either during the one-pot process or the multistage approach, always yields the *anti*-diastereomer as the major pipecolic acid product. Comparison with previously reported cases of diastereoselective cyclisations gave insights into the possible mechanism and therefore the rationalisation of the stereochemical outcome for the reductive amination/cylisation reaction.

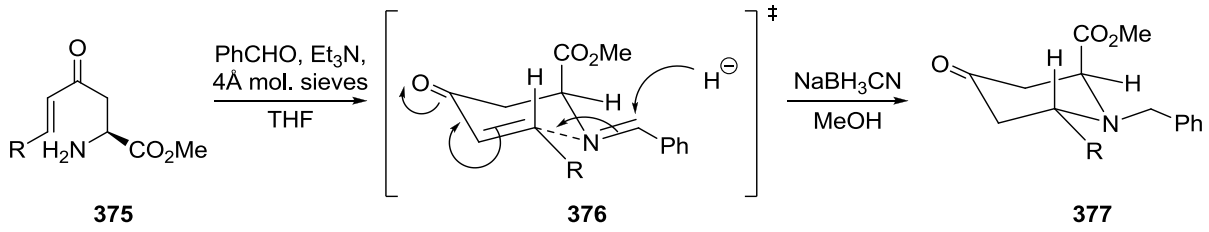
Several examples of diastereoselective 6-*endo-trig* cyclisations to produce 2,6-disubstituted piperidines can be found in the literature. In almost all cases, a 6-membered chair-like transition state is adopted. This is a highly favoured transition state conformation as it is intrinsically strain-free. Substituents tend to occupy equatorial positions where possible because of the severe strain associated with 1,3-diaxial interactions.[140]

Research conducted by Krishna and Sreeshailam demonstrated that a conjugate addition reaction can give rise to an *anti*-diastereomeric piperidone as the major product *via* a 6-membered chair-like transition state.[141] The hypothesised transition state **372** depicts the energetically favourable equatorial positioning of the *N*-benzyl group to minimise 1,2-allylic strain *via* eclipsing interactions with the endocyclic alkene (Scheme 3.6). The geometry of the enone enables the R group to adopt a favourable equatorial position and the stereogenic centre is positioned axial. 6-*Endo-trig* cyclisation therefore produces the *anti*-diastereomer of piperidone **374** as the major product with a 3:1 *anti*:*syn* diastereomeric ratio.



Scheme 3.6 Krishna and Sreeshailam's *anti*-diastereoselective 6-*endo-trig* cyclisation

Interpretation of the results for the previous example of a diastereoselective 6-*endo*-*trig* cyclisation enables parellels to be made with the one-pot reductive amination/cyclisation strategy. A similar argument as Krishna's hypothesis is presented, as the substrate under investigation is *N*-substituted and yields the *anti*-diastereomer. Following imine formation, a postulated 6-membered chair-like conformation **376** is adopted by the molecule (Scheme 3.7). To avoid 1,2-allylic strain with the endocyclic alkene, the imine will adopt an energetically favourable equatorial position. The *E*-configured enone enables the R group to be equatorial and the methyl ester is positioned axial. Reduction of the imine initiates the cyclisation, which results in the ester and R group having an *anti*-relationship to one another in the 4-oxopipecolic acid product **377**.



Scheme 3.7 Possible explanation for the stereochemical outcome of the one-pot reductive amination/6-*endo*-*trig* cyclisation

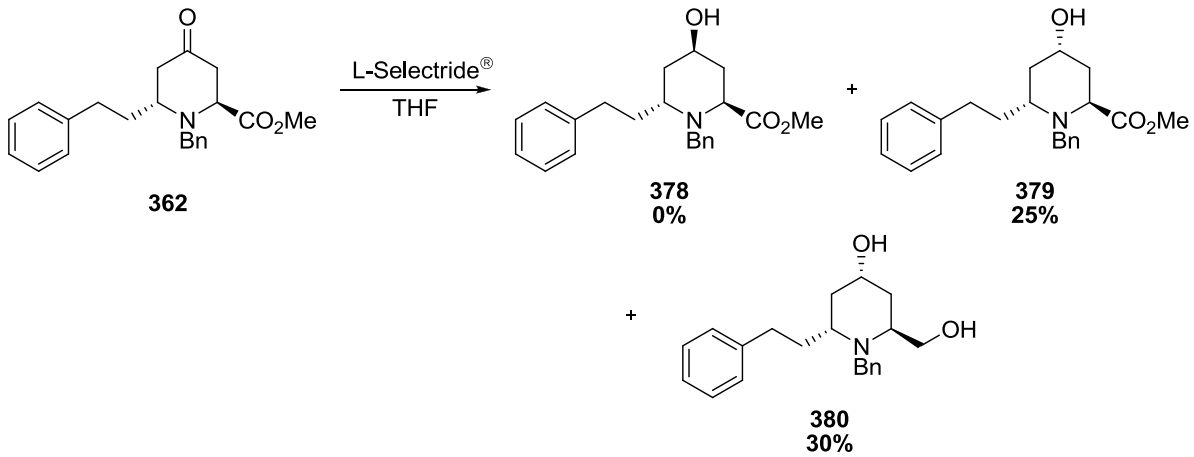
The reductive amination/cyclisation reaction gives rise to a diastereomeric ratio that ranges from 2:1 to 5:1 *anti*:*syn* depending on the substrate employed. Stereochemical preference for the *anti*-diastereomer is not highly biased. The reversibility of the reaction was questioned as a possible explanation for the moderate diastereocontrol. An experiment to determine this would require separation of the diastereomers and then the minor *syn*-product should be resubmitted to the reaction conditions. If the reaction is reversible, the same 2:1 d.r. should be obtained.

To summarise, the *anti*-diastereomer is formed as the major 4-oxopipecolic acid product as a result of the one-pot reductive amination/cyclisation reaction. Stereoelectronic factors control the process whereby the postulated 6-membered chair-like transition state strives to adopt a low energy conformation to minimise repulsive steric interactions.

3.4 Reduction of 4-Oxo- to 4-Hydroxypipecolic Acid Derivatives

A diastereoselective one-pot reductive amination/cyclisation stategy was developed to synthesise highly desirable 4-oxopipecolic acid derivatives. This approach enabled rapid access from novel enone-functionalised α-amino acids. The 4-hydroxy permutation of the pipecolic acid scaffold is also a sought after motif. The importance of 4-hydroxypipecolic acid has been made apparent by the numerous biological and synthetic applications of the molecule. Reduction of the 6-substituted-4-oxopipecolic acid derivatives would enable fast and efficient access to the hydroxyl analogues.

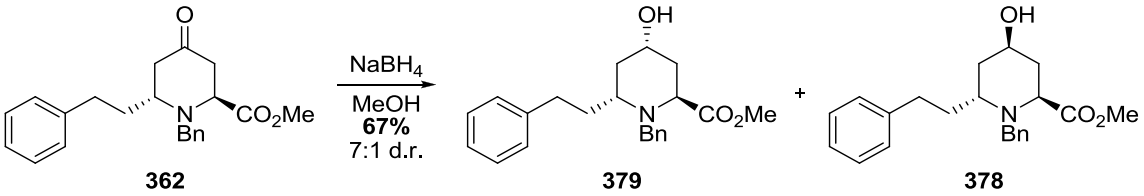
The reduction of 4-oxo- to 4-hydroxypipecolic acid was initially investigated using phenethyl derivative **362** (Scheme 3.8). L-Selectride® was chosen as the reducing agent because it is bulky and known to prefer equatorial attack on cyclic ketones and therefore will generally provide good stereocontrol.[142] Phenethyl derivative **362** was subjected to the reducing conditions, however anticipated axial 4-hydroxypipecolic acid **378** was not formed. An unusual result was obtained as equatorial 4-hydroxypipecolic acid **379** was produced in a low 25% yield which implied axial L-Selectride® attack had occurred. The poor yield of 4-hydroxypipecolic acid resulted from a lack of chemoselectivity as the methy ester was also reduced to generate a 30% yield of diol **380**.



Scheme 3.8 Reduction of 4-oxopipecolic acid derivative **362** with L-Selectride®

To overcome the chemoselectivity issue, the milder reducing agent, sodium borohydride, was selected for the reduction to produce 4-hydroxypipecolic acids. Small reducing agents such as sodium borohydride commonly attack cyclic ketones with an axial trajectory to produce

equatorial hydroxyl products. Reduction of phenethyl derivative **362** was readily achieved using sodium borohydride in methanol at 0 °C to produce the corresponding 4-hydroxypipecolic acids (Scheme 3.9). Unfortunately, the sodium borohydride reduction did not produce a single diastereomer, however a good 7:1 diastereomeric ratio of (4*S*)- to (4*R*)-4-hydroxypipecolic acid **379** and **378** was observed in a 67% combined yield.



362 **379** **378**

Scheme 3.9 Reduction of 4-oxopipecolic acid derivative **362** with sodium borohydride

A small library of 4-hydroxylated pipecolic acid analogues were synthesised using the sodium borohydride reduction (Figure 3.2). All analogues produced equatorial 4-hydroxypipecolic acid as the major diastereomer, however the diastereomeric ratio varied with different derivatives. Quantitative yields were observed for the reduction of 4-oxopipecolic acids with aromatic rings in the 6-position as exemplified with phenyl **381** and *para*-methoxy **382** analogues. The diastereomeric ratio was moderate for the aromatic derivatives. Alkyl analogues **383** and **384** were also formed in excellent yields. Moderate stereocontrol was observed with the *iso*-butyl analogue **383**, however the small methyl-substituted 4-hydroxypipecolic acid **384** provided the lowest diastereomeric ratio. Phenethyl analogue **379** gave the highest diasteroselective bias.

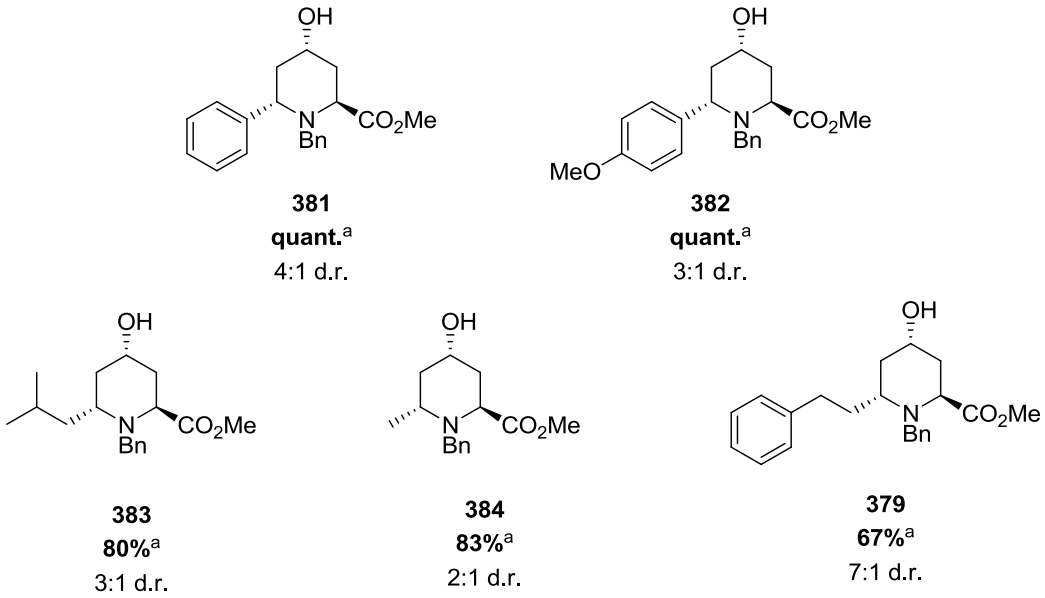


Figure 3.2 Small library of 4-hydroxypipecolic acid analogues [a]Represents overall isolated yield for both diastereomers

Overall, five examples of 4-hydroxypipecolic acid derivatives were synthesised in good to excellent yield. (4*S*)-4-Hydroxypipecolic acid was produced as the major diastereomer in moderate to good diastereomeric ratio. The diastereomers can be readily separated using column chromatography to yield diastereomerically pure samples of 4-hydroxypipecolic acid.

3.4.1 Rationale for the Observed Stereochemical Outcome of the Reduction

Nucleophilic attack on cyclohexanes and cyclohexanones are important organic reactions and therefore extensive research has been carried out in order to elucidate the mechanism and postulate viable transition states. Similar theories and reasoning can be applied to nucleophilic attack on saturated heterocyclic compounds. Taking into account previous findings, a hypothesis is presented for the observed stereochemical outcome for the reduction of 4-oxopipecolic acid to (4*S*)-4-hydroxypipecolic acid.

As mentioned previously, (4*S*)-4-hydroxypipecolic acid is formed as the major product from the sodium borohydride reduction. There are several contributing factors that may determine the stereochemical outcome of the reaction. Nucleophilic attack on a carbonyl group will occur *via* the Bürgi-Dunitz trajectory to maximise orbital overlap with the nucleophile HOMO and the carbonyl *anti*-bonding orbital and minimise repulsive interactions with the filled bonding orbital of

the carbonyl.[143] The combination of these factors results in the direction of nucleophilic attack on the carbonyl at an obtuse, 109° angle.[144] Obscuring the favourable Bürgi-Dunitz angle of attack by means of steric hindrance can reduce the rate of addition and potentially alter the stereochemical outcome.

In cyclic systems, the Bürgi-Dunitz angle restricts the direction of attack of the incoming nucleophile. The nucleophile can approach a cyclic ketone in an axial manner, despite strain caused by 1,3-diaxial interactions (Figure 3.3). Alternatively, the nucleophile can approach equatorial, parallel to adjacent 1,3-diaxial hydrogens. Several features such as the size of nucleophile and ring substituents impact the direction of attack.

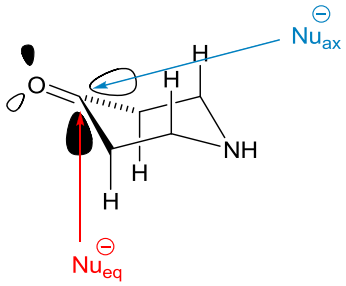
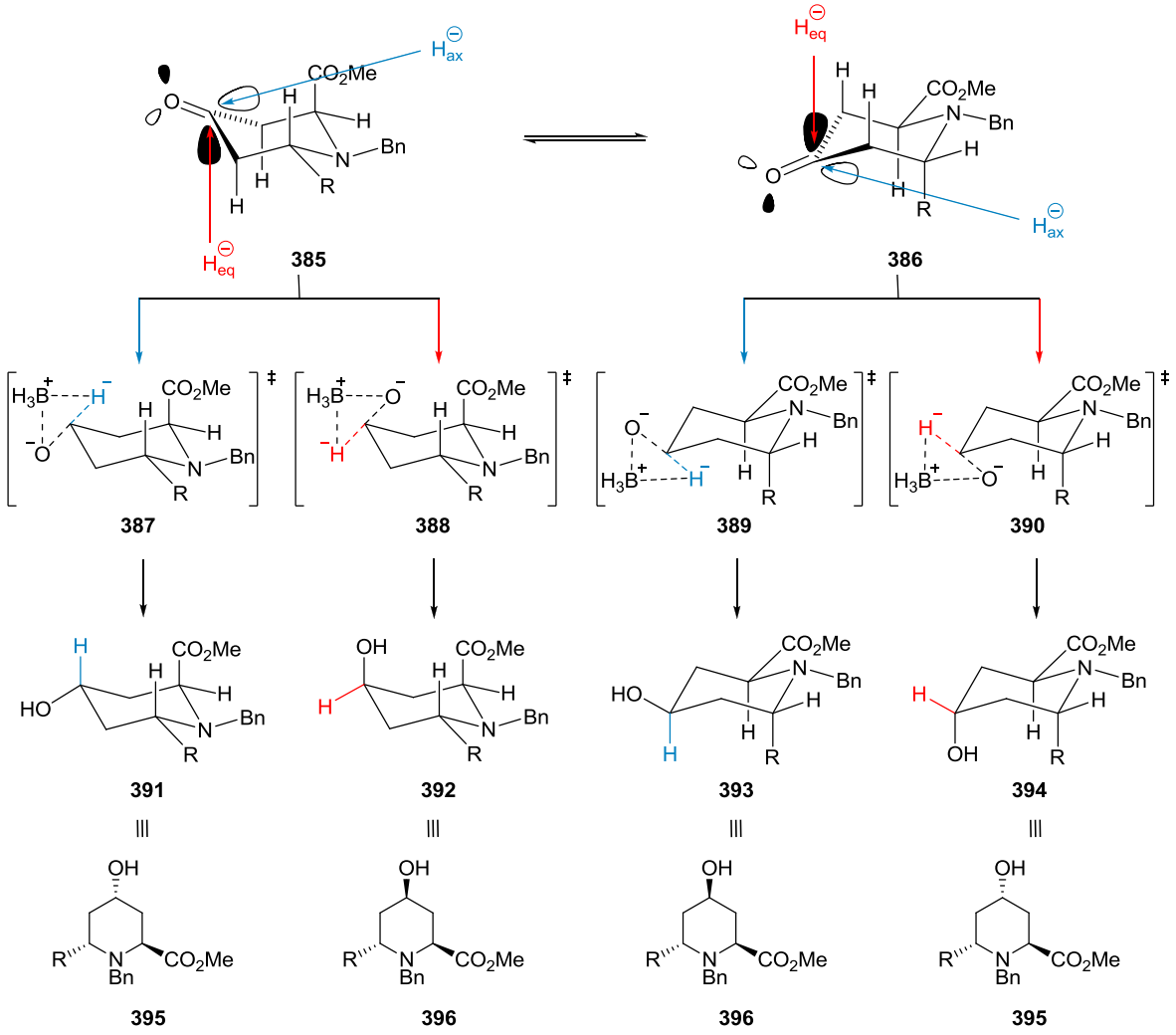


Figure 3.3 Angle of attack on an *N*-heterocyclic ketone (certain hydrogen atoms have been omitted for clarity)

Small reducing agents such as sodium borohydride are known to reduce piperidones with an axial trajectory.[65,93,142,145] A combination of postulated stereoelectronic factors influence the borohydride attack.[146] Small nucleophiles have an inherent preference for axial attack, however as mentioned previously, this approach encounters unfavourable 1,3-diaxial steric hindrance. Preferential axial attack occurs because the transition state is more stable with the small hydride axial and the larger hydroxyl group equatorial. The energetically favourable transition state leads to the more stable product.

The results from the diastereoselective reduction of 4-oxopipecolic acid demonstrate that axial hydride attack occurs to give the anticipated equatorial 4-hydroxypipecolic acid as the major product. It is postulated that *anti*-4-oxopipecolic acid **385** will mainly exist with methyl ester axial and the larger R group equatorial (Scheme 3.10). Axial hydride attack will give rise to hypothesised transition state **387** to yield the equatorially hydroxylated product **391** equivalent to (4*S*)-4-hydroxypipecolic acid **395**. Analysis of the results from the small library of 4-hydroxypipecolic acids reveals that a large 6-substituent as in phenethyl 4-oxopipecolic acid

derivative **362** will provide high levels of stereocontrol (7:1 d.r.), presumably due to the preference for the large R group to reside equatorial. Medium-sized substituents as with phenyl **364**, *para*-methoxyphenyl **365** and *iso*-butyl **367** analogues allow moderate diastereocontrol. The small methyl derivative **368** produced the poorest diastereoselective discrimination. This can be rationalised as the conformation of methyl derivative **368** can presumably easily alternate between conformations **385** and **386** due to the similar size of *C*-2 and *C*-6 substituents. Consequently, axial hydride attack on conformation **386** will generate equatorial hydroxyl product **393** *via* transition state **389**. Coupled with axial attack on conformation **385** results in a low 2:1 diastereomeric ratio obtained with methyl analogue **368** to give (4*S*)- and (4*R*)-4-hydroxypipecolic acids.



Scheme 3.10 Postulated mechanism and transition states for a diastereoselective reduction of 4-oxopipecolic acid derivatives (certain hydrogen atoms have been omitted for clarity)

To explain the anomaly observed with the L-Selectride® reduction of phenethyl derivative **362**, examination of the postulated transition states was carried out. In contrast with small reducing agents, bulky reductants tend to prefer an equatorial line of attack on cyclic ketones. The less sterically hindered equatorial approach parallel to axial hydrogens avoids the disfavoured 1,3-diaxial strain associated with axial attack. It was postulated that equatorial attack of L-Selectride® on conformation **385** *via* transition state **388** would yield axial hydroxyl product **396**. Instead, equatorial product **395** was observed. There is literature precedent for L-Selectride® reduction of pipecolic acid derivatives to yield the products of axial reduction.[58,147] The reasons for this anomaly however are not known for certain.

Using previous examples of cyclic ketone reductions, a hypothesis is presented to rationalise the experimentally observed results. Further investigation and computational analysis would be required to confirm the postulated mechanism, which gives rise to the relative stereochemical outcome.

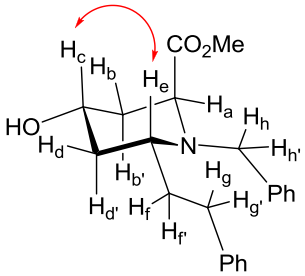
3.4.2 Relative Stereochemistry

The diastereoselective one-pot reductive amination/cyclisation strategy, then subsequent reduction of the ketone establishes three stereogenic centres on the piperidine ring system. Elucidation of the relative stereochemistry was required for the major diastereomeric product. To confirm the relative stereochemistry of the pipecolic acid derivatives, nuclear Overhauser experiments (nOe) were carried out to determine the spacial relationships within the 4-hydroxypipecolic acid analogues.

Determination of the relative 2,6-configuration of 4-oxopipecolic acid derivatives **362**, **364**-**370** was not possible directly using nOe spectroscopy because enhancements through quadrupolar nuclei such as nitrogen atoms are not easily observed. If no enhancement was detected, the *anti*-configuration could not be confirmed as quadrupolar relaxation may have affected the result. An unambiguous result could be obtained by irradiation of the three stereogenic centres of 4-hydroxypipecolic acid derivatives **379**, **381**, **383** and **384** to establish their relationship to one another.

Phenethyl derivative **379** was irradiated at stereogenic centre H_a to determine the spacial orientation relative to H_c and H_e. No enhancement was observed with either of the other stereogenic centres which implies they have an *anti*-relationship to one another (Figure 3.4). This

was confirmed using ^{1}H NMR spectroscopic coupling constants (*vide infra*). Stereocentre H_c was then irradiated and an enhancement was identified with H_e indicating that H_c and H_e are on the same side of the pipecolic acid core. No enhancement was detected for signal H_a. The relative stereochemistry was confirmed by irradiating H_e to demonstrate the *syn*-relationship with H_c and *anti*-relationship to H_a.

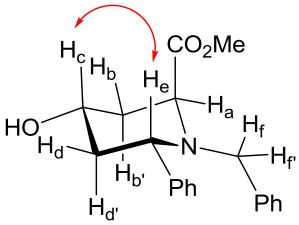


379

Saturation	% nOe
3.52 ppm (H_a)	1.4 (H_b)
	1.1 ($H_{b'}$)
	0.5 (H_h)
	0.5 ($H_{h'}$)
3.75 ppm (H_c)	1.1 (H_b)
	1.6 (H_d)
	1.2 (H_e)
3.21 ppm (H_e)	1.5 (H_c)
	2.6 (H_d/H_f)
	1.2 ($H_{f'}$)
	1.0 (H_g)

Figure 3.4 Key nOe enhancement of phenethyl derivative **379** and percentage enhancements

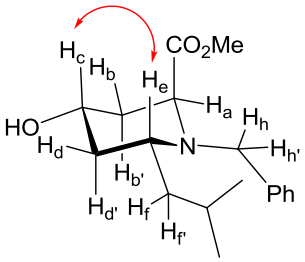
Similar nOe spectroscopic experiments were carried out on phenyl **381**, iso-butyl **383** and methyl **384** derivatives to demonstrate the H_a/H_e anti-relationship and H_c/H_e *syn*-relationship (Figure 3.5 – Figure 3.7).



381

Saturation	% nOe
3.71 ppm (H_a)	0.4 (H_b)
	0.3 ($H_{b'}$)
	1.7 (H_f)
3.96 ppm (H_c)	1.1 (OH)
	1.2 (H_b)
	1.2 (H_d)
	1.1 (H_e)
4.53 ppm (H_e)	0.8 (H_c)
	1.1 (H_d)
	0.8 (H_f)
	0.7 ($H_{f'}$)

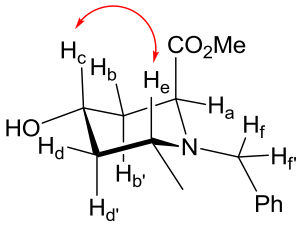
Figure 3.5 Key nOe enhancement of phenyl derivative **381** and percentage enhancements



383

Saturation	% nOe
3.60 ppm (H_a)	1.2 ($H_{b'}$)
	0.9 (H_b)
	0.6 (H_h)
3.86 ppm (H_c)	0.7 (OH)
	1.1 (H_b)
	1.1 (H_d)
	0.9 (H_e)
3.17 ppm (H_e)	0.5 (CH_3)
	0.8 (CH_3)
	1.1 (H_c)
	0.3 (H_f)

Figure 3.6 Key nOe enhancement of *iso*-butyl derivative **383** and percentage enhancements



384

Saturation	% nOe
3.60 ppm (H_a)	0.7 ($H_{b'}$)
	0.5 (H_b)
	1.9 (H_f)
3.80 ppm (H_c)	0.4 (OH)
	0.9 (H_b)
	0.8 (H_d)
	0.6 (H_e)
3.45 ppm (H_e)	1.1 (CH_3)
	0.6 (H_c)
	0.7 (H_d)
	0.3 (H_f)
	0.8 ($H_{f'}$)

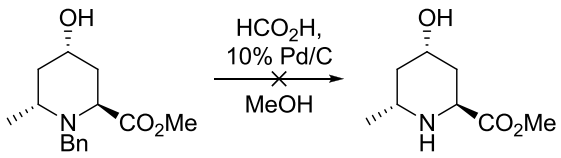
Figure 3.7 Key nOe enhancement of methyl derivative **384** and percentage enhancements

The nOe spectroscopy and ^{1}H NMR spectroscopic coupling constants clearly demonstrate the relative H_a/H_e *anti*-configuration and the H_c/H_e *syn*-arrangement of 4-hydroxypipecolic acid analogues **379**, **381**, **383** and **384**.

3.5 Deprotection of 4-Hydroxypipecolic Acid

With the relative stereochemistry of the 4-hydroxypipecolic acid derivatives established *via* nOe spectroscopy, the subsequent goal was to fully deprotect the scaffold to give the parent pipecolic acid motif. Deprotection to yield the cyclic amino acid is desirable to reveal the biological potential of the *N*-heterocycle. Liberating the amino acid would also allow subsequent synthetic modifications to the molecule.

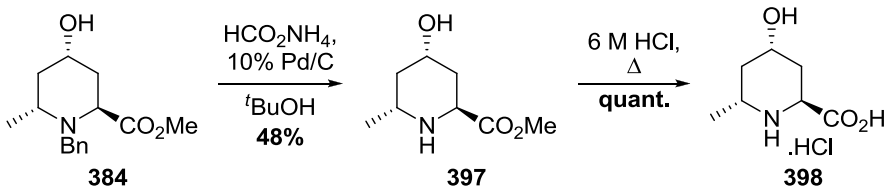
6-Methyl-4-hydroxypipecolic acid derivative **384** was employed as the model substrate. The proposed strategy was to remove the *N*-benzyl protecting group prior to ester hydrolysis. Conditions for removal of the *N*-benzyl protecting group were investigated. Standard conditions involve heterogeneous hydrogenation over palladium on carbon at high pressures. It was however desirable to avoid reactions at high pressures and avoid the use of highly flammable hydrogen gas. Consequently, transfer hydrogenation conditions were explored, which negated the need for hydrogen gas or high pressures. Initial conditions employed a mixture of formic acid and palladium on carbon (Scheme 3.11).[148] Starting material was recovered from the reaction and there was no evidence of product.



384 **397**

Scheme 3.11 Formic acid transfer hydrogenation for *N*-benzyl deprotection of 4-hydroxypipecolic acid derivative **384**

Alternative transfer hydrogenation conditions were explored using ammonium formate and palladium on carbon (Scheme 3.12). The free amine **397** was produced in a moderate 48% yield. Finally, acid-catalysed hydrolysis of the methyl ester in hydrochloric acid under reflux generated the hydrochloride salt of 6-methyl-4-hydroxypipecolic acid **398** as a white solid in quantitative yield.



Scheme 3.12 Deprotection of 6-methyl-4-hydroxypipecolic acid derivative **384**

Deprotection of 6-methyl-4-hydroxypipecolic acid derivative **384** has been demonstrated successfully using a simple transfer hydrogenation to remove the *N*-benzyl group followed by hydrolysis of the ester to yield the parent *N*-heterocyclic amino acid as a crystalline solid.

3.5.1 X-Ray Crystal Structure of 6-Methyl-4-Hydroxypipecolic Acid

The relative stereochemistry of 4-hydroxypipecolic acid analogues had been ascertained using nOe spectroscopy. It was however desirable to confirm the absolute stereochemistry of the pipecolic acid derivatives *via* X-ray crystallography. Deprotected 6-methyl-4-hydroxypipecolic acid **398** was obtained as a crystalline salt and therefore an X-ray crystal structure of this product was desirable.

Following recrystallisation to give appropriately sized crystals, X-ray crystallography was carried out to determine the absolute stereochemistry of the two new stereogenic centres. Absolute stereochemical information can be obtained as enantiomerically pure L-aspartic acid was employed as the starting material and was proven to be unaltered by chemical transformations using chiral HPLC prior to cyclisation (*vide supra*). Therefore the carboxylic acid stereogenic centre at *C*-2 is already defined. 4-Hydroxypipecolic acid **398** crystallises in the orthorhombic space group P212121. An ORTEP representation of the X-ray crystal structure obtained shows the *N*-heterocyclic core resides in a chair conformation (Figure 3.8). The *C*-2 carboxylic acid stereocentre is axial, the *C*-4 hydroxyl group is equatorial and the *C*-6 methyl stereogenic centre is also equatorial. The X-ray crystal structure has proven the stereochemistry as (2*S*,4*S*,6*R*)-6-methyl-4-hydroxypipecolic acid **398**.

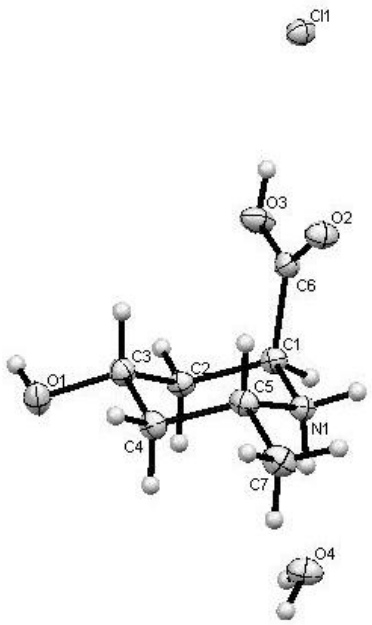


Figure 3.8 ORTEP representation of X-ray crystal structure of the hydrochloride salt of (2*S*,4*S*,6*R*)-6-methyl-4-hydroxypipecolic acid **398**

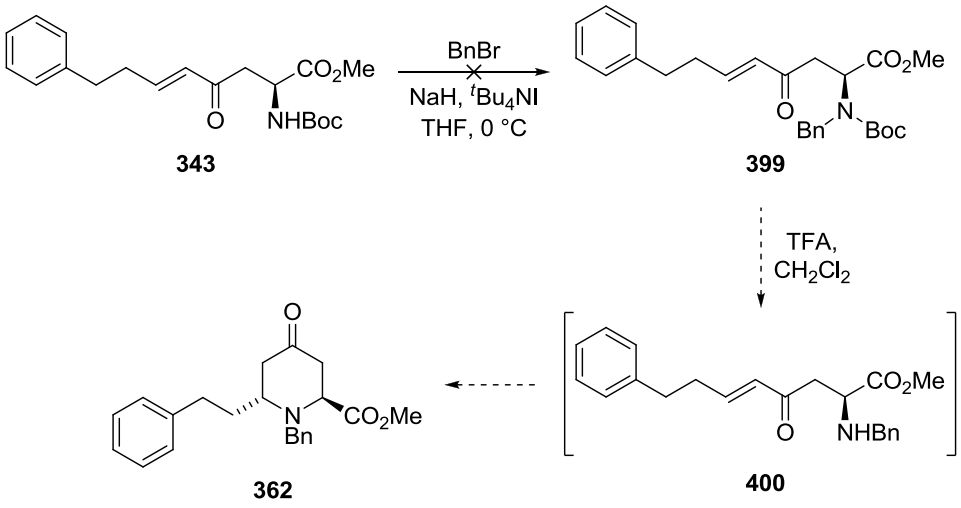
Confirmation of the relative and absolute stereochemistry of the deprotected pipecolic acid product has been demonstrated with the aid of X-ray crystallography.

3.6 Alternative Approach to 4-Oxopipecolic Acid Derivatives

A rapid approach for the synthesis of 6-substituted-4-oxopipecolic acid derivatives has been developed using a reductive amination/cyclisation strategy. The specifications for a new method to 4-oxopipecolic acid required a fast and efficient synthesis. The strategy devised is rapid, yet the yields are moderate and therefore the synthetic route is not highly efficient. Attempts to optimise the reductive amination did not improve the yield above approximately 50%. The approach is compromised because the chemoselectivity is low for reduction of the imine over the enone and therefore it was proposed to develop an alternative strategy to achieve higher yields of the cyclised product. Avoidance of reductive conditions in the presence of the enone may improve yields and therefore a strategy where the *N*-benzyl group is incorporated prior to enone formation is desirable.

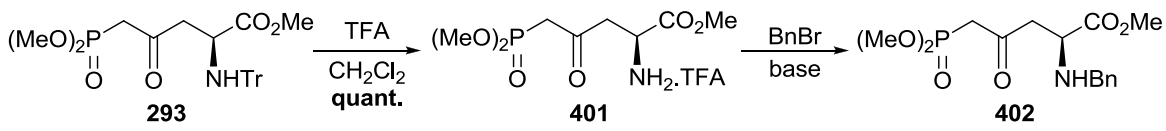
The initial strategy to probe if this hypothesis would be feasible was to alkylate Boc-protected enone derivative **343** to give orthogonally protected amine **399**, then remove the Boc group

(Scheme 3.13). It was anticipated that the *N*-benzyl enone **400** should cyclise with an improved yield of cycloadduct **362**. Alkylation of Boc-protected phenethyl analogue **343** was not possible with benzyl bromide. No product was obtained and starting material was returned, presumably due to the low nucleophilicity of the carbamate nitrogen. No further investigation of this method was carried out.



Scheme 3.13 Attempted incorporation of an *N*-benzyl group onto Boc-protected enone **343**

Attempts to incorporate the *N*-benzyl group at an earlier stage of the synthesis were also explored. Mono-*N*-benzyl protection of the phosphonate ester was investigated. Alkylation of nitrogen with benzyl bromide is prone to over-alkylation, however the reaction was explored using a limited range of conditions. Phosphonate ester **293** was deprotected with TFA to remove the trityl protecting group to give phosphonate ester **401** quantitatively (Scheme 3.14). Alkylation with benzyl bromide and mild bases was investigated, however complex, polar mixtures were obtained and no product was identified (Table 3.4).

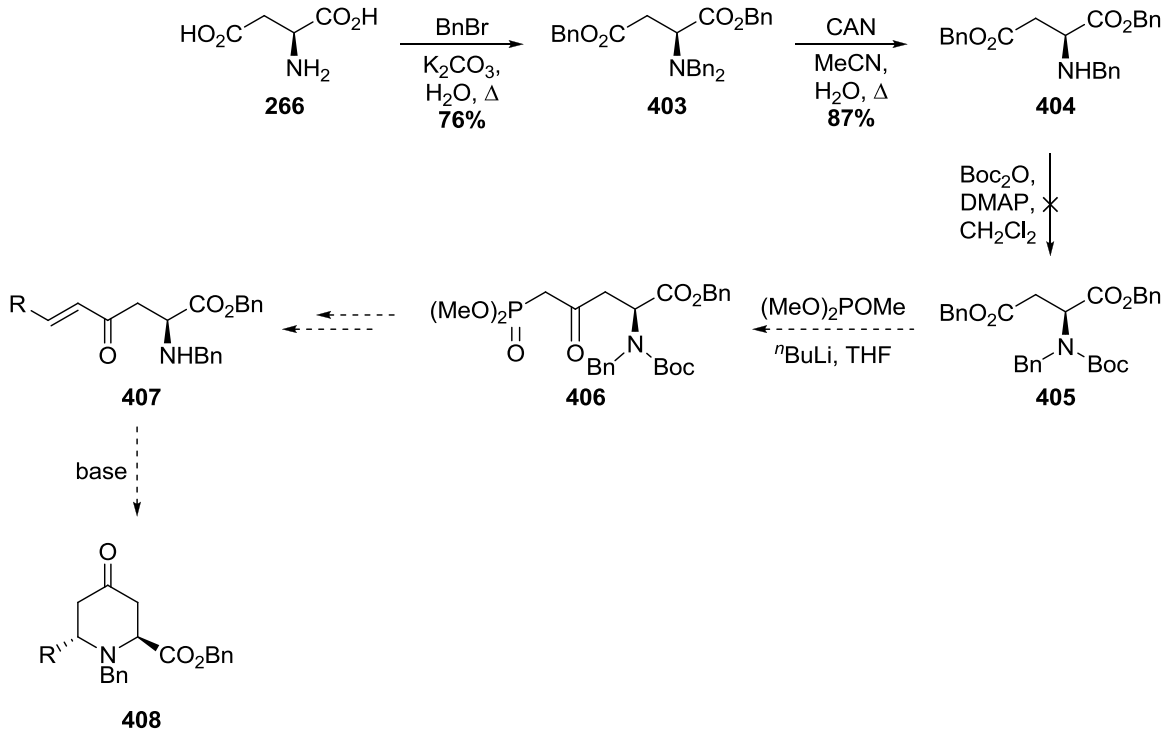


Scheme 3.14 Attempted *N*-Benzyl protection of phosphonate ester **401**

Entry	Base	Solvent	Outcome
1	K_2CO_3	MeCN	complex mixture
2	DBU	MeCN	complex mixture
3	Et_3N	CH_2Cl_2	complex mixture

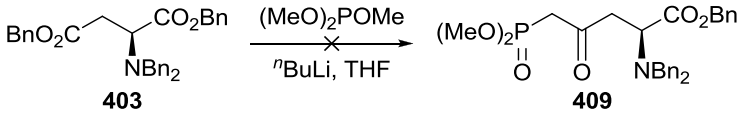
Table 3.4 Conditions for attempted *N*-benzyl protection of phosphonate ester **401**

N-Benzyl protection of the densely functionalised enone derivative **343** or phosphonate ester **401** proved unsuccessful. It was therefore proposed to install the *N*-benzyl group as the first step in the synthetic sequence. An alternative scheme was devised to fully protect L-aspartic acid **266** with benzyl groups. The approach involved reaction of excess benzyl bromide with L-aspartic acid **266** to give per-benzylated intermediate **403** in good yield (Scheme 3.15).[149] Removal of one of the *N*-benzyl groups was achieved using oxidative conditions with cerium ammonium nitrate to afford *N*-benzyl derivative **404** in excellent yield.[150] In order to achieve high regioselectivity for the subsequent phosphonate ester formation, steric bulk is required on the nitrogen, and therefore a Boc-protecting group was deemed necessary. Unfortunately, Boc-protection of intermediate **404** was not possible under standard conditions and therefore the route was terminated.



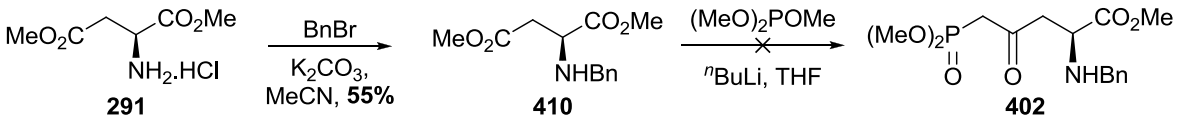
Scheme 3.15 Alternative route to 4-oxopipecolic acid derivatives

Alternatively, it was postulated that di-*N*-benzyl compound **403** would be sufficiently hindered to control the regioselectivity of phosphonate ester synthesis. Following formation of the HWE substrate **409**, removal of an *N*-benzyl group could potentially be achieved *via* the CAN oxidative conditions. *N*,*N*-Dibenzyl protected L-aspartic acid derivative **403** was subjected to the previously developed conditions for phosphonate ester synthesis, however the reaction gave inseparable complex, polar mixtures (Scheme 3.16). Possibly benzyl alcohol is not as effective a leaving group as methanol.



Scheme 3.16 Attempted synthesis of *N*,*N*-dibenzyl phosphonate ester **409**

The final attempt to arrive at a suitable *N*-benzyl protected intermediate was investigated. *O*-Benzyl L-aspartic acid derivative **403** appeared to be unsuitable for the phosphonate ester synthesis and therefore, an attempt to synthesise mono-*N*-benzyl protected bis-methyl ester aspartic acid **410** was explored. The methyl ester was anticipated to allow the phosphonate ester synthesis to occur, yet the question was whether the *N*-benzyl protecting group would induce sufficient regioselective discrimination. Previously synthesised dimethyl ester hydrochloride salt **291** was reacted with benzyl bromide in the presence of base (Scheme 3.17).[151] Both mono-*N*- and *N*,*N*-dibenzyl products were formed, however separation was feasible to give the desired mono-*N*-benzyl product **410** in a moderate 55% yield. *N*-Benzyl protected aspartic acid **410** was subjected to conditions for phosphonate ester synthesis. A complex, polar mixture resulted from the reaction, however trace quantities of a mixture of phosphonate ester regioisomers were observed by ^{1}H NMR spectroscopy. This indicated that the *N*-benzyl group did not provide adequate regioselectivity and therefore this method was no longer explored.



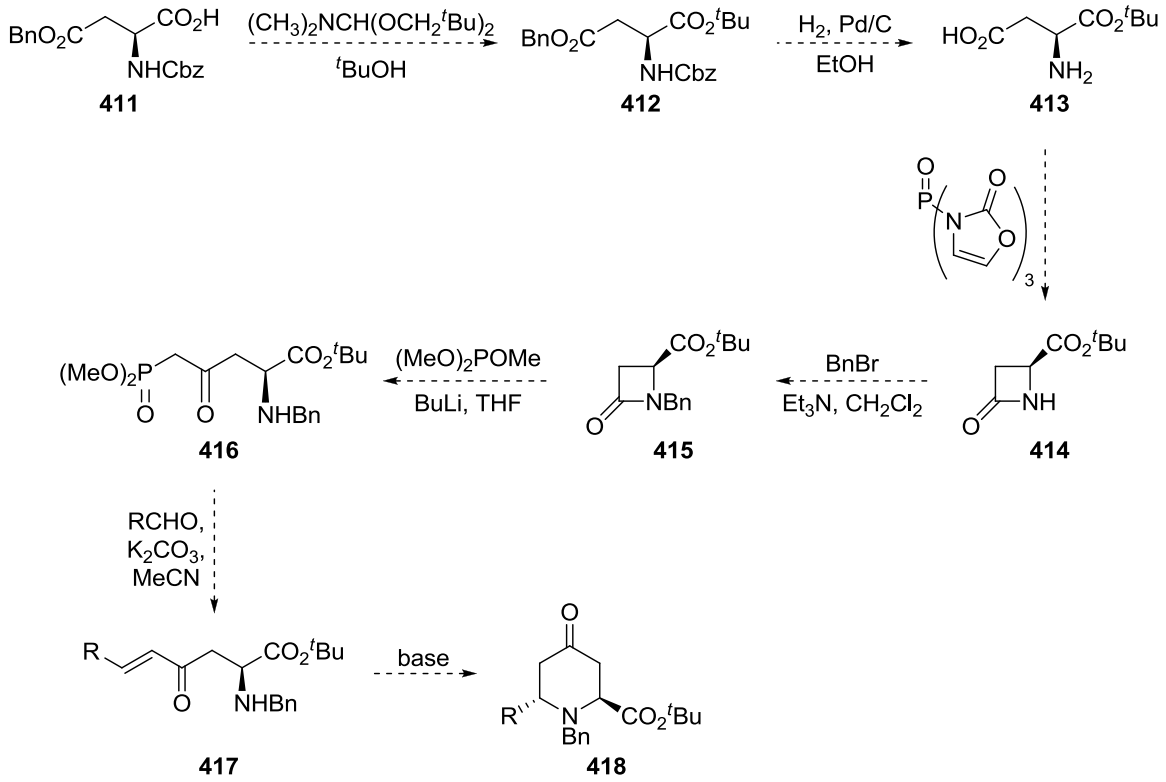
Scheme 3.17 Attempted alternative route to *N*-benzyl protected phosphonate ester **402**

Initial investigation into an alternative route to 6-substituted-4-oxopipecolic acids was unsuccessful. The goal was to incorporate the nucleophilic *N*-benzyl group in advance of the cyclisation in order to optimise the yield of pipecolic acid products. Alkylation of advanced intermediates from the synthetic scheme proved unsuccessful. Whereas, alkylation of early, simple intermediates was possible, however subsequent transformations were compromised, which prevented further progress of the synthetic route.

3.7 Future Work

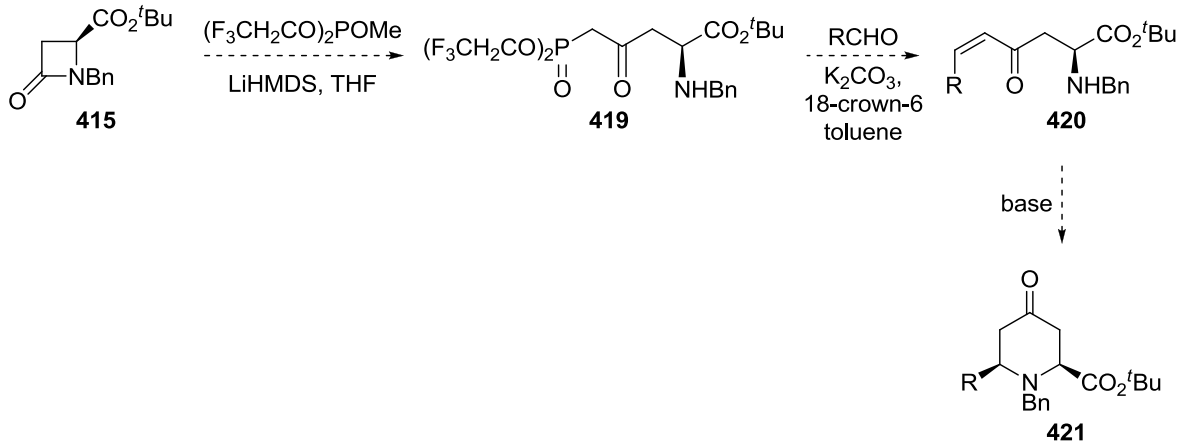
Further research into this project will focus on the development of a more efficient route to 4-oxopipecolic acids. The general principle of an intramolecular conjugate addition reaction of an enone-functionalised α-amino acid will be retained, however a different route to arrive at the unsaturated amino acids will be explored.

The proposed method will involve esterification of commercially available protected L-aspartic acid **411** to give *tert*-butyl ester **412** (Scheme 3.18). Hydrogenation of the benzyl ester and Cbz-protecting group will provide β-amino acid **413**. β-Lactam **414** will be formed *via* a dehydration reaction using tris(2-oxo-3-oxazolinyl)phosphine oxide.[152] The crucial *N*-benzyl group will then be incorporated to generate protected β-lactam **415**. Chemoselective ring-opening of the β-lactam with the anion of dimethyl methylphosphonate will be attempted. The bulky *tert*-butyl ester should allow for a selective, high yielding reaction for the formation of the HWE precursor **416**.[153] HWE reaction under the previously established conditions with a range of aldehydes, followed by base-mediated cyclisation should allow generation of 4-oxopipecolic acids in improved yields. It is feasible that the bulky *tert*-butyl ester may also enhance the diastereoselectivity of the reaction.



Scheme 3.18 Proposed improved route to 4-oxopipecolic acid analogues using an *E*-enone

If the proposed route is successful, a further modification could be made to enable access to *syn*-pipecolic acid analogues *via* the *Z*-enones. It is possible that β-lactam **415** could be chemoselectively opened with the anion of bis(2,2,2-trifluoroethyl) methylphosphonate to give phosphonate ester **419** (Scheme 3.19). Still-Gennari conditions as previously described would enable the formation of *N*-benzyl protected *Z*-enone **420**. The necessary functionality for the cyclisation reaction would already be in place and therefore cyclisation could be initiated with a mild base to potentially give rise to the *syn*-4-oxopipecolic acid diastereomer **421**. This approach would negate the need for the acidic or Lewis acid conditions for protecting group cleavage, which previously resulted in geometric isomerisation of the *Z*-enones.



Scheme 3.19 Proposed improved route to 4-oxopipecolic acid analogues using a *Z*-enone

Further work in this area would be beneficial to develop a robust and reliable method for the synthesis of both *anti*- and *syn*-substituted 4-oxopipecolic acid derivatives in high diastereomeric excess. If a complimentary, divergent route to both diastereomers was achievable, access to multiple natural products and therapeutic agents would be possible quickly and efficiently.

3.8 Summary

A fast synthetic strategy has been devised which utilises novel enone-containing α-amino acid derivatives as substrates for a one-pot reductive amination/6-*endo*-trig cyclisation reaction to afford highly sought after 6-substituted-4-oxopipecolic acid scaffolds.

Using the one-pot strategy, eight examples of 4-oxopipecolic acid analogues were synthesised in moderate yields and diastereoselectivity. The 4-oxopipecolic acid derivatives differed at the 6-position depending on the R group of the enone employed. This enables variation at a late stage in the synthetic route and therefore access to a range of analogues is possible as illustrated by the small, diverse library synthesised.

Further modifications to the 4-oxopipecolic acid motif have been demonstrated. Diastereoselective reduction of the ketone moiety led to five examples of 4-hydroxypipecolic acid analogues in excellent yields and with good diastereoselective discrimination. These are also highly desirable synthetic scaffolds within organic synthesis and medicinal chemistry.

Deprotection of the pipecolic acid scaffold was exemplified with 6-methyl-4-hydroxypipecolic acid **384**. The *N*-benzyl group was readily removed *via* transfer hydrogenation, followed by acidic ester cleavage to produce the parent *N*-heterocyclic α-amino acid **398**.

The relative and absolute stereochemistry of the analogues was proven using nOe spectroscopic analysis and X-ray crystallography of the deprotected 4-hydroxypipecolic acid salt **398** to demonstrate the relationship of the substituents around the *N*-heterocyclic core.

Following scrutiny of the devised approach, it was apparent that the objective for a highly efficient route had not been met. The route was fast, however the moderate yields could be improved. Several attempts were made to develop a route where reductive conditions were avoided. The aim was to incorporate the *N*-benzyl group, necessary for the 6-*endo*-*trig* cyclisation, at an earlier stage in the synthetic scheme. Unfortunately, an efficient, alternative method was not developed, therefore further investigation is required.

Future goals of the research include development of a more efficient strategy to 4-oxopipecolic acid. Exploration of the cyclisation of *Z*-enones is also of interest to investigate whether the opposite diastereomeric 4-oxopipecolic acid products are formed and if stereoselectively is improved. Examination of *Z*-enone cyclisation was not possible using the current route as deprotection of the *Z*-enones was previously unsuccessful.

4 Conclusions

To reiterate, the two primary objectives of the research programme were to develop a fast and efficient route to novel enone-containing α-amino acids and then to employ the enones as substrates for an intramolecular conjugate addition reaction to generate 4-oxopipecolic acid scaffolds.

There are a limited number of examples of enone-containing α-amino acids in the literature, as illustrated previously. Consideration of the positive and negative features of these synthetic routes aided the development of an optimal strategy. Utilising a naturally occurring α-amino acid as the starting material was favourable because it provided >99% enantiomeric excess. Selection of the trityl protecting group for the synthetic scheme gave superior results in terms of regioselectivity and yield for phosphonate ester formation in comparison to previously reported cases. Overall, the phenyl-substituted *E*-enone derivative **294** was synthesised in an excellent 80% yield over 4 synthetic steps making the route fast and highly efficient. The connective double bong forming strategy also enabled variation at a late stage, which was a desirable feature and allowed the production of numerous enone-functionalised α-amino acid analogues.

Conversely, there are innumerable approaches for the synthesis of pipecolic acid derivatives in the current literature. This is due to the significance of these *N*-heterocyclic compounds, and therefore extensive research has been carried out to develop efficient synthetic routes. This has proved challenging and is a contemporary problem with plenty of scope for improvement. In an attempt to provide an alternative strategy to 4-oxopipecolic acid, the novel enone-containing α-amino acids were subjected to a one-pot reductive amination/cyclisation strategy. The desired 4-oxopipecolic acid analogues were obtained in moderate yields over the one-pot, 3 step process to give the *anti*-diastereomer as the major product. Phenethyl derivative **362** was the highest yielding cycloadduct, which provided an overall 41% yield from L-aspartic over 5 synthetic steps. The one-pot cyclisation of enone-functionalised α-amino acids allows generation of these important targets in fewer steps and with higher overall yields, in comparison with several previously reported literature strategies. The diastereomeric selectivity of the reaction is not as high as other literature examples. One advantage of the route in contrast to other approaches is the ability to easily functionalise the 6-substituent of 4-oxopipecolic acid derivatives. Diversity is easily attained by variation of the R group of the enones employed in the intramolecular cyclisation.

To conclude, a facile and general approach has been developed for the synthesis of novel enone-containing α-amino acids, which have several potential applications within organic, biological and medicinal research. These compounds have also been employed as substrates for an intramolecular conjugate addition reaction to give rise to 4-oxopipecolic acid derivatives, which may serve as useful synthetic scaffolds for organic chemists or for the synthesis of novel therapeutic agents.

5 Experimental

5.1 General Considerations

Reactions were carried out in flame-dried glassware under a positive atmosphere of argon. Dry solvents were purified using a PureSolv 500 MD solvent purification system. Unless otherwise noted, reagents were commercially available and used without further purification. Brine refers to a saturated solution of sodium chloride in distilled water. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to TMS (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments, respectively. Mass spectra were obtained using a JEOL JMS-700 spectrometer. Infrared spectra were obtained neat using a Shimadzu IRPrestige-21 spectrometer. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. Chiral HPLC was performed on a Hewlett Packard Agilent 1100 Series instrument and was calibrated with the appropriate racemic mixture.

5.2 General Experimental

General Procedure 1: Horner-Wadsworth-Emmons reaction

Methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)pentanoate **293** (0.20 g, 0.40 mmol) was dissolved in acetonitrile (4.0 mL) at room temperature under argon. Anhydrous potassium carbonate (0.058 g, 0.42 mmol) was added to the solution, and then an aldehyde (0.80 mmol) was added to the suspension and heated at 50 °C until the reaction was complete by TLC. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The resultant residue was dissolved in ethyl acetate (30 mL), washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude products were purified by column chromatography on silica eluting with 20–40% diethyl ether in petroleum ether.

General Procedure 2: Still-Gennari reaction

A suspension of finely ground anhydrous potassium carbonate (0.27 g, 1.9 mmol) and 18-crown-6 (1.0 g, 3.8 mmol, recrystallised from acetonitrile) in toluene (3.0 mL) at room temperature under argon was stirred for 1 h. The suspension was cooled to −20 °C and then a solution of methyl (2*S*)-5-[bis(2,2,2-trifluoroethylphosphoryl)]-4-oxo-2-(tritylamino)pentanoate **321** (0.20 g, 0.32 mmol) in toluene (2.0 mL) was added followed by an aldehyde (0.32 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 2.5 h. The reaction was quenched with a saturated solution of ammonium chloride (20 mL), and then extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), and then concentrated *in vacuo*. The crude products were purified by column chromatography on silica eluting with 10–20% diethyl ether in petroleum ether.

General Procedure 3: Suzuki-Miyaura cross-coupling reaction

To a solution of the aldehyde (1.6 mmol) in 95:5 DMF–water (10 mL) was added a boronic acid (2.4 mmol), tetrakis(triphenylphosphine)palladium (0.94 g, 0.081 mmol) and potassium carbonate (0.56 g, 4.1 mmol). The reaction mixture was heated to 110 °C and stirred for 4 h. The solution was allowed to cool to room temperature, and then concentrated *in vacuo*. The residue was dissolved in chloroform, filtered through Celite®, and then the filtrate was concentrated *in vacuo.* The resultant residue was dissolved in diethyl ether (100 mL), washed with water (6 × 100 mL), a saturated solution of copper sulphate (3 × 100 mL), brine (2 × 100 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude products were purified by flash column chromatography on silica eluting with 10–15% ethyl acetate in petroleum ether.

General Procedure 4: Synthesis of Boc-protected enones

To a solution of the trityl protected amino acid (1.8 mmol) in dichloromethane (20 mL) at room temperature under argon was added trifluoroacetic acid (1.3 mL, 18 mmol) and the reaction mixture was stirred for 2 h. The reaction mixture was concentrated *in vacuo*, and then the residue was dissolved in water (40 mL) and washed with diethyl ether (2 × 40 mL). The aqueous layer was concentrated *in vacuo*, azeotroping with ethyl acetate–chloroform to give the TFA salts. These were dissolved in dichloromethane (18 mL) under argon and cooled to 0 °C. To the solution was added triethylamine (0.50 mL, 3.6 mmol) and di-*tert*-butyl dicarbonate (0.59 g, 2.7 mmol), and the

reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was diluted with dichloromethane (10 mL), washed with water (2 × 30 mL), brine (30 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude products were purified by column chromatography on silica eluting with 20–40% diethyl ether in petroleum ether.

General Procedure 5: Deprotection of Boc-protected enones

To a solution of Boc-protected amino methyl ester (0.25 mmol) in 1:1 methanol–water (8.0 mL) was added cesium carbonate (0.11 g, 0.33 mmol). The resultant suspension was stirred at room temperature for 48 h. The reaction mixture was concentrated *in vacuo*, the residue was dissolved in water (20 mL) and acidified to pH 1 with hydrochloric acid (1.0 M). The aqueous layer was washed with dichloromethane (3 × 20 mL) and the combined organic layers were concentrated *in vacuo*. To a solution of the resulting residue in dichloromethane (5.0 mL) was added trifluoroacetic acid (0.068 mL, 0.92 mmol) and the reaction mixture was stirred at room temperature under argon for 2 h. The reaction mixture was concentrated *in vacuo* to give the TFA salts, which were purified by recrystallisation from chloroform and methanol.

General Procedure 6: Synthesis of 6-substituted-4-oxopipecolic acid derivatives

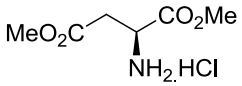
To a solution of the trityl protected enone (2.5 mmol) in dichloromethane (25 mL) at room temperature under argon was added trifluoroacetic acid (1.9 mL, 25 mmol), and the reaction mixture was stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved in water (50 mL) and washed with diethyl ether (2 × 50 mL). The aqueous layer was concentrated *in vacuo*, azeotroping with ethyl acetate–chloroform to give the TFA salts. These were dissolved in tetrahydrofuran (25 mL) at room temperature under argon. To the solution was added 4Å molecular sieves, triethylamine (0.34 mL, 2.5 mmol) and benzaldehyde (0.25 mL, 2.5 mmol) and the mixture was stirred for 2 h. The reaction mixture was filtered and then concentrated *in vacuo*. The residue was dissolved in methanol (30 mL) at room temperature under argon and sodium cyanoborohydride (0.15 g, 2.5 mmol) was added to the solution and allowed to stir for 1 h. The reaction mixture was quenched with a saturated sodium hydrogen carbonate solution (1.0 mL), and then concentrated *in vacuo*. The residue was dissolved in dichloromethane (100 mL), then washed with a saturated sodium hydrogen carbonate solution (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude products were purified by column chromatography on silica eluting with 20%–25% diethyl ether in petroleum ether.

General Procedure 7: Synthesis of 6-substituted-4-hydroxypipecolic acid derivatives

To a solution of 6-substituted-4-oxopipecolic acid (0.44 mmol) in methanol (5.0 mL) under argon at 0 °C was added sodium borohydride (0.017 g, 0.44 mmol). The reaction mixture was allowed to warm gradually to room temperature and stirred for 16 h. The reaction mixture was quenched with hydrochloric acid (1.0 M, 0.1 mL), and then concentrated *in vacuo*. The residue was dissolved in dichloromethane (20 mL), washed with a saturated sodium hydrogen carbonate solution (20 mL), brine (20 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude products were purified by column chromatography on silica eluting with 40–50% diethyl ether in petroleum ether.

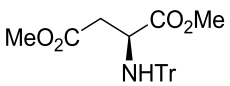
5.3 Experimental Procedures

Dimethyl (2*S*)-2-aminobutandioate hydrochloride 291[111]



To a suspension of L-aspartic acid **266** (5.0 g, 38 mmol) in methanol (100 mL) at 0 °C under argon was added dropwise thionyl chloride (3.8 mL, 53 mmol). The reaction mixture was allowed to warm to room temperature and then heated under reflux for 3 h. The solution was allowed to cool to room temperature and then concentrated *in vacuo*, azeotroping with toluene–dichloromethane to give **291** as a white solid (7.4 g, 100%). Mp 115–116 °C (lit.,[111] mp 114–115 °C); $[\alpha]_D^{24}$ +22.0 (*c* 1.0, MeOH); δ_H (400 MHz, $(CD_3)_2SO$) 2.99 (1H, dd, *J* 18.0, 5.5 Hz, 3-*H*H), 3.05 (1H, dd, *J* 18.0, 5.5 Hz, 3-H*H*), 3.66 (3H, s, OMe), 3.74 (3H, s, OMe), 4.35 (1H, t, *J* 5.5 Hz, 2-H), 8.72 (3H, br s, CHNH_3^+); δ_C (100 MHz, $(CD_3)_2SO$) 34.0 (CH_2), 48.4 (CH), 52.2 (CH_3), 53.0 (CH_3), 168.7 (C), 169.6 (C); *m/z* (CI) 162 (MH^+, 100%), 148 (5), 102 (20).

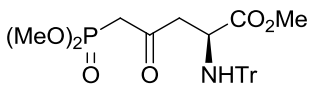
Dimethyl (2*S*)-2-(tritylamino)butandioate 292[107]



To a solution of dimethyl (2*S*)-2-aminobutandioate hydrochloride **291** (7.4 g, 38 mmol) in dichloromethane (300 mL) at 0 °C under argon was added dropwise triethylamine (11 mL, 76

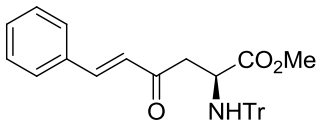
mmol) followed by triphenylmethyl chloride (13 g, 45 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The mixture was diluted with dichloromethane (50 mL), washed with citric acid (2.0 M, 300 mL), water (300 mL), brine (300 mL), dried ($MgSO_4$), and then concentrated *in vacuo* to give a colourless oil. The crude product was purified by column chromatography on silica eluting with 20% diethyl ether in petroleum ether to give **292** as a white solid (15 g, 100%). Mp 71–72 °C (lit.,[107] mp 70–71 °C); $[\alpha]_D^{24}$ +36.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.51 (1H, dd, *J* 14.7, 7.0 Hz, 3-*H*H), 2.66 (1H, dd, *J* 14.7, 5.4 Hz, 3-H*H*), 2.93 (1H, d, *J* 10.1 Hz, NH), 3.25 (3H, s, OMe), 3.65–3.74 (4H, m, 2-H and OMe), 7.15–7.20 (3H, m, ArH), 7.23–7.28 (6H, m, ArH), 7.46–7.51 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 39.0 (CH_2), 50.5 (CH_3), 50.7 (CH_3), 52.4 (CH), 69.9 (C), 125.2 (CH), 126.6 (CH), 127.5 (CH), 144.4 (C), 169.7 (C), 172.6 (C); *m/z* (EI) 403 (M^+, 1%), 326 (35), 258 (14), 243 (100), 228 (4), 192 (6), 165 (30), 160 (4), 83 (70).

Methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)pentanoate 293[107]



A solution of dimethyl methylphosphonate (3.5 mL, 33 mmol) in THF (40 mL) was cooled to −78 °C under argon. ^{n}Butyl lithium (2.5 M in hexane, 14 mL, 34 mmol) was added dropwise and the reaction mixture was stirred for 0.75 h. In a separate reaction vessel, a solution of dimethyl (2*S*)-2-(tritylamino)butandioate **292** (6.0 g, 15 mmol) in THF (100 mL) was cooled to −78 °C under argon and the dimethyl methylphosphonate/^{n}butyl lithium solution was transferred *via* cannula into the flask, and the reaction mixture stirred at −78 °C for 3 h to give a yellow solution. The reaction was quenched with a saturated solution of ammonium chloride (2.0 mL) and allowed to warm to room temperature. The mixture was concentrated *in vacuo*. The resulting residue was diluted with ethyl acetate (250 mL), washed with water (250 mL), brine (250 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 80% ethyl acetate in petroleum ether to give **293** as a white solid (6.2 g, 84%). Mp 117–118 °C (lit.,[107] mp 117–119 °C); $[\alpha]_D^{24}$ +31.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.78 (1H, dd, *J* 16.7, 6.9 Hz, 3-*H*H), 2.85–2.95 (2H, m, 3-H*H* and NH), 3.06 (2H, d, $J_{H–C–P}$ 22.7 Hz, 5-H_2), 3.29 (3H, s, OMe), 3.65–3.73 (1H, m, 2-H), 3.76 (3H, s, OMe), 3.79 (3H, s, OMe), 7.15–7.30 (9H, m, ArH), 7.44–7.51 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 41.8 (d, $J_{C–P}$ 128 Hz, CH_2), 48.7 (CH_2), 52.0 (CH_3), 52.9 (CH_3), 53.0 (CH_3), 53.1 (CH), 71.2 (C), 126.5 (CH), 127.9 (CH), 128.7 (CH), 145.6 (C), 174.0 (C), 199.2 (C); δ_P (160 MHz, $CDCl_3$) 22.3; *m/z* (CI) 496 (MH^+, 1%), 301 (5), 292 (5), 254 (90), 243 (100), 237 (55), 182 (8), 167 (45).

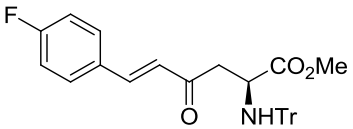
Methyl (2*S*,5*E*)-4-oxo-6-phenyl-2-(tritylamino)hex-5-enoate 294



Method A: To a solution of methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)pentanoate **293** (0.10 g, 0.20 mmol) in acetonitrile (5.0 mL) at room temperature under argon was added anhydrous lithium chloride (0.010 g, 0.24 mmol) and DBU (0.040 mL, 0.24 mmol). Benzaldehyde (0.040 g, 0.24 mmol) was added to the solution and stirred for 48 h. The reaction mixture was concentrated *in vacuo*, and then the resulting residue was dissolved in ethyl acetate (20 mL), washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 20% diethyl ether in petroleum ether to give **294** as a yellow oil (0.039 g, 42%). ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3068, 3023 (ArH), 2950 (CH), 1737 (CO), 1687 (CO), 1657, 1608 (C=C), 1492, 1448, 1205, 1174; $[\alpha]_D^{25}$ +111.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.80 (1H, dd, *J* 15.2, 7.0 Hz, 3-*H*H), 2.88–2.97 (2H, m, 3-H*H* and NH), 3.28 (3H, s, OMe), 3.79–3.89 (1H, m, 2-H), 6.69 (1H, d, *J* 16.2 Hz, 5-H), 7.10–7.31 (9H, m, ArH), 7.35–7.61 (12H, m, ArH and 6-H); δ_C (100 MHz, $CDCl_3$) 45.7 (CH_2), 48.7 (CH), 52.0 (CH_3), 71.3 (C), 126.4 (CH), 126.6 (CH), 128.0 (CH), 128.4 (CH), 128.9 (CH), 129.0 (CH), 130.7 (CH), 134.4 (C), 143.4 (CH), 145.8 (C), 174.5 (C), 197.6 (C); *m/z* (FAB) 476.2231 (MH^+. $C_{32}H_{30}NO_3$ requires 476.2226), 398 (15%), 259 (6), 243 (100), 232 (25), 166 (23), 132 (24).

Method B: Using general procedure 1 above with benzaldehyde (0.50 g, 1.0 mmol) gave **294** after 36 h as a yellow oil (0.46 g, 95%). Spectroscopic data as reported above.

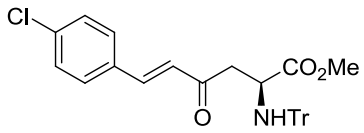
Methyl (2*S*,5*E*)-6-(4'-fluorophenyl)-4-oxo-2-(tritylamino)hex-5-enoate 303



Using general procedure 1 above with 4-fluorobenzaldehyde (0.086 mL, 0.80 mmol) gave **303** after 3 days as a yellow oil (0.14 g, 69%). ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3057, 3021 (ArH), 2950 (CH), 2922, 1738 (CO), 1686 (CO), 1658, 1612 (C=C), 1598, 1508, 1490, 1447, 1233; $[\alpha]_D^{25}$ +128.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.78 (1H, dd, *J* 15.2, 7.0 Hz, 3-*H*H), 2.87–2.95 (2H, m, 3-H*H* and NH), 3.28 (3H, s, OMe), 3.78–3.85 (1H, m, 2-H), 6.61 (1H, d, *J* 16.3 Hz, 5-H), 6.96–7.35 (11H, m, ArH),

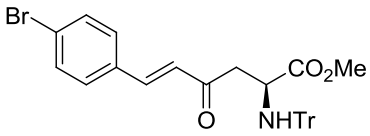
7.44 (1H, d, *J* 16.3 Hz, 6-H), 7.47–7.59 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 44.9 (CH_2), 51.1 (CH_3), 52.9 (CH), 70.4 (C), 115.3 (d, $J_{C–C–F}$ 22.1 Hz, CH), 125.1 (CH), 127.0 (CH), 127.2 (CH), 128.2 (CH), 129.4 (CH), 129.7 (C), 141.1 (CH), 144.8 (C), 163.2 (d, $J_{C–F}$ 251.5 Hz, C), 173.6 (C), 196.4 (C); *m/z* (FAB) 494.2128 (MH^+. $C_{32}H_{29}FNO_3$ requires 494.2131), 416 (31%), 258 (6), 243 (100), 166 (34), 150 (35).

Methyl (2*S*,5*E*)-6-(4'-chlorophenyl)-4-oxo-2-(tritylamino)hex-5-enoate 304



Using general procedure 1 above with 4-chlorobenzaldehyde (0.11 g, 0.40 mmol) gave **304** after 2 days as a white solid (0.16 g, 77%). Mp 121–122 °C; ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3056, 3021 (ArH), 2950 (CH), 1737 (CO), 1687, 1658 (CO), 1608 (C=C), 1592, 1490, 1447, 1205, 1174, 1090; $[\alpha]_D^{25}$ +144.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.77 (1H, dd, *J* 15.2, 6.9 Hz, 3-*H*H), 2.86–2.93 (2H, m, 3-H*H* and NH), 3.29 (3H, s, OMe), 3.75–3.82 (1H, m, 2-H), 6.65 (1H, d, *J* 16.2 Hz, 5-H), 7.11–7.30 (10H, m, ArH and 6-H), 7.33–7.57 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 44.7 (CH_2), 50.9 (CH_3), 52.6 (CH), 70.2 (C), 125.4 (CH), 125.6 (CH), 127.0 (CH), 128.0 (CH), 128.4 (CH), 128.7 (CH), 132.2 (C), 135.4 (C), 140.6 (C), 144.9 (CH), 173.3 (C), 196.2 (C); *m/z* (FAB) 510.1847 (MH^+. $C_{32}H_{29}{}^{35}ClNO_3$ requires 510.1836), 432 (11%), 267 (17), 243 (100), 166 (19).

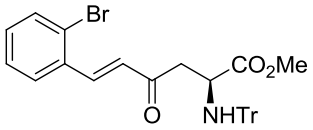
Methyl (2*S*,5*E*)-6-(4'-bromophenyl)-4-oxo-2-(tritylamino)hex-5-enoate 305



Using general procedure 1 above with 4-bromobenzaldehyde (0.37 g, 2.0 mmol) gave **305** after 2 days as a white solid (0.54 g, 96%). Mp 134–135 °C; ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3084, 3057, 3021 (ArH), 2950 (CH), 1737 (CO), 1687, 1659 (CO), 1608 (C=C), 1586, 1488, 1447, 1215, 1173, 1071; $[\alpha]_D^{27}$ +64.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.77 (1H, dd, *J* 15.2, 7.0 Hz, 3-*H*H), 2.86–2.95 (2H, m, 3-H*H* and NH), 3.29 (3H, s, OMe), 3.75–3.83 (1H, m, 2-H), 6.66 (1H, d, *J* 16.2 Hz, 5-H), 7.10–7.20 (10H, m, ArH and 6-H), 7.35–7.57 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 45.8 (CH_2), 51.9 (CH_3), 53.7 (CH), 71.2 (C), 124.9 (C), 126.2 (CH), 126.5 (CH), 127.9 (CH), 129.0 (CH), 129.7 (CH), 132.2 (CH),

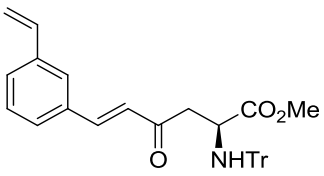
133.3 (C), 141.7 (C), 145.7 (CH), 174.3 (C), 197.2 (C); *m/z* (FAB) 554.1332 (MH^+. $C_{32}H_{29}{}^{79}BrNO_3$ requires 554.1331), 478 (16%), 476 (16), 378 (3), 312 (13), 310 (12), 243 (100), 209 (16), 166 (43).

Methyl (2*S*,5*E*)-6-(2'-bromophenyl)-4-oxo-2-(tritylamino)hex-5-enoate 306



Using general procedure 1 above with 2-bromobenzaldehyde (0.093 mL, 0.80 mmol) gave **306** after 24 h as a yellow oil (0.16 g, 70%). ν_{max}/cm^{-1} (NaCl) 3321 (NH), 3058, 3021 (ArH), 2950 (CH), 1737 (CO), 1691 (CO), 1662 (C=C), 1605, 1490, 1465, 1447, 1437, 1204, 1173, 1027; $[\alpha]_D{}^{25}$ +48.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 15.4, 6.8 Hz, 3-*H*H), 2.88–2.97 (2H, m, NH and 3-H*H*), 3.30 (3H, s, OMe), 3.78–3.83 (1H, m, 2-H), 6.60 (1H, d, *J* 16.2 Hz, 5-H), 7.13–7.33 (11H, m, ArH), 7.48–7.53 (6H, m, ArH), 7.59 (2H, td, *J* 8.0, 1.1 Hz, ArH), 7.85 (1H, d, *J* 16.2 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 45.3 (CH_2), 52.1 (CH_3), 53.8 (CH), 71.3 (C), 125.9 (C), 126.6 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.9 (CH), 129.1 (CH), 131.6 (CH), 133.6 (CH), 134.4 (C), 141.7 (CH), 145.8 (C), 174.4 (C), 197.5 (C); *m/z* (FAB) 554.1322 (MH^+. $C_{32}H_{29}{}^{79}BrNO_3$ requires 554.1331), 478 (7%), 476 (7), 312 (13), 310 (13), 243 (100), 209 (7), 165 (19).

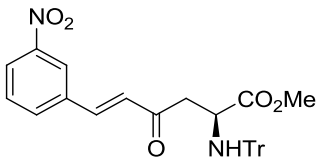
Methyl (2*S*,5*E*)-4-oxo-2-(tritylamino)-6-(3'-vinylphenyl)hex-5-enoate 307



Using general procedure 1 above with 3-vinylbenzaldehyde (0.10 g, 0.80 mmol) gave **307** after 4 days as a yellow oil (0.11 g, 56%). ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3086, 3057, 3020 (ArH), 2950 (CH), 2922, 1737 (CO), 1658 (CO), 1609 (C=C), 1490, 1447, 1215, 1172; $[\alpha]_D{}^{27}$ +52.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.79 (1H, dd, *J* 15.1, 7.0 Hz, 3-*H*H), 2.89–2.96 (2H, m, 3-H*H* and NH), 3.27 (3H, s, OMe), 3.76–3.85 (1H, m, 2-H), 5.31 (1H, d, *J* 10.9 Hz, 8'-*H*H), 5.79 (1H, d, *J* 17.6 Hz, 8'-H*H*), 6.66–6.76 (2H, m, 7'-H and 5-H), 7.13–7.28 (9H, m, ArH), 7.31–7.55 (11H, m, Ar and 6-H); δ_C (100 MHz, $CDCl_3$) 45.8 (CH_2), 52.0 (CH_3), 53.9 (CH), 71.3 (C), 115.1 (CH_2), 126.3 (CH), 126.7 (CH), 126.8 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 129.1 (CH), 129.2 (CH), 134.7 (C), 136.1 (CH), 138.4 (C), 143.2

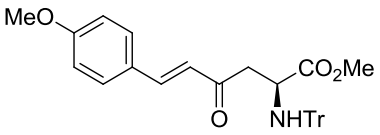
(CH), 145.8 (C), 174.5 (C), 197.5 (C); *m/z* (FAB) 502.2388 (MH^+. $C_{34}H_{32}NO_3$ requires 502.2382), 424 (45%), 258 (72), 243 (100), 166 (83), 158 (77).

Methyl (2*S*,5*E*)-6-(3'-nitrophenyl)-4-oxo-2-(tritylamino)hex-5-enoate 308



Using general procedure 1 above with 3-nitrobenzaldehyde (0.12 g, 0.80 mmol) gave **308** after 5 days as a yellow solid (0.12 g, 56%). Mp 61–62 °C; ν_{max}/cm^{-1} (NaCl) 3322 (NH), 3058, 3022 (ArH), 2951 (CH), 1737 (CO), 1663 (CO), 1613 (C=C), 1530 (NO_2), 1447, 1352 (NO_2); $[\alpha]_D^{27}$ +49.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.79 (1H, dd, *J* 15.4, 7.0 Hz, 3-*H*H), 2.88–2.98 (2H, m, 3-H*H* and NH), 3.32 (3H, s, OMe), 3.77–3.85 (1H, m, 2-H), 6.79 (1H, d, *J* 16.2 Hz, 5-H), 7.10–7.31 (9H, m, ArH), 7.41–7.62 (8H, m, ArH and 6-H), 7.81 (1H, d, *J* 8.0 Hz, ArH), 8.24 (1H, d, *J* 8.0 Hz, ArH), 8.37 (1H, s, ArH); δ_C (100 MHz, $CDCl_3$) 46.2 (CH_2), 52.1 (CH_3), 53.8 (CH), 71.3 (C), 122.6 (CH), 124.8 (CH), 126.9 (CH), 127.8 (CH), 128.6 (CH), 128.8 (CH), 130.1 (CH), 133.9 (CH), 136.2 (C), 140.1 (CH), 145.7 (C), 148.8 (C), 174.3 (C), 196.9 (C); *m/z* (FAB) 521.2074 (MH^+. $C_{32}H_{29}N_2O_5$ requires 521.2076), 443 (63%), 277 (31), 243 (100), 184 (44), 166 (79).

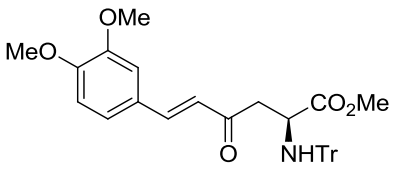
Methyl (2*S*,5*E*)-6-(4'-methoxyphenyl)-4-oxo-2-(tritylamino)hex-5-enoate 309



Using general procedure 1 above with 4-methoxybenzaldehyde (0.25 g, 2.0 mmol) gave **309** as a colourless oil (0.32 g, 66%). ν_{max}/cm^{-1} (neat) 3320 (NH), 3057, 3021 (ArH), 2951 (CH), 2839, 1736 (CO), 1682 (CO), 1653, 1595 (C=C), 1510, 1447, 1252, 1171, 1028; $[\alpha]_D^{23}$ +54.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.78 (1H, dd, *J* 15.0, 7.0 Hz, 3-*H*H), 2.84–2.99 (2H, m, 3-H*H* and NH), 3.27 (3H, s, OMe), 3.71–3.93 (4H, m, 2-H and OMe), 6.59 (1H, d, *J* 16.1 Hz, 5-H), 6.92 (2H, d, *J* 8.7 Hz, ArH), 7.11–7.35 (9H, m, ArH), 7.39–7.59 (9H, m, 6-H and ArH); δ_C (100 MHz, $CDCl_3$) 45.7 (CH_2), 52.0 (CH_3), 54.0 (CH), 55.4 (CH_3), 71.3 (C), 114.5 (CH), 124.3 (CH), 126.6 (CH), 127.1 (C), 128.0 (CH),

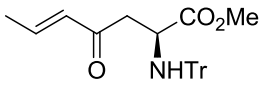
128.9 (CH), 130.2 (CH), 143.2 (CH), 145.9 (C), 161.8 (C), 174.6 (C), 197.5 (C); *m/z* (FAB) 506.2329 (MH^+. $C_{33}H_{32}NO_4$ requires 506.2331), 428 (5%), 262 (11), 243 (100), 162 (18), 86 (5).

Methyl (2*S*,5*E*)-6-(3',4'-dimethoxyphenyl)-4-oxo-2-(tritylamino)hex-5-enoate 310



Using general procedure 1 above with 3,4-dimethoxybenzaldehyde (0.13 g, 0.80 mmol) gave **310** after 10 days as a yellow solid (0.081 g, 38%). Mp 55–56 °C; ν_{max} (NaCl)/cm^{-1} 3320 (NH), 3057, 3020 (ArH), 2951 (CH), 2839, 1736 (CO), 1652 (CO), 1595 (C=C), 1513, 1464, 1448, 1265, 1161, 1140, 1025; $[\alpha]_D^{24}$ +64.7 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.79 (1H, dd, *J* 15.1, 7.1 Hz, 3-*H*H), 2.88–2.97 (2H, m, 3-H*H* and NH), 3.26 (3H, s, OMe), 3.77–3.83 (1H, m, 2-H), 3.91–3.95 (6H, m, 2 × OMe), 6.58 (1H, d, *J* 16.2 Hz, 5-H), 6.88 (1H, d, *J* 8.3 Hz, ArH), 6.98–7.35 (10H, m, ArH), 7.39–7.54 (8H, m, ArH and 6-H); δ_C (100 MHz, $CDCl_3$) 44.5 (CH_2), 50.8 (CH), 52.8 (CH_3), 54.8 (CH_3), 54.9 (CH_3), 70.2 (C), 108.6 (CH), 110.0 (CH), 122.2 (CH), 123.4 (CH), 125.4 (CH), 126.2 (C), 126.8 (CH), 127.7 (CH), 142.4 (C), 144.7 (CH), 148.2 (C), 150.4 (C), 173.4 (C), 196.3 (C); *m/z* (FAB) 558.2260 (MNa^+. $C_{34}H_{33}NO_5$ requires 558.2256), 537 (2%), 459 (9), 292 (19), 243 (100), 192 (35), 166 (19).

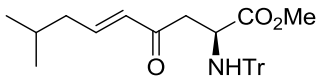
Methyl (2*S*,5*E*)-4-oxo-2-(tritylamino)hept-5-enoate 311



To a solution of methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)pentanoate **293** (1.0 g, 2.0 mmol) in acetonitrile (20 mL) at room temperature under argon in a Schlenk tube, was added anhydrous potassium carbonate (0.29 g, 2.1 mmol) and acetaldehyde (0.34 mL, 6.1 mmol). The sealed tube was heated to 40 °C and stirred for 4 days. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (60 mL), washed with water (60 mL), brine (60 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 15% diethyl ether in petroleum ether to give **311** as a colourless oil (0.65 g, 78%). ν_{max}/cm^{-1} (neat) 3320 (NH), 3058, 3022 (ArH), 2360, 1735 (CO), 1668 (CO), 1629 (C=C), 1490, 1448, 1435, 1215, 1172;

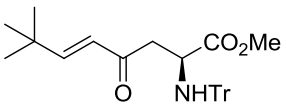
$[\alpha]_D^{25}$ +17.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.89 (3H, dd, *J* 6.8, 1.6 Hz, CH_3), 2.66 (1H, dd, *J* 15.4, 6.1 Hz, 3-*H*H), 2.79 (1H, dd, *J* 15.4, 6.1 Hz, 3-H*H*), 2.85 (1H, d, *J* 10.0 Hz, NH), 3.26 (3H, s, OMe), 3.63–3.79 (1H, m, 2-H), 6.07 (1H, dq, *J* 15.8, 1.6 Hz, 5-H), 6.77 (1H, dq, *J* 15.8, 6.8 Hz, 6-H), 7.10–7.34 (9H, m, ArH), 7.40–7.54 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 18.4 (CH_3), 45.0 (CH_2), 52.0 (CH_3), 53.6 (CH), 71.2 (C), 126.5 (CH), 128.1 (CH), 128.8 (CH), 132.2 (CH), 143.7 (CH), 145.8 (C), 174.6 (C), 197.5 (C); *m/z* (FAB) 414.2068 (MH^+. $C_{27}H_{28}NO_3$ requires 414.2069), 336 (22%), 243 (100), 170 (32), 165 (14), 104 (1), 70 (10).

Methyl (2*S*,5*E*)-8-methyl-4-oxo-2-(tritylamino)non-5-enoate 312



Using general procedure 1 above with 3-methylbutyraldehyde (0.22 mL, 2.0 mmol) gave **312** as a colourless oil (0.26 g, 57%). ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3058, 3021 (ArH), 2954 (CH), 2927, 1739 (CO), 1692, 1669 (CO), 1626 (C=C), 1491, 1465, 1448, 1435, 1207, 1172; $[\alpha]_D^{18}$ +18.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.91 (6H, d, *J* 6.7 Hz, 2 × CH_3), 1.69–1.80 (1H, m, 8-H), 2.08 (2H, td, *J* 7.4, 1.3 Hz, 7-H_2), 2.63 (1H, dd, *J* 15.4, 7.1 Hz, 3-H*H*), 2.78 (1H, dd, J 15.4, 5.2 Hz, 3-*H*H), 2.84 (1H, d, *J* 10.0 Hz, NH), 3.27 (3H, s, OMe), 3.62–3.78 (1H, m, 2-H), 6.02 (1H, dt, *J* 15.9, 1.3 Hz, 5-H), 6.71 (1H, dt, *J* 15.9, 7.4 Hz, 6-H), 7.11–7.32 (9H, m, ArH), 7.40–7.55 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 22.5 (CH_3), 27.9 (CH), 41.8 (CH_2), 44.9 (CH_2), 52.0 (CH), 53.7 (CH_3), 71.3 (C), 126.6 (CH), 128.0 (CH), 128.9 (CH), 131.7 (CH), 145.9 (C), 147.5 (CH), 174.6 (C), 197.8 (C); *m/z* (FAB) 478.2359 (MNa^+. $C_{30}H_{33}NO_3Na$ requires 478.2358), 378 (12%), 243 (100), 213 (8), 166 (17), 134 (1), 113 (4), 75 (11).

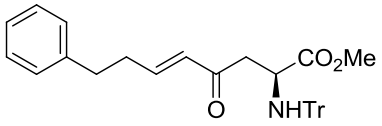
Methyl (2*S*,5*E*)-6-*tert*-butyl-4-oxo-2-(tritylamino)oct-5-enoate 313



To a solution of methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)pentanoate **293** (1.0 g, 2.0 mmol) in acetonitrile (20 mL) at room temperature under argon was added anhydrous potassium carbonate (0.29 g, 2.1 mmol) and trimethylacetaldehyde (0.66 mL, 6.1 mmol). The reaction mixture was heated under reflux for 5 days. The mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The resultant residue was dissolved in ethyl acetate

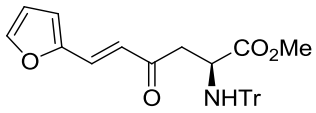
(60 mL), washed with water (60 mL), brine (60 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 20% diethyl ether in petroleum ether to give **313** as a yellow oil (0.10 g, 11%). ν_{max} (neat)/cm^{-1} 3320 (NH), 3021 (ArH), 2963, 2361, 1736 (CO), 1665 (CO), 1622 (C=C), 1490, 1448, 1215, 1203, 1171; $[\alpha]_D^{26}$ +10.8 (*c* 0.5 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.07 (9H, s, ^{t}Bu), 2.66 (1H, dd, *J* 15.4, 7.0 Hz, 3-*H*H), 2.73–3.01 (2H, m, 3-H*H* and NH), 3.27 (3H, s, OMe), 3.59–3.82 (1H, m, 2-H), 5.96 (1H, d, *J* 16.2 Hz, 5-H), 6.73 (1H, d, *J* 16.2 Hz, 6-H), 7.11–7.34 (9H, m, ArH), 7.41–7.59 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 28.7 (CH_3), 33.9 (C), 45.0 (CH_2), 51.9 (CH_3), 53.7 (CH), 71.3 (C), 125.8 (CH), 126.5 (CH), 127.9 (CH), 128.8 (CH), 145.8 (C), 158.0 (CH), 174.6 (C), 198.4 (C); *m/z* (FAB) 456.2384 (MH^+. $C_{26}H_{34}NO_6$ requires 456.2386), 378 (79%), 243 (100), 212 (71), 165 (47), 111 (66), 56 (55), 29 (56).

Methyl (2*S*,5*E*)-4-oxo-8-phenyl-2-(tritylamino)oct-5-enoate 314



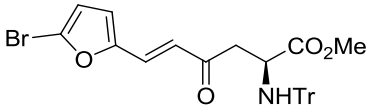
Using general procedure 1 above with 3-phenylpropionaldehyde (0.16 mL, 1.2 mmol) gave **314** after 2 days as a colourless oil (0.29 g, 93%). ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3084, 3059, 3027 (ArH), 2948 (CH), 2924, 1738 (CO), 1667 (CO), 1626, 1597 (C=C), 1492, 1448, 1205, 1173; $[\alpha]_D^{27}$ +26.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.39–3.01 (7H, m, 3-H_2, 7-H_2, 8-H_2 and NH), 3.25 (3H, s, OMe), 3.58–3.83 (1H, m, 2-H), 6.06 (1H, d, *J* 15.9 Hz, 5-H), 6.76 (1H, dt, *J* 15.9, 7.1 Hz, 6-H), 7.06–7.34 (12H, m, ArH), 7.40–7.54 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 32.4 (CH_2), 32.6 (CH_2), 43.2 (CH_2), 50.1 (CH_3), 51.9 (CH), 69.5 (C), 124.5 (CH), 125.0 (CH), 126.1 (CH), 126.6 (CH), 126.7 (CH), 127.0 (CH), 129.2 (CH), 138.9 (C), 144.0 (C), 145.3 (CH), 172.7 (C), 195.8 (C); *m/z* (FAB) 504.2534 (MH^+. $C_{34}H_{34}NO_3$ requires 504.2539), 426 (69%), 378 (2), 366 (1), 266 (6), 252 (78), 243 (100), 241 (27), 166 (78), 160 (38), 93 (31).

Methyl (2*S*,5*E*)-6-furan-2-yl-4-oxo-2-(tritylamino)hex-5-enoate 315



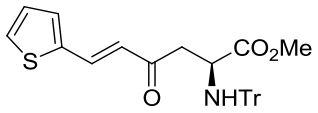
Using general procedure 1 above with 2-furaldehyde (0.10 mL, 1.2 mmol) gave **315** after 2 days as a yellow oil (0.23 g, 81%). ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3058 (NH), 2951 (ArH), 1737 (CO), 1607 (C=C), 1552, 1491, 1447, 1267, 1203, 1018; $[\alpha]_D^{23}$ +42.9 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.72 (1H, dd, *J* 15.1, 7.0 Hz, 3-*H*H), 2.82–2.94 (2H, m, 3-H*H* and NH), 3.27 (3H, s, OMe), 3.68–3.84 (1H, m, 2-H), 6.40–6.75 (3H, m, 5-H and ArH), 7.10–7.54 (17H, m, 6-H and ArH); δ_C (100 MHz, $CDCl_3$) 46.2 (CH_2), 52.0 (CH_3), 53.9 (CH), 71.3 (C), 112.7 (CH), 116.2 (CH), 123.6 (CH), 126.6 (CH), 128.0 (CH), 128.6 (CH), 129.8 (CH), 145.2 (CH), 145.8 (C), 151.0 (C), 174.5 (C), 197.1 (C); *m/z* (FAB) 488.1833 (MNa^+. $C_{30}H_{27}NO_4$ requires 488.1838), 388 (7%), 352 (3), 243 (100), 241 (5), 166 (18), 123 (7).

Methyl (2*S*,5*E*)-6-(5-bromofuran-2-yl)-4-oxo-2-(tritylamino)hex-5-enoate 316



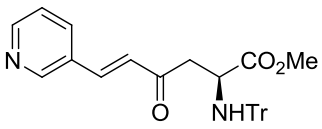
Using general procedure 1 above with 5-bromo-2-furaldehyde (0.14 g, 0.80 mmol) gave **316** after 5 days as a brown oil (0.15 g, 67%). ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3058, 2952 (CH), 1739 (CO), 1606 (C=C), 1552, 1492, 1469, 1447, 1358, 1208, 1017, 970; $[\alpha]_D^{24}$ +91.3 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.71 (1H, dd, *J* 15.0, 6.8 Hz, 3-*H*H), 2.87–3.04 (2H, m, 3-H*H* and NH), 3.27 (3H, s, OMe), 3.65–3.86 (1H, m, 2-H), 6.41 (1H, d, *J* 3.2 Hz, ArH), 6.52–6.66 (2H, m, ArH and 5-H), 7.08–7.32 (10H, m, ArH and 6-H), 7.43–7.54 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 45.4 (CH_2), 50.8 (CH_3), 52.7 (CH), 70.1 (C), 113.4 (CH), 116.9 (CH), 122.5 (CH), 124.8 (C), 125.4 (CH), 126.8 (CH), 126.9 (CH), 127.6 (CH), 144.6 (C), 151.7 (C), 173.2 (C), 195.6 (C); *m/z* (FAB) 544.1118 (MH^+. $C_{30}H_{27}{}^{79}BrNO_4$ requires 544.1123), 468 (4%), 466 (4), 413 (1), 378 (1), 302 (11), 243 (100), 241 (9), 198 (13), 166 (32), 107 (2), 85 (2).

Methyl (2*S*,5*E*)-4-oxo-6-thiophen-2-yl-2-(tritylamino)hex-5-enoate 317



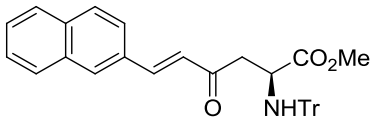
Using general procedure 1 above with 2-thiophenecarboxaldehyde (0.075 mL, 0.80 mmol) gave **317** after 7 days as a light brown oil (0.14 g, 71%). ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3058, 2949 (ArH), 1737 (CO), 1653 (CO), 1595 (C=C), 1490, 1447, 1263, 1200, 1030; $[\alpha]_D^{25}$ +52.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.65 (1H, dd, *J* 15.0, 6.9 Hz, 3-*H*H), 2.71–2.91 (2H, m, 3-H*H* and NH), 3.19 (3H, s, OMe), 3.60–3.78 (1H, m, 2-H), 6.42 (1H, d, *J* 15.8 Hz, 5-H), 6.96 (1H, dd, *J* 5.1, 3.7 Hz, 4'-H), 7.04–7.21 (10H, m, ArH and 3'-H), 7.29 (1H, d, *J* 5.1 Hz, 5'-H), 7.36–7.49 (6H, m, ArH), 7.51 (1H, d, *J* 15.8 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 44.7 (CH_2), 50.8 (CH_3), 52.7 (CH), 70.1 (C), 123.9 (CH), 125.5 (CH), 127.0 (CH), 127.2 (CH), 127.6 (CH), 127.9 (CH), 130.7 (CH), 134.5 (CH), 138.6 (C), 144.6 (C), 173.2 (C), 195.8 (C); *m/z* (FAB) 482.1793 (MH^+. $C_{30}H_{28}NO_3S$ requires 482.1790), 404 (12%), 307 (8), 289 (11), 258 (9), 243 (100), 228 (13), 193 (10), 165 (53), 155 (32), 107 (23), 77 (36), 51 (17).

Methyl (2*S*,5*E*)-4-oxo-6-pyridin-3-yl-2-(tritylamino)hex-5-enoate 318



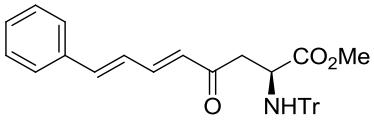
Using general procedure 1 above with 3-pyridinecarboxaldehyde (0.075 mL, 0.80 mmol) gave **318** after 24 hours as an orange oil (0.17 g, 87%). ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3056, 2949 (CH), 1737 (CO), 1691, 1662 (CO), 1612 (C=C), 1490, 1447, 1415, 1203, 1025; $[\alpha]_D$ +54.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.78 (1H, dd, *J* 15.4, 7.0 Hz, 3-*H*H), 2.84–2.30 (2H, m, 3-H*H* and NH), 3.31 (3H, s, OMe), 3.69–3.88 (1H, m, 2-H), 6.73 (1H, d, *J* 16.1 Hz, 5-H), 7.10–7.3 (9H, m, ArH), 7.34 (1H, dd, *J* 7.9, 4.7 Hz, ArH), 7.44 (1H, d, *J* 16.1 Hz, 6-H), 7.46–7.59 (6H, m, ArH), 7.83 (1H, d, *J* 7.9 Hz, ArH), 8.63 (1H, d, *J* 4.7 Hz, ArH), 8.74 (1H, s, ArH); δ_C (100 MHz, $CDCl_3$) 45.9 (CH_2), 52.1 (CH_3), 53.7 (CH), 71.3 (C), 123.9 (CH), 126.6 (CH), 127.8 (CH), 128.8 (CH), 130.2 (C), 134.4 (CH), 139.4 (CH), 145.8 (C), 151.2 (CH), 151.7 (CH), 174.4 (C), 197.0 (C); *m/z* (FAB) 477.2180 (MH^+. $C_{31}H_{29}N_2O_3$ requires 477.2178), 399 (12%), 243 (100), 233 (14), 215 (5), 165 (21), 132 (11), 104 (4), 83 (20).

Methyl (2*S*,5*E*)-6-naphthalen-2-yl-4-oxo-2-(tritylamino)hex-5-enoate 319



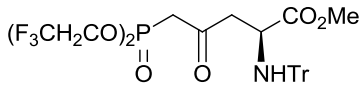
Using general procedure 1 above with 2-naphthaldehyde (0.13 g, 0.80 mmol) gave **319** after 2 days as a yellow solid (0.16 g, 78%). Mp 62–63 °C; ν_{max}/cm^{-1} (NaCl) 3321 (NH), 3055, 3021 (ArH), 2982 (CH), 1734 (CO), 1655 (CO), 1604 (C=C), 1593, 1489, 1447, 1198, 1172, 1159; $[\alpha]_D^{24}$ +64.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.84 (1H, dd, *J* 15.1, 7.0 Hz, 3-*H*H), 2.89–3.02 (2H, m, 3-H*H* and NH), 3.29 (3H, s, OMe), 3.78–3.87 (1H, m, 2-H), 6.80 (1H, d, *J* 16.2 Hz, 5-H), 7.12–7.33 (9H, m, ArH), 7.48–7.70 (10H, m, ArH and 6-H), 7.78–7.98 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 45.9 (CH_2), 52.1 (CH_3), 54.0 (CH), 71.4 (C), 123.6 (CH), 126.6 (CH), 126.6 (CH), 126.9 (CH), 127.6 (CH), 128.0 (CH), 128.0 (CH), 128.2 (CH), 128.7 (CH), 128.9 (CH), 130.7 (CH), 132.0 (C), 133.4 (C), 134.5 (C), 143.5 (CH), 145.9 (C), 174.6 (C), 197.6 (C); *m/z* (FAB) 526.2388 (MH^+. $C_{36}H_{32}NO_3$ requires 526.2382), 448 (7%), 289 (7), 273 (11), 243 (100), 242 (14), 181 (19), 165 (24), 152 (17), 107 (12), 77 (19).

Methyl (2*S*,5*E*,7*E*)-4-oxo-8-phenyl-2-(tritylamino)octa-5,7-dienoate 320



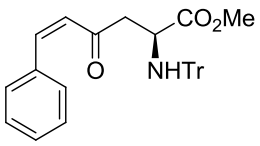
Using general procedure 1 above with *trans*-cinnamaldehyde (0.10 mL, 0.80 mmol) gave **320** after 5 days as a yellow solid (0.084 g, 42%). Mp 66–67 °C; ν_{max}/cm^{-1} (NaCl) 3322 (NH), 3083, 3058, 3024 (ArH), 2950 (CH), 2925, 1737 (CO), 1655 (CO), 1619 (C=C), 1586, 1491, 1448, 1215, 1173; $[\alpha]_D^{27}$ +64.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.72 (1H, dd, *J* 15.0, 7.0 Hz, 3-*H*H), 2.83–2.93 (2H, m, 3-H*H* and NH), 3.26 (3H, s, OMe), 3.64–3.84 (1H, m, 2-H), 6.22 (1H, d, *J* 15.5 Hz, 5-H), 6.86 (1H, dd, *J* 15.5, 10.2 Hz, 7-H), 6.94 (1H, d, *J* 15.5 Hz, 8-H) 7.09–7.40 (13H, m, ArH), 7.42–7.59 (8H, m, ArH and 6-H); δ_C (100 MHz, $CDCl_3$) 45.6 (CH_2), 52.0 (CH_3), 53.9 (CH), 71.3 (C), 126.5 (CH), 126.7 (CH), 127.3 (CH), 127.9 (CH), 128.8 (CH), 128.9 (CH), 129.4 (CH), 129.8 (CH), 136.0 (C), 141.8 (CH), 143.5 (CH), 145.8 (C), 174.5 (C), 197.6 (C); *m/z* (FAB) 502.2387 (MH^+. $C_{34}H_{32}NO_3$ requires 502.2382), 424 (21%), 258 (22), 243 (100), 194 (17), 166 (91), 158 (55), 129 (13), 106 (9).

Methyl (2*S*)-5-[bis(2,2,2-trifluoroethyl)phosphoryl]-4-oxo-2-(tritylamino)pentanoate 321



A solution of bis(2,2,2-trifluoroethyl) methylphosphonate (0.92 mL, 5.5 mmol) in tetrahydrofuran (15 mL) under argon was cooled to −100 °C. To the solution was added lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 6.0 mL, 6.0 mmol) and stirred for 0.5 h. A solution of dimethyl (2*S*)-2-(tritylamino)butandioate **292** (1.0 g, 2.5 mmol) in tetrahydrofuran (10 mL) was added to the bis(2,2,2-trifluoroethyl) methylphosphonate/lithium bis(trimethylsilyl)amide solution and stirred for 2 h. The reaction mixture was quenched with a saturated solution of ammonium chloride (0.5 mL) and allowed to warm to room temperature. The mixture was diluted with brine (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 50% diethyl ether in petroleum ether to give **321** as a colourless oil (1.3 g, 81%). ν_{max}/cm^{-1} (neat) 3320 (NH), 3020 (ArH), 2360, 2342, 2333, 1720 (CO), 1491, 1449, 1294 (P=O), 1261, 1169, 1069, 1029 (P–O); $[\alpha]_D^{26}$ +15.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.59 (1H, dd, *J* 16.4, 7.0 Hz, 3-*H*H), 2.71 (1H, dd, *J* 16.4, 4.4 Hz, 3-H*H*), 2.98 (1H, br s, NH), 3.17 (2H, d, $J_{H\text{-}C\text{-}P}$ 16.4 Hz, 5-H_2), 3.36 (3H, s, OMe), 3.59–3.85 (1H, m, 2H), 4.29–4.53 (4H, m, 2 × O*C*H_2CF_3), 7.12–7.33 (9H, m, ArH), 7.38–7.57 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 41.8 (d, $J_{C\text{-}P}$ 138.9 Hz, CH_2), 48.7 (CH_2), 52.2 (CH_3), 52.9 (CH), 62.4 (q, $J_{C\text{-}C\text{-}F}$ 6.0 Hz, CH_2), 71.3 (C), 122.5 (q, $J_{C\text{-}F}$ 277.3 Hz, C), 126.7 (CH), 128.0 (CH), 128.7 (CH), 145.5 (C), 173.8 (C), 198.8 (C); δ_P (160 MHz, $CDCl_3$) 23.2.

Methyl (2*S*,5*Z*)-4-oxo-6-phenyl-2-(tritylamino)hex-5-enoate 322

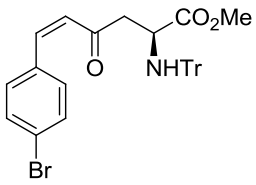


Method A: A solution of methyl (2*S*)-5-[bis(2,2,2-trifluoroethyl)phosphoryl]-4-oxo-2-(tritylamino)pentanoate **321** (0.20 g, 0.32 mmol) in tetrahydrofuran (6.0 mL) under argon was cooled to −78 °C. To the solution was added 18-crown-6 (0.42 g, 1.6 mmol, recrystallised from acetonitrile), potassium bis(trimethylsilyl)amide solution (0.5 M in toluene, 0.64 mL, 0.32 mmol) and benzaldehyde (0.032 mL, 0.32 mmol). The reaction mixture was stirred at −78 °C for 48 h. The

mixture was diluted with a saturated solution of ammonium chloride (20 mL), extracted with diethyl ether (3 × 20 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 15% diethyl ether in petroleum ether to give **322** as a yellow oil (0.12 g, 76%). ν_{max}/cm^{-1} (neat) 3320 (NH), 3021 (ArH), 1735 (CO), 1686 (CO), 1596 (C=C), 1492, 1448, 1216, 1173; $[\alpha]_D^{25}$ +54.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.63 (1H, dd, *J* 15.6, 7.0 Hz, 3-*H*H), 2.73 (1H, dd, *J* 15.6, 4.8 Hz, 3-H*H*), 2.89 (1H, br s, NH), 3.24 (3H, s, OMe), 3.56–3.88 (1H, m, 2-H), 6.10 (1H, d, *J* 12.8 Hz, 5-H), 6.80 (1H, d, *J* 12.8 Hz, 6-H), 7.09–7.68 (20H, m, ArH); δ_C (100 MHz, $CDCl_3$) 48.7 (CH_2), 51.9 (CH), 53.5 (CH_3), 71.3 (C), 126.5 (CH), 127.9 (CH), 128.3 (CH), 128.8 (CH), 129.5 (CH), 129.8 (CH), 130.7 (CH), 135.1 (C), 140.6 (CH), 145.8 (C), 174.4 (C), 199.7 (C); *m/z* (CI) 234.1131 (MH^+–Tr. $C_{13}H_{15}NO_3$ requires 234.1130), 318 (1%), 301 (4), 285 (3), 257 (3), 243 (98), 219 (12), 182 (8), 167 (48), 147 (13), 133 (2), 113 (5), 85 (15).

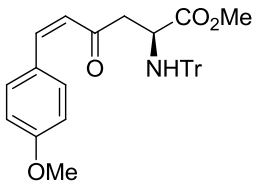
Method B: Using general procedure 2 above with benzaldehyde (0.20 g, 0.32 mmol) gave **322** as a yellow oil (0.14 g, 91%). Spectroscopic data as reported above.

Methyl (2*S*,5*Z*)-6-(4'-bromophenyl)-4-oxo-2-(tritylamino)hex-5-enoate 323



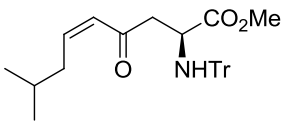
Using general procedure 2 above with 4-bromobenzaldehyde (0.089 g, 0.48 mmol) gave **323** as a yellow oil (0.21 g, 78%). ν_{max}/cm^{-1} (neat) 3320 (NH), 3057, 3020 (ArH), 2360, 2343, 2331, 1733 (CO), 1690, 1663 (CO), 1597 (C=C), 1486, 1448, 1213, 1172; $[\alpha]_D^{25}$ +52.4 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.61 (1H, dd, *J* 15.8, 7.0 Hz, 3-*H*H), 2.73 (1H, dd, *J* 15.8, 4.8 Hz, 3-H*H*), 2.90 (1H, br d, *J* 9.6 Hz, NH), 3.26 (3H, s, OMe), 3.58–3.86 (1H, m, 2-H), 6.13 (1H, d, *J* 12.8 Hz, 5-H), 6.68 (1H, d, *J* 12.8 Hz, 6-H), 7.10–7.31 (9H, m, ArH), 7.35–7.58 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 48.8 (CH_2), 52.0 (CH_3), 53.5 (CH), 71.3 (C), 123.8 (C), 126.6 (CH), 127.9 (CH), 128.2 (CH), 128.8 (CH), 131.5 (CH), 131.6 (CH), 133.8 (C), 139.6 (CH), 145.7 (C), 174.3 (C), 199.0 (C); *m/z* (CI) 312.0227 (MH^+–Tr. $C_{13}H_{15}{}^{79}BrNO_3$ requires 312.0235), 299 (7%), 297 (7), 285 (3), 258 (2), 243 (98), 219 (7), 167 (67), 147 (6), 113 (8), 85 (33).

Methyl (2*S*,5*Z*)-6-(4'-methoxyphenyl)-4-oxo-2-(tritylamino)hex-5-enoate 324



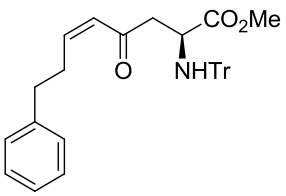
Using general procedure 2 above with 4-methoxybenzaldehyde (0.058 mL, 0.48 mmol) gave **324** as a yellow oil (0.17 g, 70%). ν_{max}/cm^{-1} (neat) 3320 (NH), 3057, 3020 (ArH), 1732 (CO), 1681, 1649 (CO), 1588 (C=C), 1560, 1510, 1490, 1448, 1256, 1214, 1172; $[\alpha]_D^{25}$ +69.6 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.65 (1H, dd, *J* 15.4, 6.8 Hz, 3-*H*H), 2.77 (1H, dd, *J* 15.4, 5.0 Hz, 3-H*H*), 2.88 (1H, br d, *J* 10.0 Hz, NH), 3.25 (3H, s, OMe), 3.65–3.91 (4H, m, 2-H and OMe), 6.02 (1H, d, *J* 12.8 Hz, 5-H), 6.70 (1H, d, *J* 12.8 Hz, 6-H), 6.86 (2H, d, *J* 8.7 Hz, ArH), 7.07–7.33 (9H, m, ArH), 7.38–7.59 (6H, m, ArH), 7.72 (2H, d, *J* 8.7 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 49.0 (CH_2), 51.9 (CH), 53.7 (CH_3), 55.3 (CH_3), 71.3 (C), 113.6 (CH), 125.1 (CH), 126.5 (CH), 127.7 (CH), 127.9 (C), 128.8 (CH), 132.5 (CH), 141.6 (CH), 145.8 (C), 160.9 (C), 174.6 (C), 198.8 (C); *m/z* (CI) 264.1237 (MH^+–Tr. $C_{14}H_{18}NO_4$ requires 264.1236), 243 (99%), 214 (2), 177 (16), 167 (69), 137 (3), 121 (5), 97 (17).

Methyl (2*S*,5*Z*)-8-methyl-4-oxo-2-(tritylamino)non-5-enoate 325



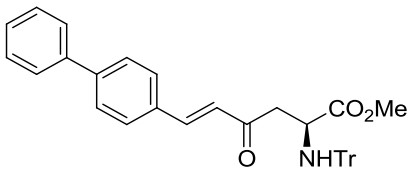
Using general procedure 2 above with 3-methylbutyraldehyde (0.085 mL, 0.79 mmol) gave **325** as a colourless oil (0.30 g, 83%). ν_{max}/cm^{-1} (neat) 3320 (NH), 3057, 3021 (ArH), 2956, 2927 (CH), 2870, 2360, 2341, 2333, 1734 (CO), 1689 (CO), 1613, 1597 (C=C), 1490, 1447, 1216, 1172; $[\alpha]_D^{25}$ +40.5 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 3.0 Hz, 9-H_3), 0.92 (3H, d, *J* 3.0 Hz, 8-CH_3), 1.64–1.77 (1H, m, 8-H), 2.43–2.63 (3H, m, 3-*H*H and 7-H_2), 2.71 (1H, dd, *J* 15.6, 5.0 Hz, 3-H*H*), 2.87 (1H, d, *J* 7.3 Hz, NH), 3.28 (3H, s, OMe), 3.62–3.79 (1H, m, 2-H), 6.04–6.15 (2H, m, 5-H and 6-H), 7.11–7.36 (9H, m, ArH), 7.40–7.57 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_3), 28.7 (CH), 38.3 (CH_2), 49.1 (CH_2), 51.9 (CH), 53.4 (CH_3), 71.3 (C), 126.6 (CH), 127.3 (CH), 128.0 (CH), 128.6 (CH), 145.8 (C), 148.6 (CH), 174.6 (C), 198.5 (C); *m/z* (CI) 214.1447 (MH^+–Tr. $C_{11}H_{20}NO_3$ requires 214.1443), 344 (1%), 312 (3), 301 (5), 285 (3), 270 (5), 243 (98), 197 (8), 167 (61), 154 (3), 127 (3), 97 (5), 81 (15).

Methyl (2*S*,5*Z*)-4-oxo-8-phenyl-2-(tritylamino)oct-5-enoate 326



Using general procedure 2 above with 3-phenylpropionaldehyde (0.11 g, 0.79 mmol) gave **326** as a colourless oil (0.38 g, 74%). ν_{max}/cm^{-1} (neat) 3320 (NH), 3086, 3061, 3024 (ArH), 2950, 2926 (CH), 2920, 2360, 2331, 1735 (CO), 1686 (CO), 1604, 1491, 1449, 1216, 1174; $[\alpha]_D^{25}$ +36.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.52 (1H, dd, *J* 15.5, 7.0 Hz, 3-*H*H), 2.61–3.01 (6H, m, 3-H*H*, 7-H_2, 8-H_2 and NH), 3.26 (3H, s, OMe), 3.62–3.77 (1H, m, 2-H), 6.01–6.15 (2H, m, 5-H and 6-H), 7.04–7.35 (14H, m, ArH), 7.41–7.54 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 31.1 (CH_2), 34.6 (CH_2), 49.1 (CH_2), 52.0 (CH_3), 53.5 (CH), 71.3 (C), 126.1 (CH), 126.5 (CH), 127.1 (CH), 127.9 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 140.3 (C), 146.1 (C), 148.2 (CH), 174.6 (C), 198.4 (C); *m/z* (CI) 262.1445 (MH^+–Tr. $C_{15}H_{20}NO_3$ requires 262.1443), 357 (1%), 343 (1), 318 (3), 301 (5), 243 (98), 230 (5), 202 (4), 167 (63), 165 (2), 133 (3), 117 (4), 88 (11).

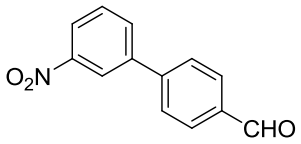
Methyl (2*S*,5*E*)-6-biphen-4-yl-4-oxo-2-(tritylamino)hex-5-enoate 328



To a solution of methyl (2*S*,5*E*)-6-(4'-bromophenyl)-4-oxo-2-(tritylamino)hex-5-enoate **305** (0.10 g, 0.18 mmol) in 5:1 toluene/methanol (12 mL) under argon at room temperature was added phenylboronic acid (0.044 g, 0.36 mmol), tetrakis(triphenylphosphine)palladium (0.010 g, 0.0090 mmol) and potassium phosphate tribasic (0.076 g, 0.36 mmol). The reaction mixture was heated to 80 °C and stirred for 24 h. The mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (20 mL), washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 20% diethyl ether in petroleum ether to give **328** as a colourless oil (0.014 g, 14%). ν_{max}/cm^{-1} (NaCl) 3313 (NH), 3083, 3057, 3029 (ArH), 2949 (CH), 1737 (CO), 1687 (CO), 1599 (C=C), 1489, 1446, 1211; $[\alpha]_D^{25}$ +27.3 (*c* 1.9, $CHCl_3$); δ_H (400

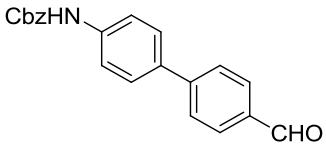
MHz, $CDCl_3$) 2.81 (1H, dd, *J* 15.1, 7.0 Hz, 3-*H*H), 2.87–2.30 (2H, m, 3-H*H* and NH), 3.75–3.87 (1H, m, 2-H), 6.73 (1H, d, *J* 16.2 Hz, 5-H), 7.13–7.72 (25H, m, ArH and 6-H); δ_C (100 MHz, $CDCl_3$) 45.8 (CH_2), 52.0 (CH_3), 53.9 (CH), 71.3 (C), 126.6 (CH), 126.6 (CH), 127.1 (CH), 127.7 (CH), 127.9 (CH), 128.2 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 133.4 (C), 140.1 (C), 142.9 (CH), 145.8 (C), 148.6 (C) 174.5 (C), 197.5 (C); *m/z* (FAB) 552.2542 (MH^+. $C_{38}H_{34}NO_3$ requires 552.2539), 474 (11%), 414 (3), 378 (2), 325 (1), 266 (4), 243 (100), 207 (38), 182 (92), 166 (73), 106 (22).

4-(3'-Nitrophenyl)benzaldehyde 331[154]



Using general procedure 3 above with 3-nitrophenylboronic acid (0.14 g, 0.81 mmol) and 4-bromobenzaldehyde (0.10 g, 0.54 mmol) gave **331** as a yellow solid (0.13 g, 100%). 4-(3'-Nitrophenyl)benzaldehyde **331** was used without further purification. δ_H (400 MHz, $CDCl_3$) 7.67 (1H, d, *J* 8.0 Hz, ArH), 7.82 (2H, d, *J* 8.0 Hz, ArH), 7.97 (1H, d, *J* 7.6 Hz, ArH), 8.04 (2H, d, *J* 8.4 Hz, ArH), 8.29 (1H, d, *J* 8.0 Hz, ArH), 8.51 (1H, s, ArH), 10.10 (1H, s, CHO). Spectroscopic data as previously reported.[154]

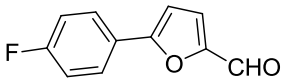
4-(4'-Benzyloxycarbonylaminophenyl)benzaldehyde 334



Using general procedure 3 above with (4-benzyloxycarbonylaminophenyl)boronic acid (0.66 g, 2.4 mmol) and 4-bromobenzaldehyde (0.30 g, 1.6 mmol) gave **334** as a white solid (0.19 g, 36%). Mp 132–133 °C; ν_{max}/cm^{-1} (neat) 3331 (NH), 3291, 3275, 1730 (CO), 1697, 1593, 1533, 1514, 1325, 1219, 1188, 1169; δ_H (400 MHz, $CDCl_3$) 5.23 (2H, s, PhCH_2), 6.81 (1H, s, NH), 7.29–7.46 (5H, m, ArH), 7.51 (2H, d, *J* 8.2 Hz, ArH), 7.60 (2H, d, *J* 8.2 Hz, ArH), 7.72 (2H, d, *J* 8.0 Hz, ArH), 7.93 (2H, d, *J* 8.0 Hz, ArH), 10.04 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 67.2 (CH_2), 119.1 (CH), 127.2 (CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 130.4 (CH), 134.5 (C), 134.9 (C), 136.0 (C), 138.5 (C),

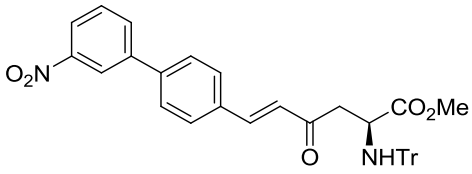
146.5 (C), 153.4 (C), 192.1 (CH); *m/z* (EI) 331.1207 (M^+. $C_{21}H_{17}NO_3$ requires 331.1208), 287 (33%), 223 (92), 222 (60), 166 (23), 139 (20), 91 (98), 83 (78).

5-(4'-Fluorophenyl)-2-furaldehyde 337[155]



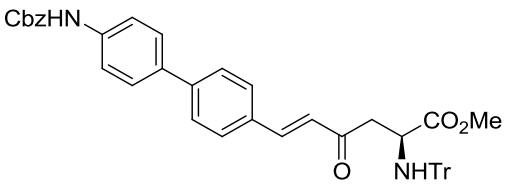
Using general procedure 3 above with 4-fluorophenylboronic acid (0.60 g, 4.3 mmol) and 5-bromo-2-furaldehyde (0.50 g, 2.9 mmol) gave **337** as a white solid (0.54 g, 99%). 5-(4'-Fluorophenyl)-2-furaldehyde **337** was used without further purification. δ_H (400 MHz, $CDCl_3$) 6.79 (1H, d, *J* 3.8 Hz, ArH), 7.13 (2H, d, *J* 8.8 Hz, ArH), 7.32 (1H, d, *J* 3.8 Hz, ArH), 7.83 (2H, d, *J* 8.8 Hz, ArH), 9.65 (1H, s, CHO). Spectroscopic data as previously reported.[155]

Methyl (2*S*,5*E*)-6-(3'-nitrobiphen-4-yl)-4-oxo-2-(tritylamino)hex-5-enoate 332



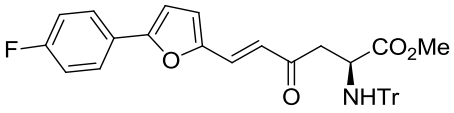
Using general procedure 1 above with 4-(3'-nitrophenyl)benzaldehyde **331** (0.37 g, 1.7 mmol) gave **332** after 3 days as an off-white foam (0.19 g, 59%). ν_{max}/cm^{-1} (neat) 3320 (NH), 3056, 3030 (ArH), 1736 (CO), 1688, 1657 (CO), 1603 (C=C), 1530, 1514, 1348, 1171; $[\alpha]_D^{23}$ +61.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 15.2, 6.9 Hz, 3-*H*H), 2.88–3.07 (2H, m, 3-H*H* and NH), 3.30 (3H, s, OMe), 3.70–3.91 (1H, m, 2-H), 6.75 (1H, d, *J* 16.2 Hz, 5-H), 7.10–7.34 (9H, m, ArH), 7.42–7.79 (12H, m, ArH and 6-H), 7.93 (1H, d, *J* 7.9 Hz, ArH), 8.23 (1H, d, *J* 7.9 Hz, ArH), 8.48 (1H, s, ArH); δ_C (100 MHz, $CDCl_3$) 45.9 (CH_2), 52.1 (CH_3), 53.8 (CH), 71.3 (C), 121.9 (CH), 122.7 (CH), 126.6 (CH), 127.0 (CH), 127.7 (CH), 128.0 (CH), 128.9 (CH), 129.2 (CH), 130.0 (CH), 132.9 (CH), 134.7 (C), 140.6 (C), 141.7 (C), 142.2 (CH), 145.8 (C), 148.8 (C), 174.5 (C), 197.4 (C); *m/z* (FAB) 597.2384 (MH^+. $C_{38}H_{33}N_2O_5$ requires 597.2389), 519 (23%), 503 (2), 419 (5), 353 (32), 266 (3), 243 (100), 194 (9), 166 (54), 129 (2).

Methyl (2*S*,5*E*)-6-(4'-benzyloxycarbonylaminobiphen-4-yl)-4-oxo-2-(tritylamino)hex-5-enoate 335



Using general procedure 1 above with 4-(4'-benzyloxycarbonylaminophenyl)benzaldehyde **334** (0.083 g, 0.25 mmol) gave **335** after 2 days as a yellow foam (0.057 g, 63%). ν_{max}/cm^{-1} (NaCl) 3333 (NH), 3058, 3031, 2951 (ArH), 2850, 1734 (CO), 1654 (CO), 1595 (C=C), 1559, 1534, 1517, 1499, 1318, 1217; $[\alpha]_D^{24}$ +62.3 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.79 (1H, dd, *J* 15.2, 7.2 Hz, 3-*H*H), 2.88–3.01 (2H, m, 3-H*H* and NH), 3.29 (3H, s, OMe), 3.69–3.90 (1H, m, 2-H), 5.23 (2H, s, PhCH_2), 6.65–6.81 (2H, m, 5-H and NH), 7.08–7.72 (29H, m, ArH and 6-H); δ_C (100 MHz, $CDCl_3$) 45.7 (CH_2), 52.0 (CH_3), 53.9 (CH), 67.2 (CH_2), 71.3 (C), 119.0 (CH), 126.1 (CH), 126.6 (CH), 127.2 (CH), 127.7 (CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 133.1 (C), 135.1 (C), 136.0 (C), 137.9 (C), 142.7 (C), 143.0 (CH), 145.8 (C), 153.3 (C), 174.6 (C), 197.6 (C); *m/z* (FAB) 701.3018 (MH^+. $C_{46}H_{41}N_2O_5$ requires 701.3015), 664 (1%), 623 (2), 530 (3), 457 (5), 419 (2), 356 (8), 313 (3), 243 (100), 166 (9), 120 (3), 86 (94).

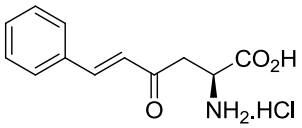
Methyl (2*S*,5*E*)-6-[5-(4'-fluorophenyl)furan-2-yl]-4-oxo-2-(tritylamino)hex-5-enoate 338



Using general procedure 1 above with 5-(4'-fluorophenyl)-2-furaldehyde **337** (0.23 g, 1.2 mmol) gave **338** after 19 h as a yellow foam (0.16 g, 73%). ν_{max}/cm^{-1} (NaCl) 3324 (NH), 3058, 3021, 2950 (CH), 1737 (CO), 1681 (CO), 1652, 1601 (C=C), 1562, 1486, 1448, 1234, 1173, 1158, 1027; $[\alpha]_D^{23}$ +63.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.77 (1H, dd, *J* 14.9, 7.0 Hz, 3-*H*H), 2.83–3.02 (2H, m, 3-H*H* and NH), 3.27 (3H, s, OMe), 3.59–3.79 (1H, m, 2-H), 6.61–6.82 (3H, m, 5-H and ArH), 7.04–7.59 (18H, m, ArH and 6-H), 7.67–7.79 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 46.3 (CH_2), 52.0 (CH_3), 54.0 (CH), 71.3 (C), 107.9 (CH), 116.1 (d, $J_{C\text{-}C\text{-}F}$ 22.1 Hz, CH), 118.8 (CH), 123.1 (CH), 126.3 (C), 126.4 (CH), 126.6 (CH), 128.0 (CH), 128.9 (CH), 129.0 (CH), 145.8 (C), 150.4 (C), 155.7 (C), 162.9 (d, $J_{C\text{-}F}$ 249.6

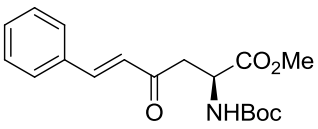
Hz, C), 174.5 (C), 196.9 (C); *m/z* (FAB) 560.2233 (MH^+. $C_{36}H_{31}FNO_4$ requires 560.2237), 498 (2%), 482 (24), 419 (4), 378 (3), 349 (2), 316 (98), 243 (100), 216 (96), 166 (71), 124 (35).

(2*S*,5*E*)-2-Amino-4-oxo-6-phenyl-hex-5-enoic acid hydrochloride 340



To a solution of methyl (2*S*,5*E*)-4-oxo-6-phenyl-2-(tritylamino)hex-5-enoate **294** (0.20 g, 0.42 mmol) in methanol (3.0 mL) was added 6.0 M hydrochloric acid (15 mL), and the reaction mixture heated under reflux for 24 h. The mixture was allowed to cool to room temperature and then extracted with diethyl ether (2 × 20 mL). The aqueous layer was concentrated *in vacuo* to give a yellow solid. The crude product was purified by column chromatography on cellulose eluting with 30:69:1 methanol/dichloromethane/acetic acid to give **340** as an off-white solid (0.034 g, 32%). Mp 151–153 °C (decomposition); $[\alpha]_D^{24}$ +35.8 (*c* 1.0, MeOH); δ_H (400 MHz, CD_3OD) 3.38–3.58 (2H, m, 3-H_2), 4.36 (1H, dd, *J* 6.6, 4.2 Hz, 2-H), 6.92 (1H, d, *J* 16.3 Hz, 5-H), 7.38–7.50 (3H, m, ArH), 7.63–7.81 (3H, m, ArH and 6-H); δ_C (100 MHz, CD_3OD) 40.7 (CH_2), 49.3 (CH), 126.0 (CH), 129.8 (CH), 130.2 (CH), 132.2 (CH), 135.6 (C), 146.2 (CH), 171.3 (C), 197.6 (C); *m/z* (CI) 220.0978 (MH^+. $C_{12}H_{14}NO_3$ requires 220.0974), 205 (98%), 203 (61), 159 (53), 147 (34), 113 (21), 97 (20), 81 (50), 69 (61).

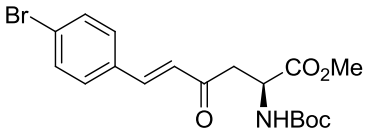
Methyl (2*S*,5*E*)-2-(*tert*-butoxycarbonylamino)-4-oxo-6-phenylhex-5-enoate 342



Using general procedure 4 above gave **342** as a colourless oil (1.4 g, 84%). ν_{max}/cm^{-1} (NaCl) 3368 (NH), 3005, 2979 (CH), 2953, 2931, 1747 (CO), 1713 (CO), 1663 (CO), 1610 (C=C), 1496, 1450, 1367, 1340, 1289, 1250, 1218, 1168; $[\alpha]_D^{17}$ +56.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, O^{t}Bu), 3.33 (1H, dd, *J* 17.8, 4.2 Hz, 3-*H*H), 3.44 (1H, dd, *J* 17.8, 4.2 Hz, 3-H*H*), 3.75 (3H, s, OMe), 4.46–4.76 (1H, m, 2-H), 5.60 (1H, d, *J* 8.5 Hz, NH), 6.71 (1H, d, *J* 16.1 Hz, 5-H), 7.31–7.67 (6H, m, ArH and 6-H); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3), 42.4 (CH_2), 49.6 (CH), 52.6 (CH_3), 79.9 (C), 125.6 (CH), 128.4 (CH), 129.2 (CH), 130.9 (CH), 134.1 (C), 143.9 (CH), 155.6 (C), 172.0 (C), 197.6 (C); *m/z*

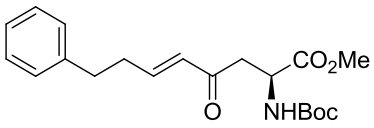
(CI) 334.1653 (MH^+. $C_{18}H_{24}NO_5$ requires 334.1654), 320 (4%), 279 (17), 278 (98), 234 (13), 233 (1), 206 (1), 179 (1), 147 (3), 113 (8), 81 (15); Chiral HPLC (OD-H®) hexane/*iso*-propanol 90:10, flow rate 1.0 mL min^{-1}: t_R = 18.3 min (minor, *R*), t_R = 21.6 min (major, *S*) showed >99% e.e..

Methyl (2*S*,5*E*)-6-(4'-bromophenyl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-enoate 327



Using general procedure 4 above gave **327** as a white solid (0.33 g, 93%). Mp 78–79 °C; ν_{max}/cm^{-1} (NaCl) 3437 (NH), 3370, 2978 (CH), 2953, 2929, 1747 (CO), 1712 (CO), 1666 (CO), 1611 (C=C), 1586, 1488, 1436, 1403, 1392, 1367, 1217, 1168; $[\alpha]_D^{20}$ +42.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, O^{t}Bu), 3.22 (1H, br d, *J* 17.8 Hz, 3-*H*H), 3.41 (1H, br d, *J* 17.8 Hz, 3-H*H*), 3.75 (3H, s, OMe), 4.30–4.80 (1H, m, 2-H), 5.56 (1H, br d, *J* 8.0 Hz, NH), 6.69 (1H, d, *J* 16.0 Hz, 5-H), 7.32–7.63 (5H, m, ArH and 6-H); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3), 42.6 (CH_2), 49.6 (CH), 52.7 (CH_3), 80.0 (C), 125.2 (C), 126.0 (CH), 129.8 (CH), 132.3 (CH), 133.0 (C), 142.5 (CH), 155.6 (C), 172.0 (C), 197.5 (C); *m/z* (FAB) 412.0755 (MH^+. $C_{18}H_{23}{}^{79}BrNO_5$ requires 412.0760), 358 (98%), 356 (84), 355 (8), 314 (93), 312 (98), 296 (7), 254 (9), 252 (10), 227 (13), 225 (20), 212 (48), 210 (51), 183 (2), 147 (6), 114 (2), 90 (55).

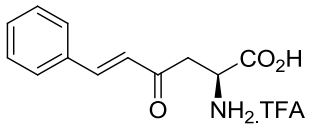
Methyl (2*S*,5*E*)-2-(*tert*-butoxycarbonylamino)-4-oxo-8-phenyloct-5-enoate 343



Using general procedure 4 above gave **343** as a colourless oil (0.37 g, 78%). ν_{max}/cm^{-1} (NaCl) 3439 (NH), 3371, 3027, 3004, 2978 (CH), 2952, 2930, 2859, 1749 (CO), 1714 (CO), 1672, 1630 (CO), 1584 (C=C), 1497, 1367, 1167; $[\alpha]_D^{19}$ +47.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, O^{t}Bu), 2.46–2.63 (2H, m, 7-H_2), 2.79 (2H, t, *J* 7.7 Hz, 8-H_2), 3.06 (1H, dd, *J* 18.0, 4.0 Hz, 3-*H*H), 3.30 (1H, dd, *J* 18.0, 4.0 Hz, 3-H*H*), 3.73 (3H, s, OMe), 4.42–4.64 (1H, m, 2-H), 5.53 (1H, br d, *J* 8.8 Hz, NH), 6.10 (1H, dt, *J* 16.0, 1.4 Hz, 5-H), 6.88 (1H, dt, *J* 16.0, 6.8 Hz, 6-H), 7.11–7.37 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3), 34.2 (CH_2), 34.3 (CH_2), 41.8 (CH_2), 49.5 (CH), 52.6 (CH_3), 79.9 (C), 126.3 (CH), 128.3 (CH), 128.6 (CH), 130.3 (CH), 140.5 (C), 147.8 (CH), 155.6 (C), 172.0 (C), 197.7 (C); *m/z*

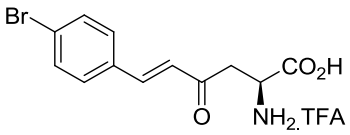
(FAB) 362.1974 (MH^+. $C_{20}H_{28}NO_5$ requires 362.1967), 306 (94%), 262 (100), 203 (11), 176 (14), 160 (34), 93 (35), 90 (32).

(2*S*,5*E*)-2-Amino-4-oxo-6-phenylhex-5-enoic acid 339



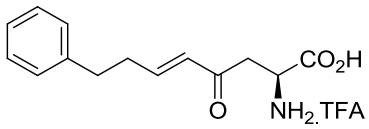
Using general procedure 5 above gave **339** as a white solid (0.13 g, 95%). Mp 112–114 °C (decomposition); ν_{max}/cm^{-1} (neat) 3028 (NH_3^+), 3015 (ArH), 2915, 1738 (CO), 1655 (CO), 1626, 1614, 1184, 1134; $[\alpha]_D^{19}$ +23.3 (*c* 1.0, MeOH); δ_H (400 MHz, CD_3OD) 3.37–3.59 (2H, m, 3-H_2), 4.24–4.39 (1H, m, 2-H), 6.90 (1H, d, *J* 16.2 Hz, 5-H), 7.29–7.82 (6H, m, ArH and 6-H); δ_C (100 MHz, CD_3OD) 40.9 (CH_2), 50.2 (CH), 126.1 (CH), 129.7 (CH), 130.2 (CH), 132.1 (CH), 135.6 (C), 146.0 (CH), 171.8 (C), 198.0 (C); *m/z* (FAB) 220.0973 (MH^+. $C_{12}H_{14}NO_3$ requires 220.0974), 220 (3%), 175 (7), 148 (16), 132 (12), 104 (1), 76 (6).

(2*S*,5*E*)-2-Amino-6-(4'-bromophenyl)-4-oxohex-5-enoic acid 344



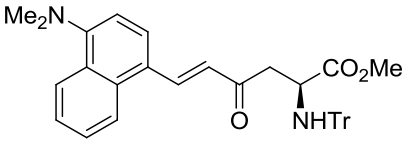
Using general procedure 5 above gave **344** as a white solid (0.14 g, 93%). Mp 151–152 °C (decomposition); ν_{max}/cm^{-1} (neat) 3094 (NH_3^+), 3080, 3050, 3034 (ArH), 2955 (OH), 2930, 1684 (CO), 1640, 1607 (C=C), 1545, 1487, 1397, 1337, 1055; $[\alpha]_D^{18}$ +55.0 (*c* 0.3, MeOH); δ_H (400 MHz, CD_3OD) 3.23 (1H, dd, *J* 18.8, 9.3 Hz, 3-*H*H), 3.46 (1H, dd, *J* 18.8, 3.4 Hz, 3-H*H*), 3.95 (1H, dd, *J* 9.3, 3.4 Hz, 2-H), 6.91 (1H, d, *J* 16.3 Hz, 5-H), 7.54–7.73 (5H, m, ArH and 6-H); δ_C (100 MHz, CD_3OD) 40.9 (CH_2), 50.2 (CH), 126.2 (C), 126.7 (CH), 131.3 (CH), 133.4 (CH), 134.8 (C), 144.6 (CH), 171.5 (C), 197.7 (C); *m/z* (FAB) 298.0067 (MH^+. $C_{12}H_{13}{}^{79}BrNO_3$ requires 298.0079), 292 (16%), 254 (12), 243 (21), 211 (13), 209 (16), 155 (29), 138 (15), 137 (13), 92 (1), 75 (10).

(2*S*,5*E*)-2-Amino-4-oxo-8-phenyloct-5-enoic acid 345



To a solution of methyl (2*S*,5*E*)-2-(*tert*-butoxycarbonylamino)-4-oxo-8-phenyloct-5-enoate **343** (0.056 g, 0.15 mmol) in 1:1 acetonitrile–water (8.0 mL) was added cesium carbonate (0.065 g, 0.20 mmol). The resultant suspension was stirred at room temperature for 48 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in water (10 mL) and acidified to pH 1 with 1.0 M hydrochloric acid. The aqueous layer was washed with dichloromethane (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$), and then concentrated *in vacuo*. To a solution of the resulting residue (0.052 g, 0.15 mmol) in dichloromethane (2.0 mL) was added trifluoroacetic acid (0.056 mL, 0.75 mmol) and the reaction mixture was stirred at room temperature under argon for 2 h. The reaction mixture was concentrated *in vacuo* to give the TFA salt, which was purified by recrystallisation from chloroform and methanol to give **345** as a white solid (0.10 g, 98%). Mp 94–96 °C (decomposition); ν_{max}/cm^{-1} (neat) 3161 (NH_3^+), 3144, 3088, 3030 (ArH), 3009, 2988, 2918 (CH), 1736 (CO), 1661 (CO), 1640, 1604 (C=C), 1180, 1136; $[\alpha]_D^{18}$ +10.2 (*c* 0.3, MeOH); δ_H (400 MHz, CD_3OD) 2.51–2.91 (4H, m, 7-H_2 and 8-H_2), 3.20 (1H, dd, *J* 18.8, 8.0 Hz, 3-*H*H), 3.30–3.39 (1H, m, 3-H*H*), 4.11 (1H, dd, *J* 8.0, 3.6 Hz, 2-H), 6.17 (1H, dt, *J* 16.0, 1.4 Hz, 5-H), 7.03 (1H, dt, *J* 16.0, 6.9 Hz, 6-H), 7.09–7.35 (5H, m, ArH); δ_C (100 MHz, CD_3OD) 35.3 (CH_2), 35.5 (CH_2), 40.4 (CH_2), 50.5 (CH), 127.3 (CH), 129.5 (CH), 129.6 (CH), 130.8 (CH), 142.1 (C), 150.5 (CH), 172.5 (C), 198.1 (C); *m/z* (FAB) 248.1289 (MH^+. $C_{14}H_{18}NO_3$ requires 248.1287), 247 (2%), 203 (8), 176 (12), 160 (8), 132 (4), 100 (1), 90 (3), 76 (4).

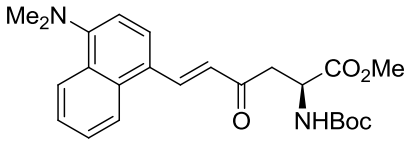
Methyl (2*S*,5*E*)-6-(4'-dimethylaminonaphthalen-1-yl)-4-oxo-2-(tritylamino)hex-5-enoate 349



Using general procedure 1 above with 4-dimethylamino-1-naphthaldehyde (0.24 g, 1.2 mmol) gave **349** after 4 days as an orange oil (0.24 g, 72%). ν_{max}/cm^{-1} (NaCl) 3321 (NH), 3057, 3019 (ArH), 2948, 2835, 2787, 1737 (CO), 1651 (CO), 1597 (C=C), 1569, 1449, 1390, 1337, 1202; $[\alpha]_D^{18}$ +73.7 (*c* 0.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.84 (1H, dd, *J* 14.8, 6.8 Hz, 3-*H*H), 2.88–3.05 (8H, m, 3-H*H*, NH

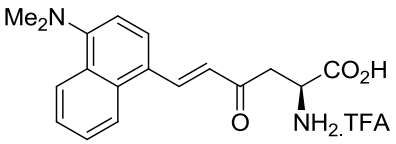
and NMe_2), 3.30 (3H, s, OMe), 3.76–3.90 (1H, m, 2-H), 6.71 (1H, d, *J* 15.7 Hz, 5-H), 7.04 (1H, d, *J* 8.0 Hz, ArH), 7.11–7.33 (9H, m, ArH), 7.44–7.64 (8H, m, ArH), 7.74 (1H, d, *J* 8.0 Hz, ArH), 8.08–8.27 (2H, m, ArH), 8.30 (1H, d, *J* 15.7 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 44.9 (CH_3), 45.8 (CH_2), 52.0 (CH_3), 54.0 (CH), 71.3 (C), 113.4 (CH), 123.6 (CH), 125.2 (CH), 125.3 (CH), 125.4 (C), 125.8 (CH), 126.5 (CH), 126.6 (CH), 126.9 (CH), 127.9 (CH), 128.4 (C), 128.9 (CH), 133.1 (C), 140.2 (CH), 145.9 (C), 153.8 (C), 174.7 (C), 197.4 (C); *m/z* (FAB) 569.2799 (MH^+. $C_{38}H_{37}N_2O_3$ requires 569.2804), 567 (3%), 491 (3), 460 (4), 443 (1), 325 (52), 243 (100), 224 (19), 120 (2), 85 (56), 84 (5).

Methyl (2*S*,5*E*)-2-(*tert*-butoxycarbonylamino)-6-(4'-dimethylaminonaphthalen-1-yl)-4-oxohex-5-enoate 350



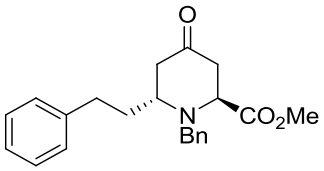
Using general procedure 4 above gave **350** as a yellow oil (0.091 g, 54%). ν_{max}/cm^{-1} (NaCl) 3438, 3362 (NH), 2978 (CH), 2950, 1747 (CO), 1709 (CO), 1512, 1499, 1391, 1366, 1338, 1167; $[\alpha]_D^{23}$ +49.3 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, O^{t}Bu), 2.96 (6H, s, NMe_2), 3.29 (1H, dd, *J* 17.7, 3.7 Hz, 3-*H*H), 3.53 (1H, dd, *J* 17.7, 3.7 Hz, 3-H*H*), 3.77 (3H, s, OMe), 4.53–4.73 (1H, m, 2-H), 5.64 (1H, d, *J* 8.7 Hz, NH), 6.75 (1H, d, *J* 15.8 Hz, 5-H), 7.04 (1H, d, *J* 8.0 Hz, ArH), 7.43–7.65 (2H, m, ArH), 7.76 (1H, d, *J* 8.0 Hz, ArH), 8.17 (1H, d, *J* 8.2 Hz, ArH), 8.23 (1H, d, *J* 8.2 Hz, ArH), 8.41 (1H, d, *J* 15.8 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 28.4 (CH_3), 42.7 (CH_2), 44.9 (CH_3), 49.7 (CH), 52.6 (CH_3), 80.0 (C), 113.3 (CH), 123.5 (CH), 125.0 (C), 125.2 (CH), 125.3 (CH), 125.4 (CH), 126.0 (CH), 126.9 (CH), 128.3 (C), 133.1 (C), 140.8 (CH), 154.0 (C), 155.6 (C), 172.2 (C), 197.5 (C); *m/z* (CI) 427.2239 (MH^+. $C_{24}H_{31}N_2O_5$ requires 427.2233), 426 (6%), 353 (6), 312 (6), 296 (2), 240 (12), 228 (5), 172 (12), 134 (10), 113 (26), 71 (32).

(2*S*,5*E*)-2-Amino-6-(4'-dimethylaminonaphthalen-1-yl)-4-oxohex-5-enoic acid 351



Using general procedure 5 above gave **351** as an orange solid (0.037 g, 46%). Mp 78–80 °C (decomposition); ν_{max}/cm^{-1} (neat) 3009, 2930, 1738 (CO), 1667 (CO), 1609 (C=C), 1566, 1393, 1180, 1126; $[\alpha]_D^{17}$ +42.5 (*c* 0.8, MeOH); δ_H (400 MHz, CD_3OD) 3.00 (6H, s, NMe_2), 3.47–3.64 (2H, m, 3-H_2), 4.39 (1H, dd, *J* 6.0, 4.4 Hz, 2-H), 6.95 (1H, d, *J* 15.9 Hz, 5-H), 7.21 (1H, d, *J* 8.1 Hz, ArH), 7.49–7.72 (2H, m, ArH), 7.94 (1H, d, *J* 8.1 Hz, ArH), 8.16–8.41 (2H, m, ArH), 8.57 (1H, d, *J* 15.9 Hz, 6-H); δ_C (100 MHz, CD_3OD) 41.0 (CH_2), 45.7 (CH_3), 50.0 (CH), 115.5 (CH), 124.7 (CH), 125.4 (CH), 126.6 (CH), 127.1 (CH), 127.2 (CH), 128.1 (C), 128.4 (CH), 129.0 (C), 134.5 (C), 142.3 (CH), 152.8 (C), 171.3 (C), 197.5 (C); *m/z* (FAB) 313.1551 (MH^+. $C_{18}H_{21}N_2O_3$ requires 313.1552), 312 (38%), 291 (4), 268 (3), 241 (8), 224 (18), 198 (8), 185 (11), 172 (2), 158 (1).

Methyl (2*S*,6*R*)-1-benzyl-4-oxo-6-phenethylpiperidine-2-carboxylate 362

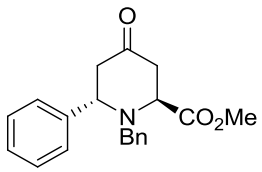


Method A: To a solution of methyl (2*S*,5*E*)-4-oxo-8-phenyl-2-(tritylamino)oct-5-enoate **314** (0.27 g, 0.53 mmol) in dichloromethane (5.0 mL) at room temperature under argon was added trifluoroacetic acid (0.39 mL, 5.3 mmol). The reaction mixture was stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved in water (10 mL) and washed with diethyl ether (2 × 10 mL). The aqueous layer was concentrated *in vacuo*, azeotroping with ethyl acetate–chloroform to give the TFA salt. The TFA salt was dissolved in tetrahydrofuran (5.0 mL) at room temperature under argon. To the solution was added 4 Å molecular sieves, triethylamine (0.074 mL, 5.3 mmol) and benzaldehyde (0.054 mL, 0.53 mmol) and the mixture was stirred for 2 h. The mixture was filtered and then concentrated *in vacuo*. The residue was dissolved in tetrahydrofuran (3.0 mL) at room temperature under argon and sodium triacetoxyborohydride (0.12 g, 0.53 mmol) was added to the solution and stirred for 48 h. The reaction mixture was quenched with a saturated sodium hydrogen carbonate solution (1.0 mL), and then concentrated *in vacuo*. The residue was dissolved in dichloromethane (15 mL), washed with saturated sodium

hydrogen carbonate solution (15 mL), brine (15 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The product was purified by column chromatography on silica eluting with 25% diethyl ether in petroleum ether to give **362** as a colourless oil (0.084 g, 45%). ν_{max}/cm^{-1} (neat) 3026 (ArH), 1731 (CO), 1714 (CO), 1496, 1453, 1437, 1216, 1171; $[\alpha]_D^{26}$ −31.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.68–1.86 (1H, m, 7-*H*H), 1.89–2.07 (1H, m, 7-H*H*), 2.37 (1H, dd, *J* 14.8, 7.4 Hz, 5-*H*H), 2.48–2.79 (5H, m, 3-H_2, 5-H*H* and 8-H_2), 3.25–3.39 (1H, m, 6-H), 3.70 (3H, s, OMe), 3.82 (1H, d, *J* 13.8 Hz, 1'-*H*H), 3.87 (1H, t, *J* 5.2 Hz, 2-H), 3.93 (1H, d, *J* 13.8 Hz, 1'-H*H*), 7.09–7.49 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 29.0 (CH_2), 32.4 (CH_2), 38.4 (CH_2), 41.5 (CH_2), 49.7 (CH), 49.9 (CH_2), 53.6 (CH_3), 56.8 (CH), 123.7 (CH), 125.1 (CH), 126.0 (CH), 126.2 (CH), 126.3 (CH), 136.2 (C), 139.3 (C), 169.8 (C), 205.0 (C); *m/z* (FAB) 352.1915 (MH^+. $C_{22}H_{26}NO_3$ requires 352.1913), 292 (77%), 260 (6), 246 (40), 218 (1), 178 (3), 158(2), 132 (4), 117 (6), 91 (93), 69 (5), 55 (5), 43 (4), 41 (4).

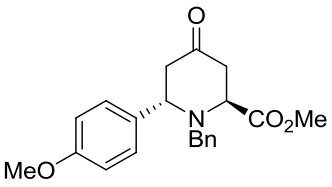
Method B: Using general procedure 6 above gave **362** as a colourless oil (0.050 g, 53%). Spectroscopic data as reported above.

Methyl (2*S*,6*S*)-1-benzyl-4-oxo-6-phenylpiperidine-2-carboxylate 364



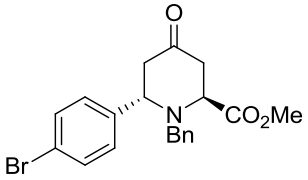
Using general procedure 6 above gave **364** as a colourless oil (0.14 g, 37%). ν_{max}/cm^{-1} (NaCl) 3030 (ArH), 2952, 2848 (CH), 1731 (CO), 1494, 1454, 1197, 1162; $[\alpha]_D^{22}$ −119.0 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.51 (1H, dt, *J* 14.8, 2.2 Hz, 3-HH_{eq}), 2.61 (1H, dd, *J* 14.9, 9.8 Hz, 5-H_{ax}H), 2.70 (1H, ddd, *J* 14.9, 4.8, 2.2 Hz, 5-HH_{eq}), 2.76 (1H, dd, *J* 14.8, 6.5 Hz, 3-H_{ax}H), 3.25 (1H, d, *J* 13.8 Hz, 1'-*H*H), 3.74–3.80 (4H, m, OMe and 1'-H*H*), 3.92 (1H, dd, $J_{eq\text{-}ax,eq\text{-}eq}$ 6.5, 2.2 Hz, 2-H), 4.40 (1H, dd, $J_{ax\text{-}ax,ax\text{-}eq}$ 9.8, 4.8 Hz, 6-H), 7.17–7.54 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 49.2 (CH_2), 51.6 (CH), 54.2 (CH_2), 58.6 (CH_3), 62.7 (CH), 127.4 (CH), 127.4 (CH), 128.0 (CH), 128.4 (CH), 128.6 (CH), 129.1 (CH), 138.3 (C), 142.9 (C), 172.0 (C), 206.0 (C); *m/z* (EI) 323.1519 (M^+. $C_{20}H_{21}NO_3$ requires 323.1521), 294 (3%), 264 (100), 246 (1), 232 (5), 218 (3), 187 (5), 161 (6), 131 (85), 103 (18), 91 (100), 83 (21), 65 (8), 44 (4).

Methyl (2*S*,6*S*)-1-benzyl-6-(4'-methoxyphenyl)-4-oxopiperidine-2-carboxylate 365



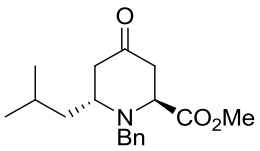
Using general procedure 6 above gave **365** as a yellow oil (0.060 g, 34%). ν_{max}/cm^{-1} (NaCl) 3030 (ArH), 2953, 2838, 1731 (CO), 1611, 1512, 1246, 1197, 1162; $[\alpha]_D^{22}$ −57.0 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.42 (1H, dt, *J* 14.9, 2.2 Hz, 3-HH_{eq}), 2.52 (1H, dd, *J* 15.2, 9.6 Hz, 5-H_{ax}H), 2.60 (1H, ddd, *J* 15.2, 4.7, 2.1 Hz, 5-HH_{eq}), 2.67 (1H, dd, *J* 14.9, 6.7 Hz, 3-H_{ax}H), 3.17 (1H, d, *J* 13.8 Hz, 1'-*H*H), 3.66–3.79 (7H, m, 2 × OMe and 1'-H*H*), 3.84 (1H, dd, $J_{eq\text{-}ax,eq\text{-}eq}$ 6.7, 2.2 Hz, 2-H), 4.27 (1H, dd, $J_{ax\text{-}ax,ax\text{-}eq}$ 9.6, 4.7 Hz, 6-H), 6.84 (2H, d, *J* 8.7 Hz, ArH), 7.12–7.28 (5H, m, ArH), 7.33 (2H, d, *J* 8.7 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 49.3 (CH_2), 51.6 (CH), 54.0 (CH_2), 55.3 (CH_3), 58.6 (CH_3), 62.0 (CH), 114.4 (CH), 127.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 134.9 (C), 138.5 (C), 159.3 (C), 172.0 (C), 206.3 (C); *m/z* (EI) 353.1629 (M^+. $C_{21}H_{23}NO_4$ requires 353.1627), 352 (4%), 294 (99), 262 (35), 224 (16), 203 (6), 161 (99), 134 (72), 91 (99), 65 (27), 44 (5).

Methyl (2*S*,6*S*)-1-benzyl-6-(4'-bromophenyl)-4-oxopiperidine-2-carboxylate 366



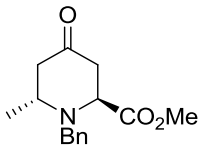
Using general procedure 6 above gave **366** as a colourless oil (0.14 g, 40%). ν_{max}/cm^{-1} (NaCl) 3029 (ArH), 2952, 2849, 1732 (CO), 1486, 1454, 1434, 1354, 1329, 1300, 1197, 1162; $[\alpha]_D^{23}$ −54.3 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.37–2.54 (2H, m, 3-HH_{eq} and 5-H_{ax}H), 2.61 (1H, ddd, *J* 15.4, 4.7, 2.3 Hz, 5-HH_{eq}), 2.69 (1H, ddd, *J* 14.9, 6.6, 0.6 Hz, 3-H_{ax}H), 3.20 (1H, d, *J* 13.8 Hz, 1'-*H*H), 3.67 (1H, d, *J* 13.8 Hz, 1'-H*H*), 3.71 (3H, s, OMe), 3.85 (1H, dd, $J_{eq\text{-}ax,eq\text{-}eq}$ 6.6, 2.2 Hz, 2-H), 4.34 (1H, dd, $J_{ax\text{-}ax,ax\text{-}eq}$ 9.6, 4.7 Hz, 6-H), 7.14–7.52 (9H, m, ArH); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 48.9 (CH_2), 51.7 (CH), 54.3 (CH_2), 58.5 (CH_3), 62.1 (CH), 121.7 (C), 127.5 (CH), 128.5 (CH), 128.6 (CH), 129.1 (CH), 132.3 (CH), 138.0 (C), 142.1 (C), 172.0 (C), 205.5 (C); *m/z* (CI) 402.0706 (MH^+. $C_{20}H_{21}{}^{79}BrNO_3$ requires 402.0705), 404 (98%), 344 (16), 342 (17), 324 (12), 264 (1), 246 (1), 178 (2), 133 (1), 91 (5).

Methyl (2*S*,6*R*)-1-benzyl-6-*iso*-butyl-4-oxopiperidine-2-carboxylate 367



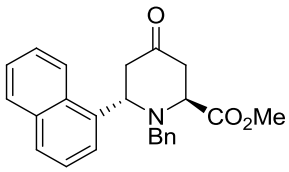
Using general procedure 6 above gave **367** as a colourless oil (0.072 g, 50%). ν_{max}/cm^{-1} (neat) 2955, 2353, 1728 (CO), 1458, 1366, 1165, 1026; $[\alpha]_D^{23}$ −37.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.84 (3H, d, *J* 6.6 Hz, 8-H_3), 0.85 (3H, d, *J* 6.6 Hz, 9-CH_3), 1.08–1.34 (1H, m, 8-H), 1.49–1.82 (2H, m, 7-H_2), 2.23 (1H, ddd, *J* 14.8, 7.5, 1.1 Hz, 5-HH_{eq}), 2.46–2.58 (2H, m, 3-HH_{eq} and 5-H_{ax}H), 2.64 (1H, ddd, *J* 15.2, 5.4, 1.4 Hz, 3-H_{ax}H), 3.22–3.33 (1H, m, 6-H), 3.69 (3H, s, OMe), 3.78 (1H, d, *J* 13.8 Hz, 1'-*H*H), 3.82–3.90 (2H, m, 1'-H*H* and 2-H) 7.21–7.45 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_3), 22.7 (CH), 24.4 (CH_3), 39.9 (CH_2), 41.9 (CH_2), 43.8 (CH_2), 51.5 (CH_2), 52.1 (CH), 54.7 (CH), 59.3 (CH_3), 127.4 (CH), 128.5 (CH), 128.5 (CH), 138.7 (C), 172.3 (C), 207.6 (C); *m/z* (FAB) 304.1914 (MH^+. $C_{18}H_{26}NO_3$ requires 304.1913), 326 (30%), 244 (90), 241 (2), 202 (2), 170 (3), 132 (3), 117 (3), 91 (98), 70 (5).

Methyl (2*S*,6*R*)-1-benzyl-6-methyl-4-oxopiperidine-2-carboxylate 368



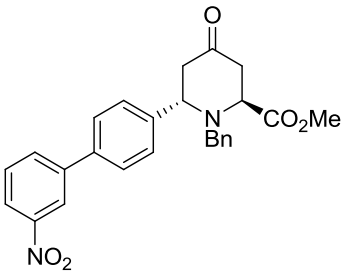
Using general procedure 6 above gave **368** as a colourless oil (0.22 g, 53%). ν_{max}/cm^{-1} (neat) 2966, 2954 , 2357, 1726 (CO), 1195, 1165; $[\alpha]_D^{25}$ −107.4 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.3 Hz, 7-H_3), 2.23 (1H, dd, *J* 15.0, 8.7 Hz, 5-H_{ax}H), 2.45–2.59 (3H, m, 3-H_2 and 5-HH_{eq}), 3.25–3.43 (1H, m, 6-H), 3.62 (1H, d, *J* 13.7 Hz, 1'-*H*H), 3.71 (3H, s, OMe), 3.79 (1H, t, *J* 4.9 Hz, 2-H), 4.08 (1H, d, *J* 13.7 Hz, 1'-H*H*), 7.17–7.50 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 20.3 (CH_3), 42.7 (CH_2), 48.3 (CH_2), 51.7 (CH), 51.8 (CH), 53.5 (CH_2), 59.3 (CH_3), 127.3 (CH), 128.5 (CH), 128.7 (CH), 138.9 (C), 172.0 (C), 207.3 (C); *m/z* (FAB) 262.1447 (MH^+. $C_{15}H_{20}NO_3$ requires 262.1443), 260 (66%), 246 (8), 202 (100), 184 (9), 170 (4), 160 (3), 114 (5), 92 (83), 70 (4).

Methyl (2*S*,6*S*)-1-benzyl-6-naphthalen-2-yl-4-oxopiperidine-2-carboxylate 369



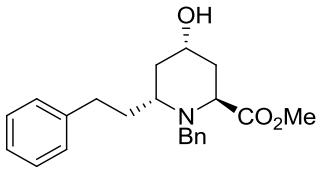
Using general procedure 6 above gave **369** as a colourless oil (0.062 g, 26%). ν_{max}/cm^{-1} (neat) 3023, 2917, 2850, 2360, 1729 (CO), 1215, 1196, 1161; $[\alpha]_D^{26}$ −28.7 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.45–2.89 (4H, m, 3-H_2 and 5-H_2), 3.58–3.89 (5H, m, 1'-H_2 and OMe), 3.97 (1H, dd, $J_{eq\text{-}ax,eq\text{-}eq}$ 6.4, 2.0 Hz, 2-H), 4.59 (1H, dd, $J_{ax\text{-}ax,ax\text{-}eq}$ 8.0, 6.0 Hz, 6-H), 7.14–7.37 (4H, m, ArH), 7.39–7.57 (2H, m, ArH), 7.61–8.07 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 48.9 (CH_2), 51.6 (CH), 54.4 (CH_2), 58.6 (CH_3), 62.8 (CH), 124.5 (CH), 126.2 (CH), 126.4 (CH), 126.9 (CH), 127.4 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 128.7 (CH), 129.3 (CH), 133.2 (C), 133.4 (C), 138.2 (C), 140.2 (C), 172.0 (C), 205.9 (C); *m/z* (CI) 374.1757 (MH^+. $C_{24}H_{24}NO_3$ requires 374.1756), 372 (1%), 337 (3), 314 (5), 282 (6), 269 (37), 253 (5), 237 (5), 217 (4), 181 (4), 147 (25), 123 (34), 107 (98), 91 (44), 71 (28).

Methyl (2*S*,6*S*)-1-benzyl-6-(3'-nitrobiphen-4-yl)-4-oxopiperidine-2-carboxylate 370



Using general procedure 6 above gave **370** as a colourless oil (0.033 g, 29%). ν_{max}/cm^{-1} (NaCl) 3029, 2953, 2918, 2850, 1730 (CO), 1531, 1514, 1350, 1198, 1163; $[\alpha]_D^{22}$ −46.8 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.48 (1H, dt, *J* 15.0, 2.2 Hz, 3-HH_{eq}), 2.56 (1H, dd, *J* 15.2, 9.6 Hz, 5-H_{ax}H), 2.68 (1H, ddd, *J* 15.2, 4.7, 2.1 Hz, 5-HH_{eq}), 2.74 (1H, dd, *J* 15.0, 6.6 Hz, 3-H_{ax}H), 3.27 (1H, d, *J* 13.8 Hz, 1'-*H*H), 3.66–3.79 (4H, m, 1'-H*H* and OMe), 3.89 (1H, dd, $J_{eq\text{-}ax,eq\text{-}eq}$ 6.6, 2.2 Hz, 2-H), 4.45 (1H, dd, $J_{ax\text{-}ax,ax\text{-}eq}$ 9.6, 4.7 Hz, 6-H), 7.11–7.34 (5H, m, ArH), 7.41–7.68 (5H, m, ArH), 7.93 (1H, d, *J* 7.6 Hz, ArH), 8.12 (1H, dd, *J* 7.6, 1.4 Hz, ArH), 8.38 (1H, s, ArH); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 49.0 (CH_2), 51.7 (CH), 54.4 (CH_2), 58.6 (CH_3), 62.3 (CH), 121.9 (CH), 122.2 (CH), 127.5 (CH), 127.9 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 129.8 (CH), 132.9 (CH), 138.1 (C), 138.4 (C), 142.3 (C), 143.5 (C), 148.7 (C), 172.0 (C), 205.7 (C); *m/z* (CI) 445.1756 (MH^+. $C_{26}H_{25}N_2O_5$ requires 445.1763), 415 (98%), 355 (15), 325 (7), 322 (5), 246 (4), 223 (3), 178 (4), 151 (4), 108 (12), 69 (11).

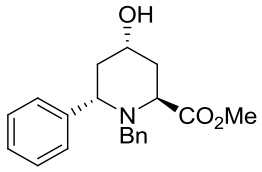
Methyl (2*S*,4*S*,6*R*)-1-benzyl-4-hydroxy-6-phenethylpiperidine-2-carboxylate 379



Method A: A solution of methyl (2*S*,6*R*)-1-benzyl-4-oxo-6-phenethylpiperidine-2-carboxylate **362** (0.065 g, 0.18 mmol) in tetrahydrofuran (3.0 mL) under argon was cooled to −78 °C. L-Selectride® was added slowly dropwise to the solution and stirred for 40 min. The reaction mixture was quenched with methanol (0.20 mL) and allowed to warm to room temperature. The mixture was concentrated *in vacuo*. The resultant residue was dissolved in water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 20% diethyl ether in petroleum ether to give **379** as a colourless oil (0.016 g, 25%). ν_{max} /cm^{-1} (neat) 3399 (OH), 2949 (CH), 2360, 2343, 1730 (CO), 1496, 1452, 1216, 1162; $[\alpha]_D^{23}$ −32.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.36 (1H, q, *J* 11.5 Hz, 5-H_{ax}H), 1.50 (1H, br s, OH), 1.58 (1H, ddd, J 12.6, 11.6, 5.6 Hz, 3-H_{ax}H), 1.66–1.79 (1H, m, 7-*H*H), 1.81–1.92 (2H, m, 5-HH_{eq} and 7-H*H*), 2.08 (1H, ddt, *J* 12.6, 4.4, 2.4 3-HH_{eq}), 2.54–2.72 (2H, m, 8-H_2), 3.11–3.32 (1H, m, 6-H), 3.52 (1H, dd, $J_{eq\text{-}ax,eq\text{-}eq}$ 5.6, 2.4 Hz, 2-H), 3.57 (3H, s, OMe), 3.63 (1H, d, *J* 14.2 Hz, 1'-HH), 3.68–3.83 (1H, m, 4-H), 3.89 (1H, d, *J* 14.2 Hz, 1'-H*H*), 6.99–7.33 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 31.2 (CH_2), 34.1 (CH_2), 35.8 (CH_2), 38.5 (CH_2), 51.5 (CH), 51.5 (CH_2), 54.2 (CH), 58.8 (CH_3), 66.5 (CH), 125.8 (CH), 127.1 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 139.7 (C), 142.5 (C), 173.7 (C); *m/z* (FAB) 354.2070 (MH^+. $C_{22}H_{28}NO_3$ requires 354.2069), 352 (20%), 336 (12), 294 (46), 248 (27), 246 (1), 207 (3), 193 (3), 172 (2), 147 (4), 117 (6), 91 (100), 73 (20).

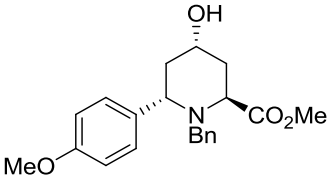
Method B: Using general procedure 7 above gave **379** as a colourless oil (0.13 g, 67%). Spectroscopic data as reported above.

Methyl (2*S*,4*S*,6*S*)-1-benzyl-4-hydroxy-6-phenylpiperidine-2-carboxylate 381



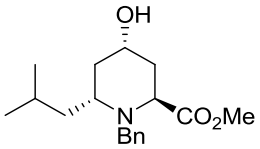
Using general procedure 7 above gave **381** as a colourless oil (0.052 g, 100%). ν_{max}/cm^{-1} (neat) 3383 (OH), 2951 (CH), 2359, 2334, 1729 (CO), 1493, 1454, 1216, 1200, 1166, 1119; $[\alpha]_D^{20}$ −5.8 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42 (1H, d, *J* 5.2 Hz, OH), 1.63 (1H, q, *J* 11.6, 5-H_{ax}H), 1.79 (1H, td, *J* 12.2, 6.0 Hz, 3-H_{ax}H), 2.07–2.30 (2H, m, 3-HH_{eq} and 5-HH_{eq}), 3.34 (1H, d, *J* 14.1 Hz, 1'-*H*H), 3.63–3.77 (5H, m, 2-H, 1'-H*H* and OMe), 3.84–4.01 (1H, m, 4-H), 4.51 (1H, dd, $J_{ax\text{-}ax,ax\text{-}eq}$ 11.6, 3.2 Hz, 6-H), 7.14–7.39 (8H, m, ArH), 7.51 (2H, d, *J* 7.2 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 36.7 (CH_2), 45.2 (CH_2), 51.2 (CH), 54.0 (CH_2), 57.7 (CH_3), 61.1 (CH), 65.8 (CH), 126.9 (CH), 127.4 (CH), 127.6 (CH), 128.3 (CH), 128.3 (CH), 128.7 (CH), 139.2 (C), 144.2 (C), 173.8 (C); *m/z* (CI) 326.1748 (MH^+. $C_{20}H_{24}NO_3$ requires 326.1756), 309 (59%), 266 (18), 248 (5), 218 (3), 186 (3), 161 (3), 137 (5), 97 (6), 69 (20).

Methyl (2*S*,4*S*,6*S*)-1-benzyl-4-hydroxy-6-(4'-methoxyphenyl)piperidine-2-carboxylate 382



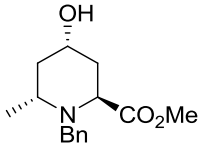
Using general procedure 7 above gave **382** as a colourless oil (0.025 g, 100%). ν_{max}/cm^{-1} (neat) 3387 (OH), 2923 (CH), 2363, 1735 (CO), 1730, 1719, 1511, 1244, 1170; $[\alpha]_D^{20}$ −5.0 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.82–2.27 (4H, m, 3-H_2 and 5-H_2), 2.61 (1H, d, *J* 6.6 Hz, OH), 3.42 (1H, d, *J* 14.2 Hz, 1'-*H*H), 3.53 (1H, dd, $J_{eq\text{-}ax,eq\text{-}eq}$ 6.2, 2.1 Hz, 2-H), 3.63–3.85 (7H, m, 1'-H*H* and 2 × OMe), 4.05–4.15 (1H, m, 4-H), 4.60 (1H, dd, $J_{ax\text{-}ax,ax\text{-}eq}$ 10.7, 4.2 Hz, 6-H), 6.87 (2H, d, *J* 8.8 Hz, ArH), 7.14–7.34 (5H, m, ArH), 7.39 (2H, d, *J* 8.8 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 34.3 (CH_2), 42.9 (CH_2), 51.3 (CH), 54.1 (CH_2), 55.1 (CH), 55.3 (CH_3), 55.8 (CH_3), 65.0 (CH), 114.0 (CH), 126.8 (CH), 128.2 (CH), 128.3 (CH), 128.7 (CH), 136.2 (C), 139.53 (C), 158.8 (C), 176.1 (C); *m/z* (CI) 356.1865 (MH^+. $C_{21}H_{26}NO_4$ requires 356.1862), 324 (98%), 296 (12), 279 (20), 248 (3), 226 (6), 216 (4), 161 (10), 137 (4), 97 (3), 69 (9).

Methyl (2*S*,4*S*,6*R*)-1-benzyl-6-*iso*-butyl-4-hydroxypiperidine-2-carboxylate 383



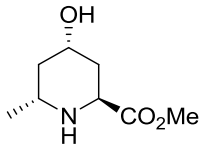
Using general procedure 7 above gave **383** as a colourless oil (0.022 g, 80%). ν_{max}/cm^{-1} (neat) 3373 (OH), 2953 (CH), 2360, 2342, 1730 (CO), 1368, 1215, 1151; $[\alpha]_D^{23}$ −27.9 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.6 Hz, 8-H_3), 0.89 (3H, d, *J* 6.6 Hz, 9-CH_3), 1.03–1.12 (1H, m, 7-*H*H), 1.22 (1H, q, *J* 11.6 Hz, 5-H_{ax}H), 1.43 (1H, br s, OH), 1.49–1.62 (3H, m, 3-H_{ax}H and 7-H*H*), 1.67–1.79 (2H, m, 5-HH_{eq} and 8-H), 2.08 (1H, ddt, *J* 12.8, 4.4, 2.2 Hz, 3-HH_{eq}), 3.00–3.15 (1H, m, 6-H), 3.51 (1H, dd, $J_{eq\text{-}ax,eq\text{-}eq}$ 5.6, 2.2 Hz, 2-H), 3.61 (3H, s, OMe), 3.67 (1H, d, *J* 14.4 Hz, 1'-*H*H), 3.70–3.82 (2H, m, 1'-H*H* and 4-H), 7.10–7.35 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 22.6 (CH), 23.0 (CH_3), 24.6 (CH_3), 32.3 (CH_2), 38.0 (CH_2), 43.4 (CH_2), 50.4 (CH_2), 51.5 (CH), 52.8 (CH), 59.0 (CH_3), 66.8 (CH), 126.9 (CH), 128.2 (CH), 128.4 (CH), 140 (C), 173.8 (C); *m/z* (CI) 306.2071 (MH^+. $C_{18}H_{28}NO_3$ requires 306.2069), 288 (82%), 275 (4), 246 (13), 242 (2), 198 (3), 184 (2), 138 (2), 113 (4), 81 (12).

Methyl (2*S*,4*S*,6*R*)-1-benzyl-4-hydroxy-6-methylpiperidine-2-carboxylate 384



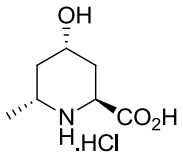
Using general procedure 7 above gave **384** as a colourless oil (0.096 g, 83%). ν_{max}/cm^{-1} (neat) 3380 (OH), 2950 (CH), 2934, 1731 (CO), 1190, 1174, 1152, 1146; $[\alpha]_D^{25}$ −89.0 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.2 Hz, 7-H_3), 1.29 (1H, q, *J* 11.4 Hz, 5-H_{ax}H), 1.53 (1H, br s, OH), 1.62 (1H, td, J 12.2, 6.0 Hz, 3-H_{ax}H), 1.94 (1H, dtd, *J* 11.4, 5.1, 2.0 Hz, 5-HH_{eq}), 2.18 (1H, ddt, *J* 12.2, 4.4, 2.0 Hz, 3-HH_{eq}), 3.37–3.48 (1H, m, 6-H), 3.52–3.62 (2H, m, 2-H and 1'-*H*H), 3.67 (3H, s, OMe), 3.71–3.82 (1H, m, 4-H), 4.11 (1H, d, *J* 14.2 Hz, 1'-H*H*), 7.16–7.39 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.8 (CH_3), 36.6 (CH_2), 43.9 (CH_2), 51.2 (CH), 51.5 (CH), 53.5 (CH_2), 59.1 (CH_3), 66.1 (CH), 126.9 (CH), 128.3 (CH), 128.3 (CH), 140.3 (C), 173.8 (C); *m/z* (CI) 264.1597 (MH^+. $C_{15}H_{22}NO_3$ requires 264.1600), 246 (62%), 232 (5), 204 (10), 172 (3), 156 (1), 124 (2), 113 (4), 81 (11), 71 (12).

Methyl (2*S*,4*S*,6*R*)-4-hydroxy-6-methylpiperidine-2-carboxylate 397



To a solution of methyl (2*S*,4*S*,6*R*)-1-benzyl-4-hydroxy-6-methylpiperidine-2-carboxylate **384** (0.032 g, 0.18 mmol) in *tert*-butanol (3.0 mL) at room temperature under argon was added palladium (10% wt.) on activated carbon (0.077 g, 0.072 mmol) and ammonium formate (0.058 g, 0.92 mmol). The reaction mixture was heated under reflux and stirred for 24 h. The mixture was allowed to cool to room temperature, then diluted with methanol (10 mL), filtered through Celite® and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 6% methanol in dichloromethane to give **397** as a colourless oil (0.015 g, 48%). ν_{max}/cm^{-1} (neat) 3438 (OH/NH), 3020, 2939 (CH), 1730 (CO), 1215; $[\alpha]_D^{28}$ +12.4 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.03–1.18 (4H, m, 5-H_{ax}H and 7-H_3), 1.62 (1H, td, *J* 12.5, 5.8 Hz, 3-H_{ax}H), 1.73 (2H, br s, OH and NH), 1.90 (1H, dtd, *J* 11.9, 4.5, 2.4, 5-HH_{eq}), 2.44 (1H, ddt, *J* 12.5, 4.5, 2.4 Hz, 3-HH_{eq}), 2.83–2.94 (1H, m, 6-H), 3.62–3.77 (4H, m, 4-H and OMe), 3.82 (1H, dd, $J_{eq\text{-}ax,eq\text{-}eq}$ 5.6, 2.4 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 22.7 (CH_3), 35.1 (CH_2), 43.1 (CH_2), 46.6 (CH), 52.0 (CH), 55.7 (CH_3), 66.5 (CH), 174.4 (C); *m/z* (CI) 174.1131 (MH^+. $C_8H_{16}NO_3$ requires 174.1130), 156 (30%), 133 (10), 113 (13), 85 (65), 69 (98).

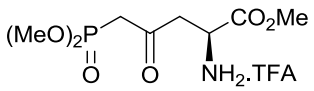
(2*S*,4*S*,6*R*)-4-Hydroxy-6-methylpiperidine-2-carboxylic acid hydrochloride 398



A solution of methyl (2*S*,4*S*,6*R*)-4-hydroxy-6-methylpiperidine-2-carboxylate **397** (0.012 g, 0.069 mmol) in hydrochloric acid (6.0 M, 5.0 mL) was heated under reflux and stirred for 24 h. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The residual oil was triturated with acetone to give an off-white solid. The product was purified by recrystallisation from methanol to give **398** as a white solid (0.017 g, 100%). Mp 140–141 °C (decomposition); ν_{max}/cm^{-1} (neat) 3333 (OH/NH), 2945 (CH), 2835, 2360, 1653, 1448, 1260, 1118, 1105; $[\alpha]_D^{24}$ +27.0 (*c* 0.7, MeOH); δ_H (400 MHz, CD_3OD) 1.23–1.63 (4H, m, 5-*H*H and 7-H_3), 1.98

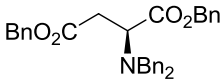
(1H, ddd, *J* 15.9, 10.5, 5.4 Hz, 3-H_{ax}H), 2.22–2.31 (1H, m, 5-H*H*), 2.59–2.71 (1H, m, 3-HH_{eq}), 3.77–3.85 (1H, m, 6-H), 3.91–3.99 (1H, m, 4-H), 4.60 (1H, dd, $J_{eq\text{-}ax,eq\text{-}eq}$ 5.3, 3.9 Hz, 2-H); δ_C (100 MHz, CD_3OD) 19.0 (CH_3), 34.0 (CH_2), 39.7 (CH_2), 47.9 (CH), 50.4 (CH), 64.0 (CH), 170.6 (C); *m/z* (CI) 160.0980 (MH^+. $C_7H_{14}NO_3$ requires 160.0974), 142 (29%), 123 (5), 114 (19), 85 (34), 69 (50).

Methyl (2*S*)-2-amino-5-(dimethoxyphosphoryl)-4-oxopentanoate trifluoroacetate 401



To a solution of methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)pentanoate **293** (0.60 g, 1.2 mmol) in dichloromethane (12 mL) under argon at room temperature was added trifluoroacetic acid (0.90 mL, 12 mmol). The reaction mixture was stirred for 2 h and then concentrated *in vacuo*. The resultant residue was dissolved in water (30 mL), washed with diethyl ether (2 × 30 mL), and then the aqueous layer was concentrated *in vacuo* to give **401** as a yellow oil (0.44 g, 100%). Methyl (2*S*)-2-amino-5-(dimethoxyphosphoryl)-4-oxopentanoate trifluoroacetate **401** was used without further purification. δ_H (400 MHz, $CDCl_3$) 3.23 (2H, d, $J_{H–C–P}$ 22.0 Hz, 5-H_2), 3.42–3.51 (2H, m, 3-H_2), 3.68–3.84 (9H, m, 3 × OMe), 4.31–4.39 (1H, m, 2-H), 8.38 (3H, br s, NH_3^+).

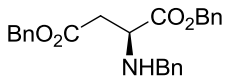
Dibenzyl (2*S*)-2-(dibenzylamino)butandioate 403[149]



To a solution of L-aspartic acid **266** (3.0 g, 23 mmol) in water (60 mL) was added potassium carbonate (16 g, 113 mmol), and the reaction mixture was heated to 100 °C. Benzyl bromide (16 mL, 135 mmol) was added portion-wise to the solution over 0.25 h and the mixture was stirred for 24 h. The reaction mixture was allowed to cool to room temperature and then diluted with water (100 mL) and extracted with dichloromethane (3 × 150 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 10% diethyl ether in petroleum ether to give **403** as a colourless oil (8.4 g, 76%). ν_{max}/cm^{-1} (neat) 3031 (ArH), 1728 (CO), 1495, 1454, 1153; $[\alpha]_D^{24}$ −61.0 (*c* 1.0, $CHCl_3$) (lit.,[149] $[\alpha]_D^{23}$ −63.0 (*c* 1.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 2.75

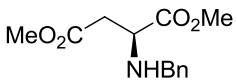
(1H, dd, *J* 15.7, 7.2 Hz, 3-*H*H), 2.96 (1H, dd, *J* 15.7, 7.9 Hz, 3-H*H*), 3.56 (2H, d, *J* 13.7 Hz, NCH_2Ph), 3.81 (2H, d, *J* 13.7 Hz, NCH_2Ph), 3.99 (1H, dd, *J* 7.9, 7.2 Hz, 2-H), 6.94 (1H, d, *J* 12.3 Hz, CO_2CH_2Ph), 5.09–5.23 (2H, m, CO_2CH_2Ph), 5.29 (1H, d, *J* 12.3 Hz, CO_2CH_2Ph), 7.18–7.52 (20H, m, ArH); δ_C (100 MHz, $CDCl_3$) 35.2 (CH_2), 54.8 (CH_2), 58.1 (CH), 66.5 (CH_2), 66.6 (CH_2), 127.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 135.7 (C), 135.8 (C), 138.9 (C), 170.9 (C), 171.4 (C); *m/z* (EI) 492 (M^+, 1%), 402 (30), 359 (98), 358 (98), 314 (2), 266 (5), 223 (14), 181 (26), 132 (65), 91 (98), 65 (44), 51 (5).

Dibenzyl (2*S*)-2-(benzylamino)butandioate 404[156]



To a solution of dibenzyl (2*S*)-2,2-(dibenzylamino)butandioate **403** (0.20, 0.41 mmol) in 3:1 acetonitrile–water (4.0 mL) at room temperature was added ammonium cerium(IV) nitrate (0.49 g, 0.85 mmol), and the reaction mixture was stirred for 2.5 h. The mixture was quenched with a saturated sodium hydrogen carbonate solution (5.0 mL), and then extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 20% diethyl ether in petroleum ether to give **404** as a colourless oil (0.14 g, 87%). Spectroscopic data consistent with literature.[156] ν_{max}/cm^{-1} (neat) 3343 (NH), 3063, 3031 (ArH), 1735 (CO), 1496, 1455, 1263, 1213, 1162; $[\alpha]_D^{22}$ −14.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.02 (1H, br s, NH), 2.64 (1H, dd, *J* 15.8, 7.0 Hz, 3-*H*H), 2.72 (1H, dd, *J* 15.8, 5.8 Hz, 3-H*H*), 3.53–3.71 (2H, m, 2-H and NCH_2Ph), 3.76 (1H, d, *J* 13.0 Hz, NCH_2Ph), 4.92–5.11 (4H, m, 2 × CO_2CH_2Ph), 7.06–7.33 (15H, m, ArH); δ_C (100 MHz, $CDCl_3$) 38.3 (CH_2), 52.0 (CH_2), 57.2 (CH), 66.6 (CH_2), 67.0 (CH_2), 127.2 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 135.6 (C), 135.7 (C), 139.5 (C), 170.6 (C), 173.4 (C); *m/z* (CI) 404 (MH^+, 100%), 402 (4), 360 (2), 314 (7), 268 (14), 223 (1), 178 (3), 147 (3), 107 (8), 69 (7).

Dimethyl (2*S*)-2-(benzylamino)butandioate 410[157]



To a solution of dimethyl (2*S*)-2-aminobutandioate hydrochloride **291** (0.10 g, 0.51 mmol) in acetonitrile (5.0 mL) at room temperature under argon was added benzyl bromide (0.073 mL, 0.61 mmol) and potassium carbonate (0.14 g, 1.0 mmol). The reaction mixture was stirred for 24 h and then concentrated *in vacuo*. The resultant residue was dissolved in ethyl acetate (20 mL), washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 20% ethyl acetate in petroleum ether to give **410** as a colourless liquid (0.071 g, 55%). ν_{max}/cm^{-1} (neat) 3350 (NH), 3028 (ArH), 2953, 1733 (CO), 1436, 1200, 1165; $[\alpha]_D^{26}$ −32.4 (*c* 1.2, $CHCl_3$) (lit.,[157] $[\alpha]_D^{20}$ −33.0 (*c* 1.4, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 2.68 (1H, dd, *J* 15.8, 7.0 Hz, 3-*H*H), 2.75 (1H, dd, *J* 15.8, 5.8 Hz, 3-H*H*), 3.60–3.81 (8H, m, NCH_2Ph, 2-H, 2 × OMe), 3.83 (1H, d, *J* 13.2 Hz, NCH_2Ph), 7.19–7.38 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 38.0 (CH_2), 51.8 (CH), 52.0 (CH_2), 52.1 (CH_3), 56.9 (CH_3), 127.1 (CH), 128.2 (CH), 128.4 (CH), 139.6 (C), 171.3 (C), 174.1 (C); *m/z* (CI) 252 (MH^+, 69%), 250 (4), 207 (3), 192 (5), 151 (4), 137 (10), 113 (13), 85 (60), 69 (100).

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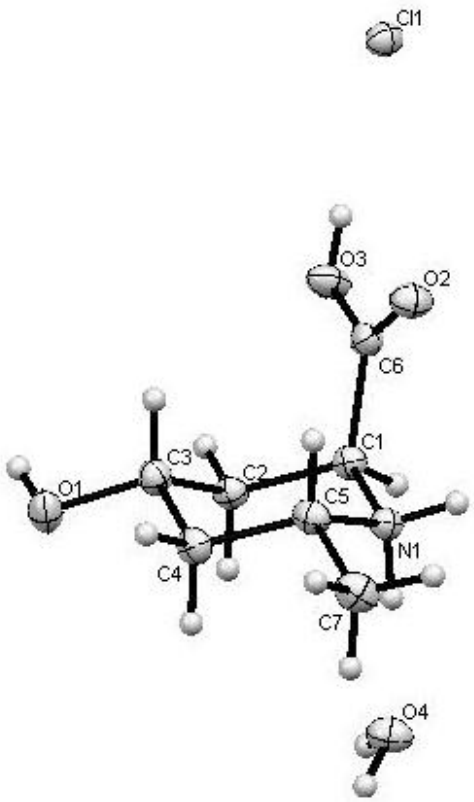
7 Appendix A



X-ray crystal structure of **398**

Table 1. Crystal data and structure refinement for lf01.

Identification code	lf01
Empirical formula	$C_7H_{16}ClNO_4$
Formula weight	213.66
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 8.2209(2) Å α= 90°.
	b = 8.9923(3) Å β= 90°.
	c = 13.8130(4) Å γ = 90°.
Volume	1021.12(5) $Å^3$
Z	4
Density (calculated)	1.390 Mg/m^3
Absorption coefficient	0.360 mm^{-1}
F(000)	456
Theta range for data collection	2.70 to 27.88°.
Index ranges	-10<=h<=9, -11<=k<=10, -18<=l<=17
Reflections collected	8583
Independent reflections	2418 [R(int) = 0.0345]
Completeness to theta = 27.88°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7455 and 0.5232
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2418 / 0 / 137
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0283, wR2 = 0.0617
R indices (all data)	R1 = 0.0352, wR2 = 0.0639
Absolute structure parameter	0.10(5)
Largest diff. peak and hole	0.231 and -0.161 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for lf01. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	7380(2)	6829(2)	6285(1)	18(1)
Cl(1)	1128(1)	4877(1)	4238(1)	21(1)
O(2)	4211(1)	6592(1)	5718(1)	23(1)
O(3)	4711(1)	4624(1)	4755(1)	25(1)
O(4)	10668(1)	6949(1)	6143(1)	24(1)
O(1)	7705(2)	2380(1)	7176(1)	24(1)
C(6)	5132(2)	5695(2)	5365(1)	19(1)
C(2)	7604(2)	4152(2)	5857(1)	18(1)
C(4)	7556(2)	4945(2)	7593(1)	20(1)
C(3)	7028(2)	3762(2)	6874(1)	20(1)
C(1)	6961(2)	5675(2)	5545(1)	17(1)
C(7)	7569(2)	7694(2)	7973(1)	26(1)
C(5)	6911(2)	6471(2)	7317(1)	20(1)

Table 3. Bond lengths [Å] and angles [°] for lf01.

N(1)-C(1)	1.4967(19)
N(1)-C(5)	1.511(2)
N(1)-H(1)	0.93(2)
N(1)-H(2)	0.92(2)
O(2)-C(6)	1.2095(19)
O(3)-C(6)	1.3253(19)
O(3)-H(3A)	0.8200
O(4)-H(4)	0.82(2)
O(4)-H(5)	0.86(2)
O(1)-C(3)	1.4245(19)
O(1)-H(1A)	0.8200
C(6)-C(1)	1.5237(19)
C(2)-C(3)	1.524(2)
C(2)-C(1)	1.530(2)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
C(4)-C(3)	1.519(2)
C(4)-C(5)	1.520(2)
C(4)-H(4A)	0.9700
C(4)-H(4B)	0.9700
C(3)-H(3B)	0.9800
C(1)-H(1B)	0.9800

C(7)-C(5)	1.524(2)
C(7)-H(7A)	0.9600
C(7)-H(7B)	0.9600
C(7)-H(7C)	0.9600
C(5)-H(5A)	0.9800
C(1)-N(1)-C(5)	115.96(12)
C(1)-N(1)-H(1)	106.8(12)
C(5)-N(1)-H(1)	108.0(13)
C(1)-N(1)-H(2)	109.4(13)
C(5)-N(1)-H(2)	110.4(13)
H(1)-N(1)-H(2)	105.6(17)
C(6)-O(3)-H(3A)	109.5
H(4)-O(4)-H(5)	105.9(19)
C(3)-O(1)-H(1A)	109.5
O(2)-C(6)-O(3)	125.27(14)
O(2)-C(6)-C(1)	124.00(14)
O(3)-C(6)-C(1)	110.71(13)
C(3)-C(2)-C(1)	110.99(12)
C(3)-C(2)-H(2A)	109.4
C(1)-C(2)-H(2A)	109.4
C(3)-C(2)-H(2B)	109.4
C(1)-C(2)-H(2B)	109.4
H(2A)-C(2)-H(2B)	108.0

C(3)-C(4)-C(5)	111.65(13)
C(3)-C(4)-H(4A)	109.3
C(5)-C(4)-H(4A)	109.3
C(3)-C(4)-H(4B)	109.3
C(5)-C(4)-H(4B)	109.3
H(4A)-C(4)-H(4B)	108.0
O(1)-C(3)-C(4)	107.91(13)
O(1)-C(3)-C(2)	110.48(13)
C(4)-C(3)-C(2)	110.65(13)
O(1)-C(3)-H(3B)	109.3
C(4)-C(3)-H(3B)	109.3
C(2)-C(3)-H(3B)	109.3
N(1)-C(1)-C(6)	109.33(13)
N(1)-C(1)-C(2)	110.43(12)
C(6)-C(1)-C(2)	113.41(13)
N(1)-C(1)-H(1B)	107.8
C(6)-C(1)-H(1B)	107.8
C(2)-C(1)-H(1B)	107.8
C(5)-C(7)-H(7A)	109.5
C(5)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(5)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5

H(7B)-C(7)-H(7C)	109.5
N(1)-C(5)-C(4)	109.86(13)
N(1)-C(5)-C(7)	108.48(13)
C(4)-C(5)-C(7)	112.26(14)
N(1)-C(5)-H(5A)	108.7
C(4)-C(5)-H(5A)	108.7
C(7)-C(5)-H(5A)	108.7

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for lf01. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	16(1)	18(1)	18(1)	-1(1)	-1(1)	0(1)
Cl(1)	19(1)	20(1)	22(1)	-3(1)	-1(1)	-2(1)
O(2)	19(1)	26(1)	25(1)	-4(1)	0(1)	1(1)
O(3)	20(1)	27(1)	30(1)	-8(1)	-7(1)	2(1)
O(4)	20(1)	31(1)	21(1)	-5(1)	-1(1)	1(1)
O(1)	33(1)	19(1)	21(1)	0(1)	-5(1)	0(1)
C(6)	20(1)	21(1)	17(1)	2(1)	-2(1)	-2(1)
C(2)	19(1)	19(1)	16(1)	-1(1)	-1(1)	-1(1)
C(4)	22(1)	23(1)	16(1)	1(1)	0(1)	-1(1)
C(3)	20(1)	19(1)	18(1)	1(1)	-1(1)	1(1)
C(1)	18(1)	20(1)	15(1)	0(1)	1(1)	-1(1)

C(7)	26(1)	27(1)	23(1)	-5(1)	-3(1)	4(1)
C(5)	19(1)	25(1)	16(1)	0(1)	0(1)	1(1)

Table 5. Torsion angles [°] for lf01.

C(5)-C(4)-C(3)-O(1)	178.98(13)
C(5)-C(4)-C(3)-C(2)	58.00(17)
C(1)-C(2)-C(3)-O(1)	-176.85(12)
C(1)-C(2)-C(3)-C(4)	-57.40(17)
C(5)-N(1)-C(1)-C(6)	73.61(17)
C(5)-N(1)-C(1)-C(2)	-51.84(17)
O(2)-C(6)-C(1)-N(1)	5.2(2)
O(3)-C(6)-C(1)-N(1)	-176.29(12)
O(2)-C(6)-C(1)-C(2)	128.87(16)
O(3)-C(6)-C(1)-C(2)	-52.59(18)
C(3)-C(2)-C(1)-N(1)	53.26(16)
C(3)-C(2)-C(1)-C(6)	-69.84(16)
C(1)-N(1)-C(5)-C(4)	51.76(17)
C(1)-N(1)-C(5)-C(7)	174.81(13)
C(3)-C(4)-C(5)-N(1)	-53.49(17)
C(3)-C(4)-C(5)-C(7)	-174.29(13)