New Approaches for the Stereoselective Synthesis of *N*-Heterocycles

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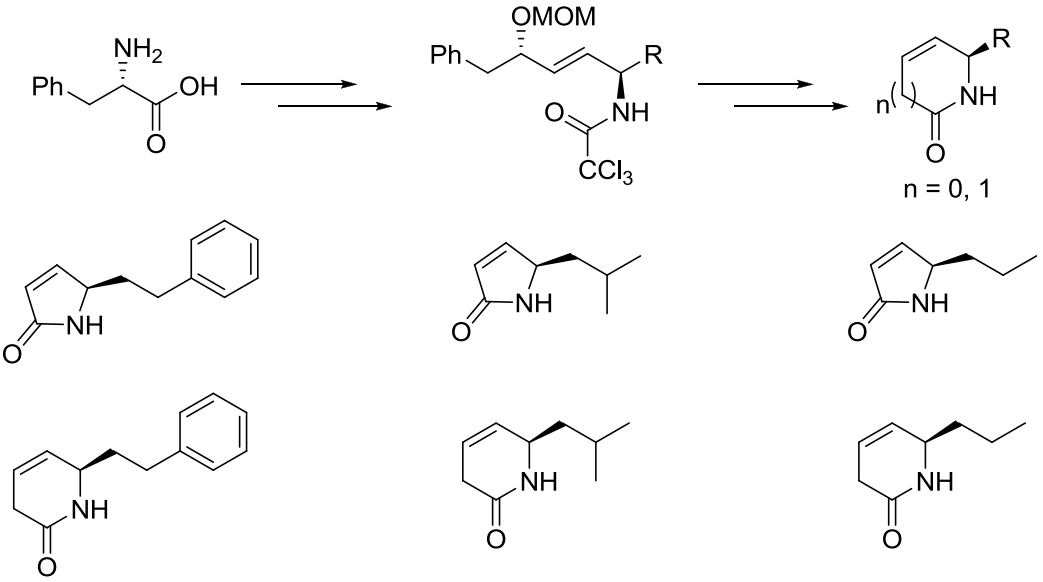
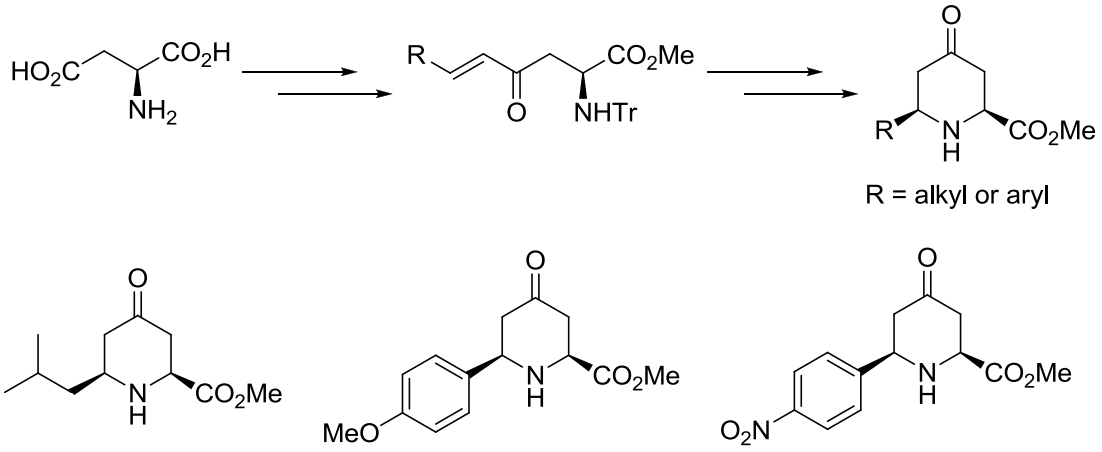
Abstract

A stereoselective approach has been developed for the flexible synthesis of substituted 2-pyrrolidones and 2-piperidones. By employing the key Overman rearrangement, efficient transfer of stereochemistry was achieved, and an acylation and ring closing metathesis strategy afforded a library of target *N*-heterocycles.



In addition, the optimisation of a synthesis of 4-oxopipecolic acid derivatives from L-aspartic acid was investigated. A novel, milder and higher yielding 6-*endo-trig* cyclisation procedure was developed. This allowed for the generation of a library of 2,6-*cis*-substituted 4-oxopipecolic derivatives. Stereoselective carbonyl reduction extended the synthesis further to include 4-hydroxypipecolic acid derivatives.



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Author's Declaration

This thesis represents the original work of Mark Daly 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:

M. Daly, K. Gill, M. Sime, G. L. Simpson and A. Sutherland, *Org. Biomol. Chem.*, 2011, **9**, 6761.

M. Daly, A. A. Cant, L. S. Fowler, G. L. Simpson, H. M. Senn, A. Sutherland, *J. Org. Chem.*, 2012, **77**, 10001.

Abbreviations

Ac	acetyl
AcO	acetate
AcOH	acetic acid
ADP	adenosine diphosphate
AIBN	azobisisobutyronitrile
Ar	aromatic
ATRC	atom transfer radical cyclisation
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
BSA	bis(trimethylsilyl)acetamide
Bu	butyl
BuLi	butyl lithium
Bz	benzoyl
°C	degrees centigrade
Cbz	carboxybenzyl
CI	chemical ionization
CN	nitrile
COD	1,5-cyclooctadiene
d	doublet
Dab	2,4-diaminobutyric acid
DBA	dibenzylideneacetone
DBAD	di-*tert*-butyl azodicarboxylate
DBU	1,8-diazabicycloundec-7-ene
DCC	dicyclohexylcarbodiimide
DEPT	distortionless enhancement by polarization transfer
DIPEA	*N*-ethyldiisopropylamine
DLP	dilauroyl peroxide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
DTBP	di-*tert*-butyl peroxide

EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI	electron impact
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
FTIR	Fourier transform infrared
g	gram(s)
Gly	glycine
h	hour(s)
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HWE	Horner-Wadsworth-Emmons
i-Pr	isopropyl
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
lit.	literature
m	multiplet
M	molar
Me	methyl
MeCN	acetonitrile
MHz	megahertz
mL	millilitre(s)
mmol	millimole(s)
mol	mol(s)
MOM	methoxymethyl ether
Mp.	melting point
m/z	mass to charge ratio
NHK	Nozaki-Hiyama-Kishi
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ph	phenyl
Pd/C	palladium on carbon

PMB	paramethoxybenzyl
PMDETA	pentamethyldiethylenetriamine
PMI	pyridylmethanimine
ppm	parts per million
p-TSA	*para*-toluenesulfonic acid
Pyr	pyridine
q	quartet
quin	quintet
RCM	ring-closing metathesis
r.t.	room temperature
s	singlet
sept	septet
sex	sextet
t	triplet
Tf	triflyl
TFA	trifluoroacetic acid
TfO	triflate
THF	tetrahydrofuran
TLC	thin layer chromatography
TPAP	tetrapropylammonium perruthenate
Tr	trityl (1,1,1-triphenylmethyl)
Ts	*para*-toluenesulfonyl
TBDMS	*tert*-butyldimethylsilyl

1 Introduction

1.1 2-Pyrrolidones and 2-Piperidones as Synthetic Targets

Heterocycles are structures of great importance throughout the natural and synthetic worlds of chemistry. The wide variety of structures that fall under the heterocycle banner are compounds ranging from natural products isolated from marine species to man-made polymers, and as a result their synthesis has received substantial attention in the literature.[1,2,3] Our contribution to heterocycle synthesis includes novel methodology towards substituted 2-pyrrolidones and 2-piperidones, also known as γ- and δ-lactams respectively. Both these moieties can be found in a variety of biologically active compounds. Examples of the 2-pyrrolidone moiety in interesting target molecules can be found in Figure 1. Levetiracetam **1** is an anticonvulsant drug used in the treatment of epileptic seizures.[4] Although the exact mechanism of action is unknown, it is believed to bind to synaptic vesicle protein SVA2, and integral membrane protein found on every synaptic vesicle, and in doing so impedes nerve conduction. Reutericyclin **2** is a product of *Lactobacillus reuteri* bacteria that shows promising antibacterial activity against Gram-positive strains, including *Clostridium difficile*, and is believed to have potential therapeutic value.[5] Glimepiride **3** is an antidiabetic sulfonylurea drug that increases insulin production in the pancreas and the activity of intracellular insulin receptors.[6]

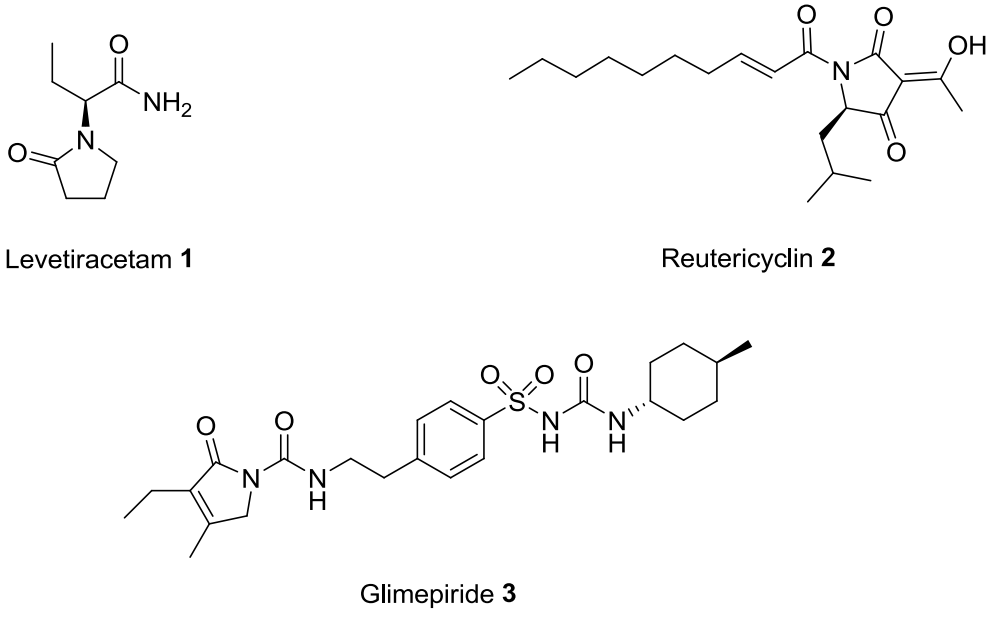
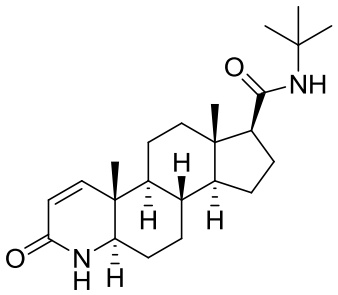
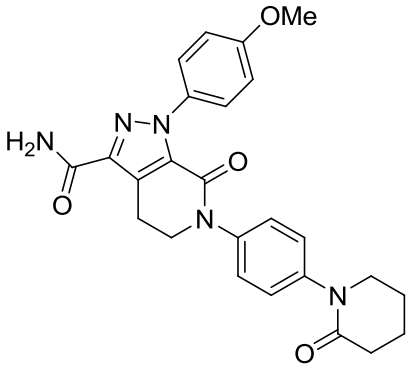


Figure 1: 2-Pyrrolidone containing compounds

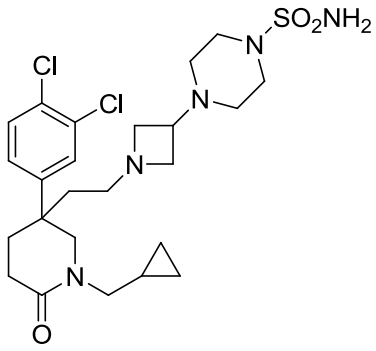
The 2-piperidone moiety is also a component of several compounds of interest (Figure 2). Finasteride **4** is an inhibitor of 5α-reductase, an enzyme that converts testosterone to dihydrotestosterone, and is used in the treatment of benign prostatic hyperplasia and male pattern baldness.[7] Apixaban **5** is a compound currently undergoing clinical trials as a treatment for venous thromboembolism.[8] Compound UK-224,671 **6** is a potent antagonist of the neurokinin 2 (NK2) receptor. The NK2 receptor is known to be involved in numerous pathways in the central nervous system, and antagonists have been postulated as potential therapies for psychiatric disorders.[9] The aforementioned compounds comprise a small selection of the range of biologically, synthetically and commercially useful compounds that bear the 2-pyrrolidone and 2-piperidone motifs. In addition, these moieties are often utilised as an intermediate in the synthesis of piperidines and pyrrolidines, which are in turn present in a wide array of useful compounds.



Finasteride **4**



Apixaban **5**



UK-224,671 **6**

Figure 2: 2-Piperidone containing compounds

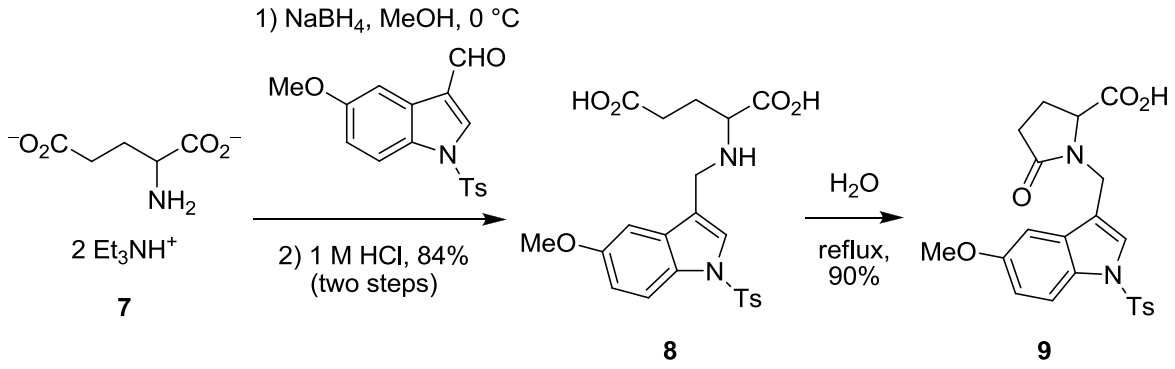
As a result of their synthetic utility and frequent presence in biologically active compounds, the synthesis of the 2-pyrrolidone and 2-piperidone moieties has received substantial attention in the literature for several decades.[10, 11, 12] Although they are

relatively simple structures, a diverse array of chemistry has been employed in their synthesis. This is perhaps due to the high level of substitution possible around the core of the 2-pyrrolidone and 2-piperidone rings, and the natural progression towards more stereoselective syntheses observed throughout the majority of the synthetic organic literature. The syntheses presented below are not intended to provide an exhaustive list of possible synthetic routes to 2-pyrrolidone and 2-piperidone based structures, but to illustrate some generalised approaches that have been used to access the aforementioned moieties.

1.2 Synthesis of 2-Pyrrolidones

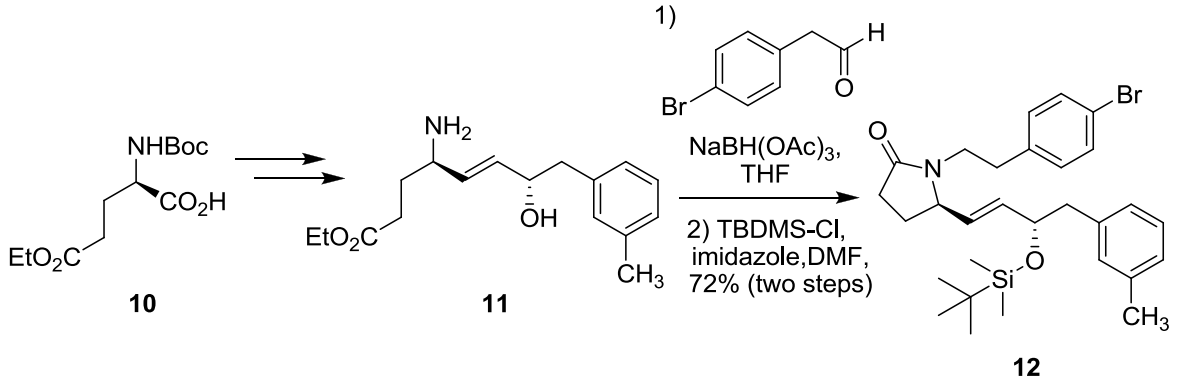
1.2.1 Lactamisation

An attractive synthetic approach towards 2-pyrrolidones is the lactamisation of γ-aminobutyric acid and derivatives thereof. With suitable compounds, this cyclisation can be remarkably straightforward, as demonstrated by Rigo and co-workers (Scheme 1).[13] Reductive amination with a range of aryl aldehydes was conducted on the triethylammonium salt of glutamic acid **7**. Following acidification to the carboxylic acid **8**, cyclisation was effected by stirring under reflux in ethanol or water to afford the 5-carboxylic acid-2-pyrrolidone **9** in good yield.



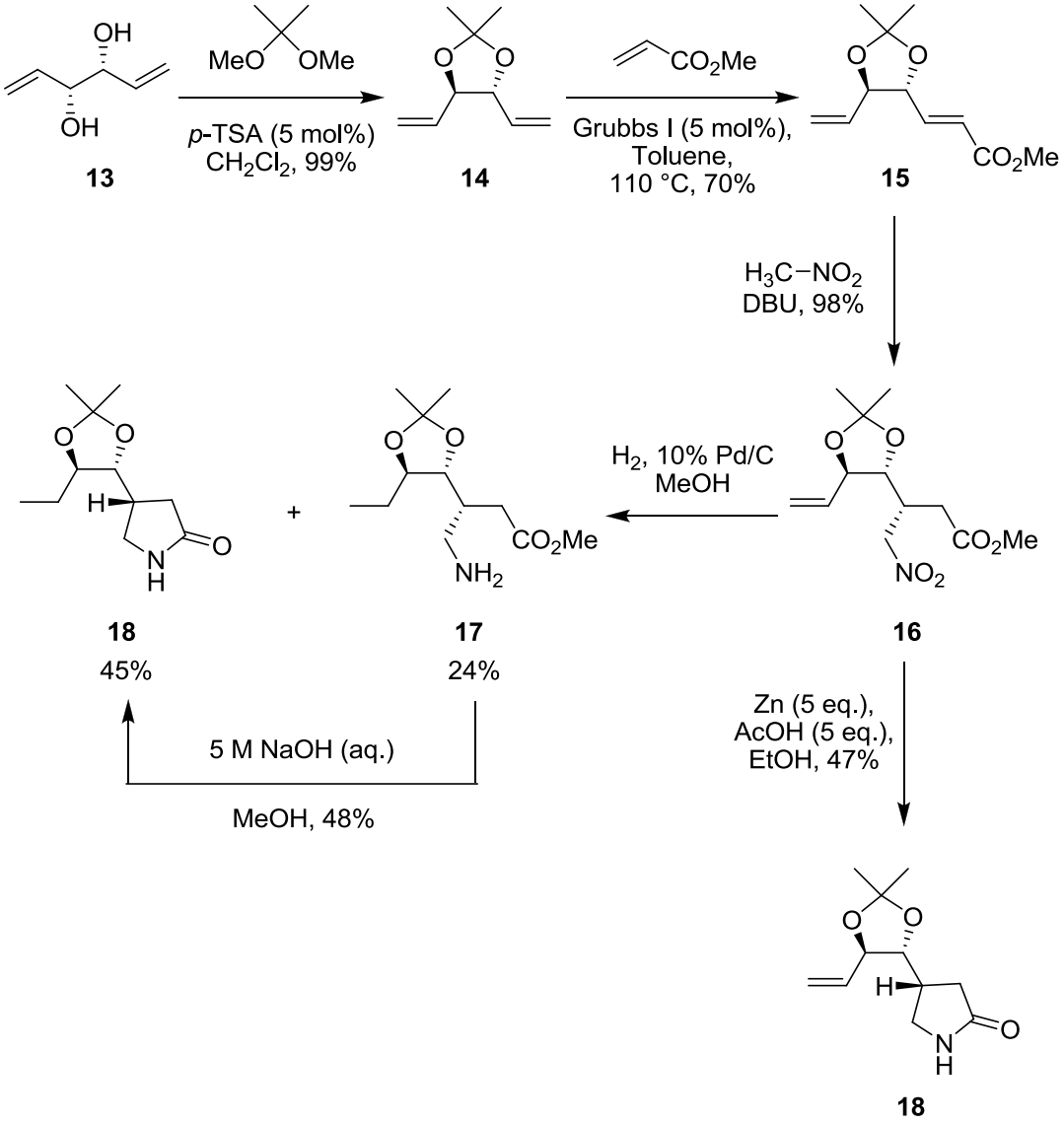
Scheme 1: Cyclisation of glutamic acid derivatives

Similar transformations were conducted in an arguably more efficient manner by Kambe and co-workers by combining the reductive amination and cyclisation in one step (Scheme 2).[14] Employing *N*-Boc-D-glutamic acid derivative **10**, a number of transformations led to allylic alcohol **11**. Imine formation with 2-(4-bromophenyl)acetaldehyde, followed by reduction with sodium triacetoxyborohydride effected cyclisation with the ester moiety; overall, an *N*-alkylation and cyclisation in a one-pot process, affording lactam **12**. This compound and a number of others with similar structural backbones were synthesised by Kambe to investigate their potential as prostaglandin mimetics. A key component of this strategy was the substitution of the naturally occurring γ-hydroxycyclopentanone moiety with the 2-pyrrolidinone core in an attempt to increase selectivity and stability.



Scheme 2: Synthesis of prostaglandin mimetics

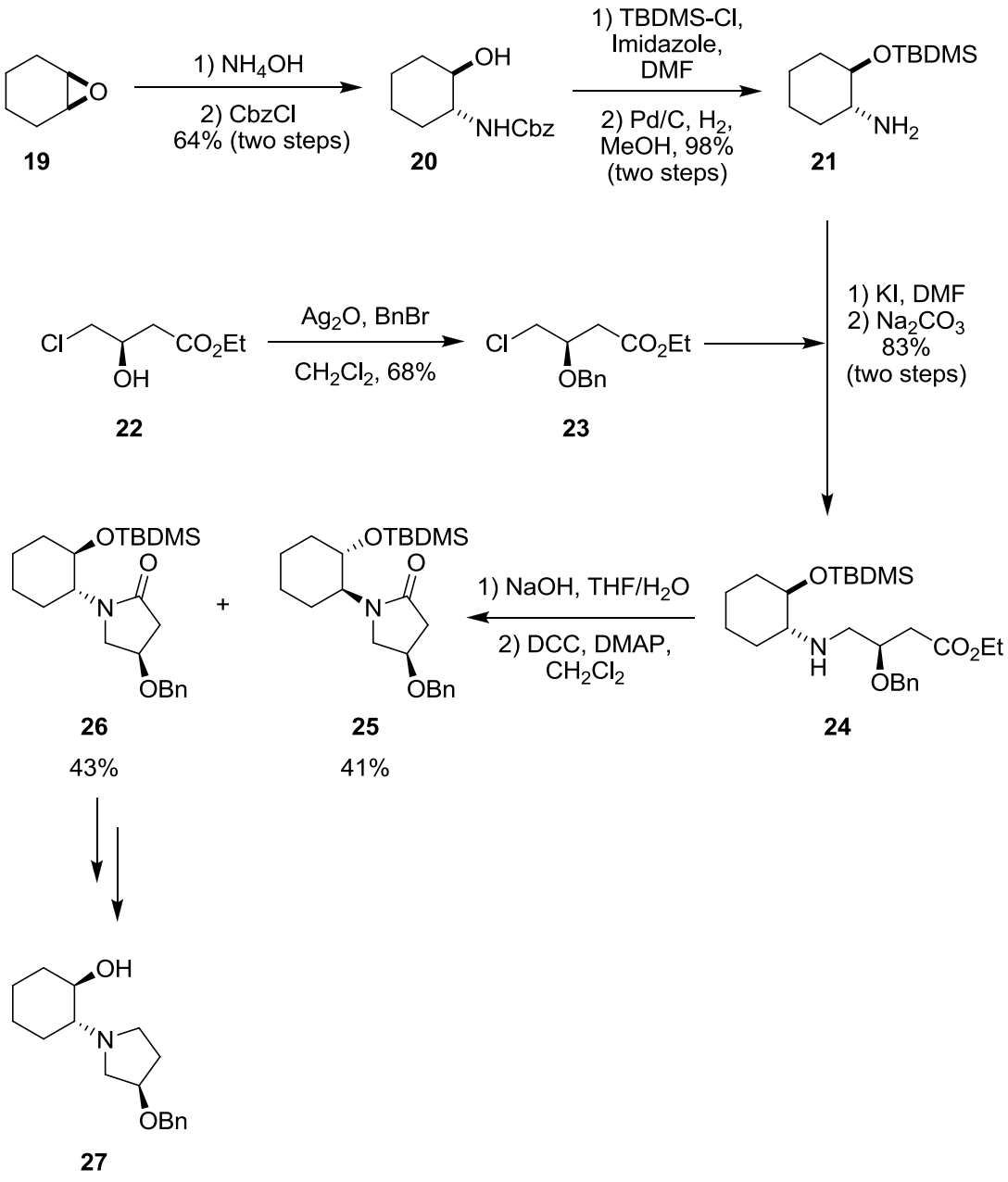
Lactamisation has also been observed occurring in situ upon the generation of appropriate functionality within the precursor, as exemplified by Schmidt and co-workers (Scheme 3).[15] Investigation of the cross metathesis between acetal diene **14** and methyl acrylate lead to conditions that favoured the formation of mono-cross-metathesis product **15**. The α,β-unsaturated ester allowed for the 1,4-addition of nitromethane, forming nitroalkane **16** as a single diastereomer in excellent yield. Nitro reduction was then investigated; hydrogenation over palladium/carbon afforded the cyclised lactam **18** in 45% yield, but the uncyclised free amine **17** was also isolated in 24% yield. This could be cyclised under basic conditions, albeit in modest yield. Alternatively, nitro reduction could be effected by employing zinc and acetic acid. This formed exclusively the lactam product, but in a moderate 47% yield. Whilst this procedure may be relatively low yielding, it may be fairer to consider it a two-step, one-pot procedure that reduces the amount of practical manipulation required.



Scheme 3: Nitro reduction and cyclisation

The coupling of an amine and a carboxylic acid to form the amide bond using carbodiimides and similar reagents is most commonly utilised in the synthesis of peptides, but as demonstrated by Yu and co-workers, it also finds utility in the cyclisation of lactams (Scheme 4).[16] This methodology can be found in their synthesis of compound **27**, a precursor to the cardiac anti-arrythmic drug vernakalant (Brinavess). Reaction of the meso compound epoxy cyclohexane **19** with aqueous ammonia followed by *N*-protection with benzyl chloroformate, silyl protection of the hydroxyl with TBDMS-Cl then Cbz removal by hydrogenation led to racemic **21**. Separately, enantiopure chloroester **23** was synthesised from commercially available ethyl (*R*)-4-chloro-3-hydroxybutanoate by reaction with benzyl bromide in the presence of silver oxide. Chloroester **23** was treated with potassium iodide and used to *N*-alkylate amine **21**. Saponification with sodium hydroxide afforded the carboxylic acid, which was cyclised with the amino moiety using

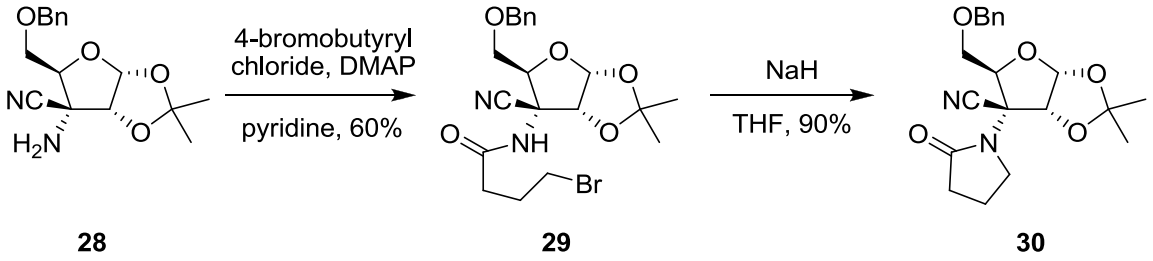
DCC and DMAP. The lactam diastereomers **25** and **26** were easily separable by column chromatography. This is reported as a significant benefit over previous syntheses; the original medicinal chemistry route required multiple chiral resolutions, and a later route used chiral ligands or boranes that were difficult to recycle. Acidic desilylation and hydride amide reduction led to the desired synthetic intermediate **27**.



Scheme 4: DCC coupling for the formation of lactams

1.2.2 Intramolecular Nucleophilic Substitution

Intramolecular nucleophilic substitution can be utilised as a cyclisation technique, as demonstrated by Postel and co-workers (Scheme 5).[17] Their study of the cyclopropanation of nitriles necessitated the protection of primary amine **28** as a tertiary amide, and the 2-pyrrolidone moiety was trialled in this role. Synthesis proved facile; amine acylation with 4-bromobutyryl chloride followed by amide deprotonation with sodium hydride and subsequent cyclisation afforded the desired compounds in good yield.

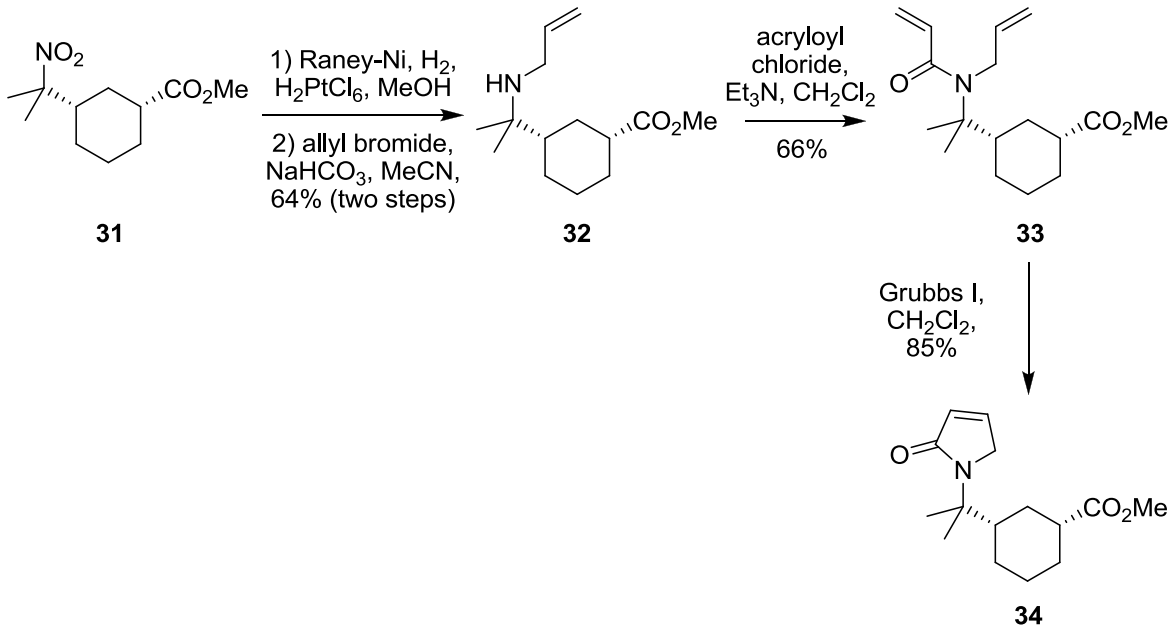


28 **29** **30**

Scheme 5: Intramolecular cyclisation

1.2.3 Ring-Closing Metathesis

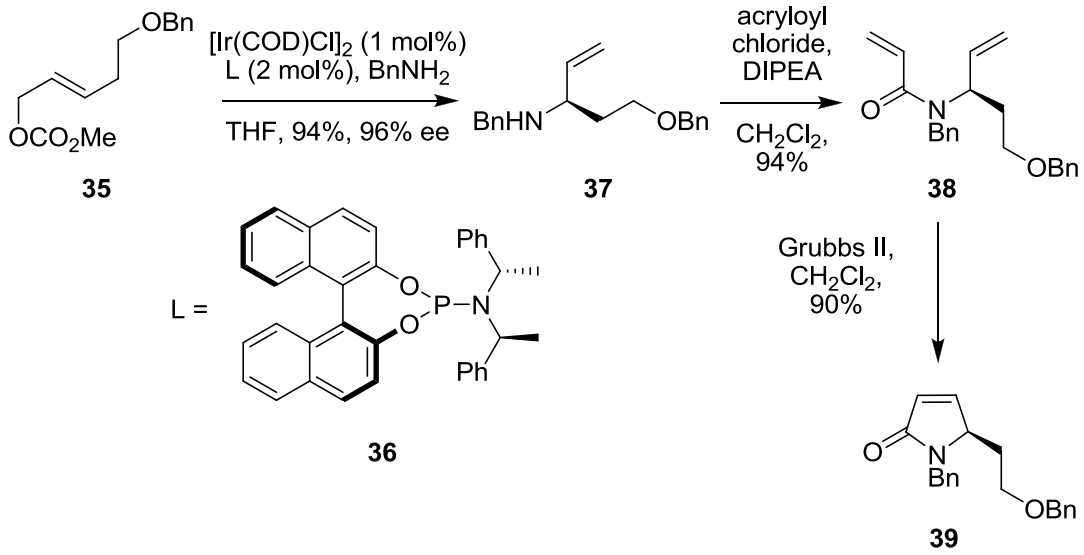
Whilst ring-closing metathesis (RCM) reactions are often applied to the synthesis of medium and large sized rings, the have also been utilised in the synthesis of smaller γ-lactam derivatives. Hanessian and co-workers used RCM reactions to good effect in their synthesis of an inhibitor for aspartyl protease β-secretase (BACE-1), an enzyme implicated in the pathogenesis of Alzheimer's disease (Scheme 6).[18] Nitro hydrogenation of substituted cyclohexane **31** afforded the primary amine derivative. Alkylation with allyl bromide followed by acylation with acryloyl chloride afforded the diene precursor **33**. Grubbs 1st generation catalyst mediated RCM then afforded the unsaturated γ-lactam intermediate **34** in good yield.



31 **32** **33** **34**

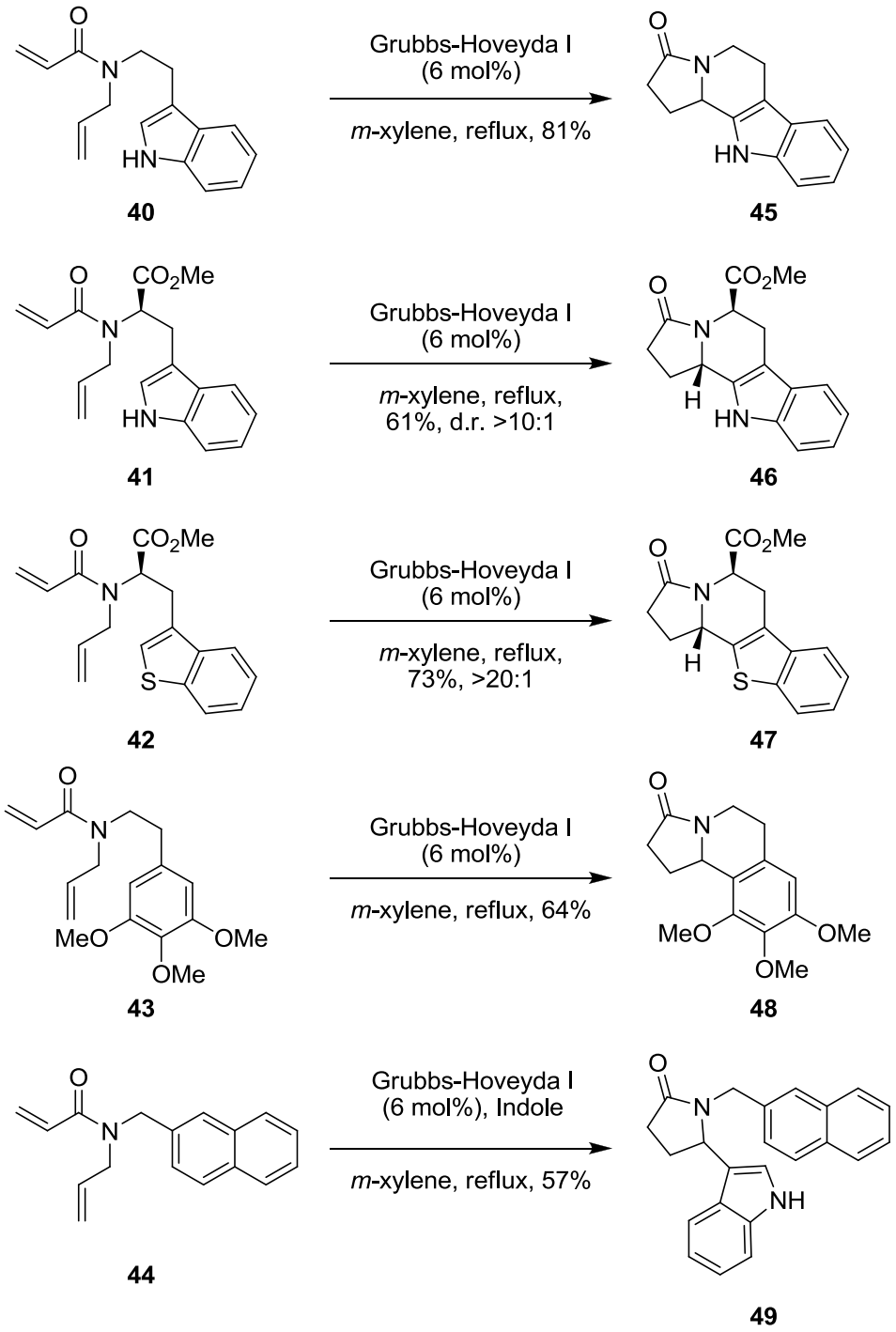
Scheme 6: RCM in the synthesis of BACE-1 inhibitor

The ring-closing metathesis of diene amides as exemplified above is often facile, and in some cases a greater challenge is experienced in the synthesis of the precursors, as was found by Lee and co-workers.[19] In this work, an intermediate in the synthesis of a variety of lactams was chiral allylic amine **37** generated from the iridium catalysed amination of allylic carbonates (Scheme 7). Once the regioselective difficulties of the amination were investigated, it was found that *O*-alkylated allylic methyl carbonate **35** could undergo amination with benzylamine in the presence of $[Ir(COD)Cl]_2$ and Feringa's phosphoramidite chiral ligand[20] **36** to afford allyl amine **37** in excellent yield and stereoselectivity. Alkylation with bromoalkenes afforded diene precursors to aza-cycles. More relevant to this discussion, acylation with acyl chlorides afforded amide dienes such as **38** that cyclised smoothly in the presence of Grubbs 2nd generation catalyst to afford a small range of lactams, including unsaturated 2-pyrrolidone **39**.



Scheme 7: Iridium catalysed amination and subsequent RCM

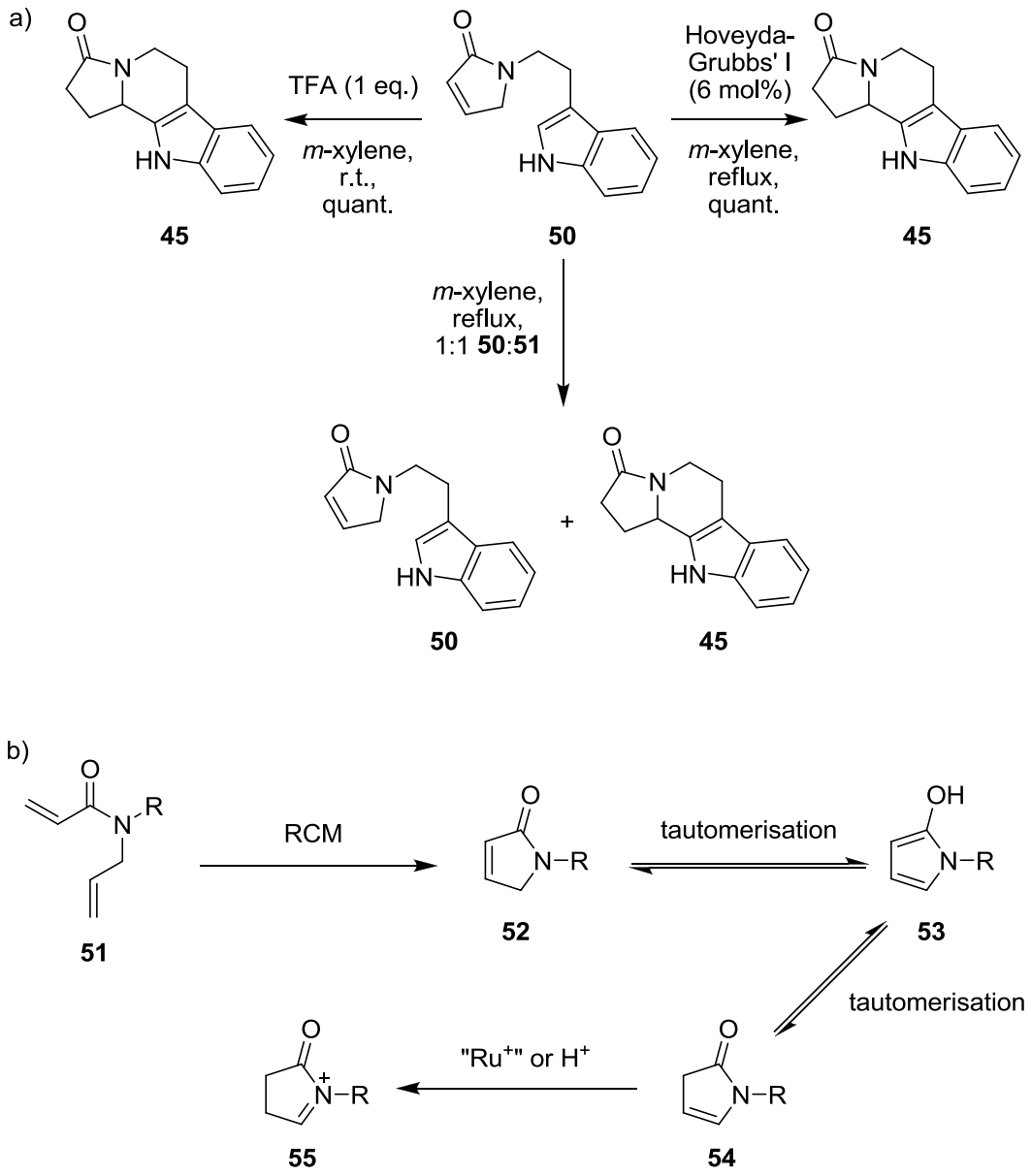
While the mainstay of ruthenium alkylidene catalysts is metathesis, several non-metathetic reactions have been noted, often originally as unintended side reactions. However, in some cases, these side reactions can be exploited to become useful methodologies in their own right. This was demonstrated in the tandem RCM/isomerisation/*N*-acyliminium cyclisation published by Nielsen and co-workers (Scheme 8).[21] Reaction of dienes containing a tethered nucleophile **40**–**43** with Hoveyda-Grubbs 1st generation catalyst in refluxing *m*-xylene afforded polycyclic compounds **45**–**48**. The presence of a stereocentre in substrates **41** and **42** promoted a diastereoselective cyclisation, forming **46** and **47** with reasonable selectivity. Product **49** demonstrates the scope of the reaction to include intermolecular nucleophilic additions.



Scheme 8: Tandem RCM/isomerisation/*N*-acyliminium cyclisation

Manipulation of the reaction conditions yielded results that alluded to some mechanistic properties of the reaction (Scheme 9a). Reaction of the diene for a reduced amount of time at 60 °C rather than under reflux afforded the metathesis product **50** only. Reflux of **50** in *m*-xylene only afforded a 1:1 mix of diene and tetracyclic product. However, addition of fresh ruthenium catalyst afforded a quantitative conversion to **45**, as did the use of trifluoroacetic acid. This suggested that while a background thermal isomerisation does

occur, addition of acid or ruthenium catalyst accelerates the reaction. As TFA promotes tetracycle formation as effectively as the ruthenium catalyst, this suggested that the ruthenium in some way effects tautomerisation rather than a ruthenium hydride species being involved. The isomerisation shown in Scheme 9b was proposed.

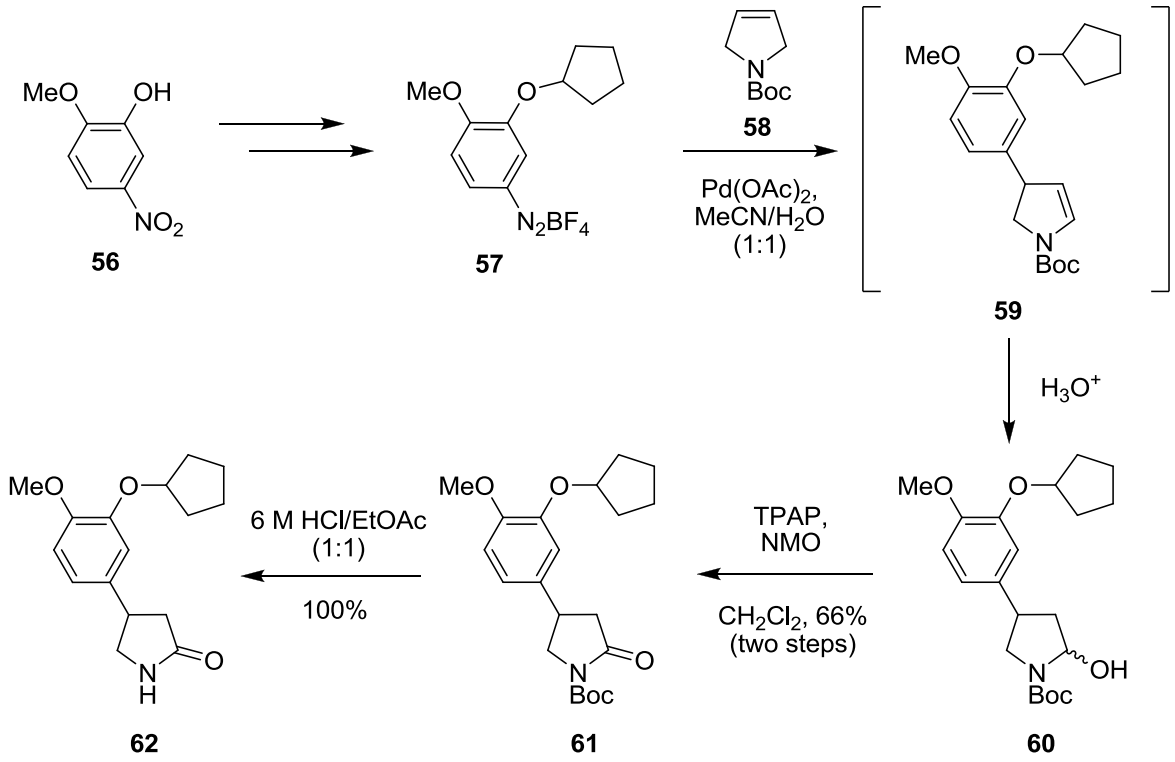


Scheme 9: Investigations into the tandem RCM/isomerisation/*N*-acyliminium cyclisation

1.2.4 Oxidation of Pyrrolidine

Whilst it is common to see reduction of pyrrolidones and piperidones to pyrrolidines and piperidines respectively, it is possible to perform the reverse transformation. This was utilised by Correia and co-workers in their synthesis of rolipram, a phosphodiesterase IV

(PDE4) inhibitor that shows promising anti-inflammatory and anti-depressant properties (Scheme 10).[22] Their synthesis began with 2-methoxy-5-nitrophenol, which after a number of straightforward reactions was converted to the aryldiazonium tetrafluoroborate **57**. Coupling of **57** with *N*-Boc-3-pyrroline **58** in a Heck-Matsuda reaction afforded intermediate **59**, which under the aqueous acidic reaction conditions was hydrolysed in situ to lactamol **60**. Oxidation of **60** using catalytic amounts of tetrapropylammonium perruthenate (TPAP) and NMO as a co-oxidant afforded 2-pyrrolidone **61**, which after acidic Boc-deprotection afforded the target rolipram **62**. This six step synthesis was performed in an overall yield of 45% and provides a cost effective and efficient route to a pharmacologically interesting molecule.

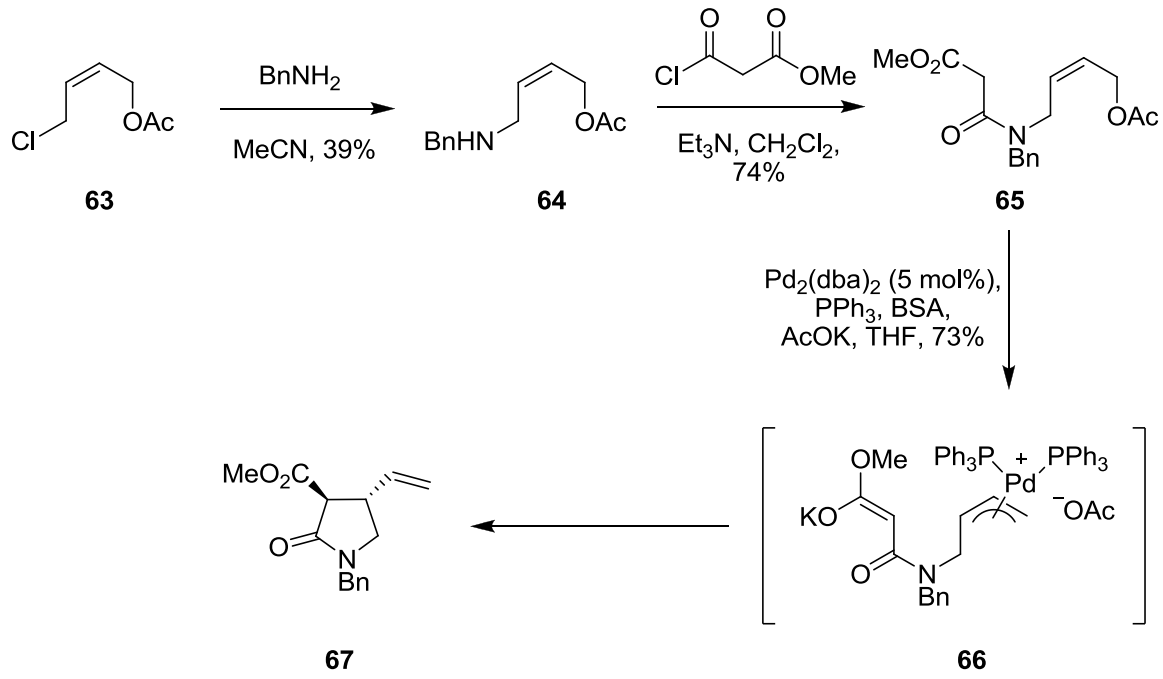


Scheme 10: Synthesis of rolipram

1.2.5 C-3 to C-4 Disconnections

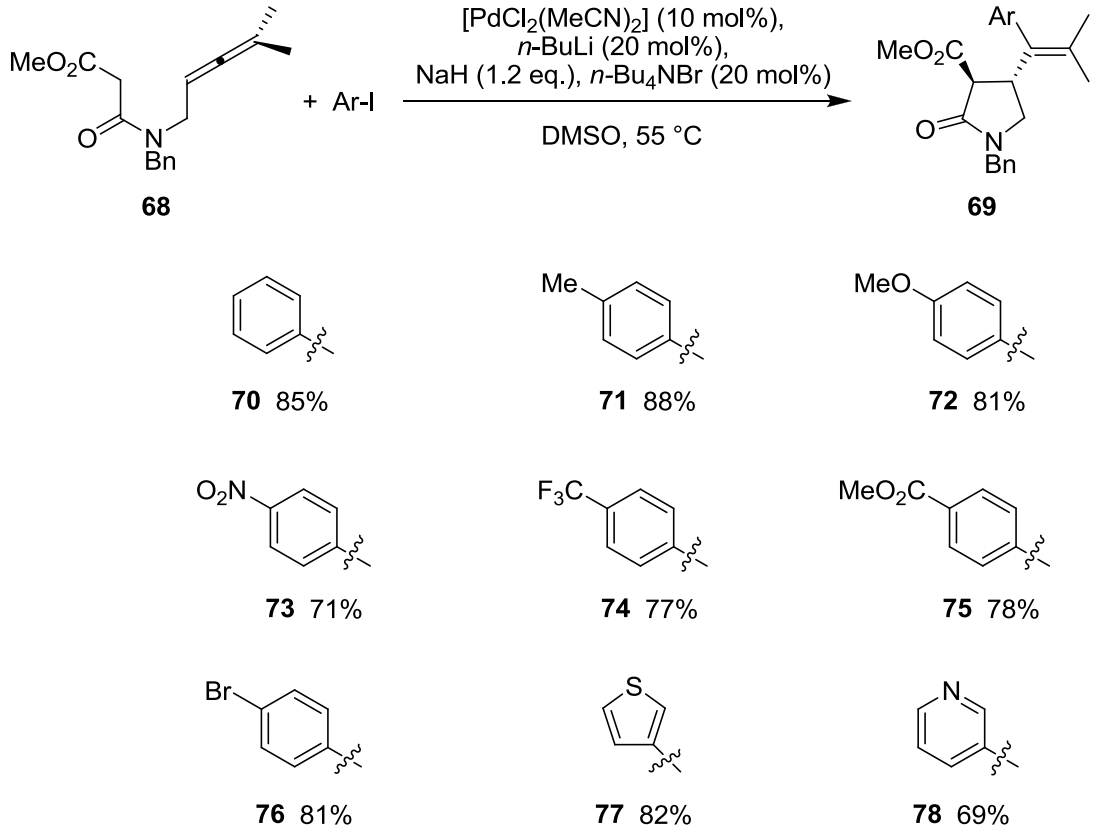
The retrosynthetic strategy of disconnection between the C-3 and C-4 of 2-pyrrolidone has received attention; for example, the palladium catalysed intramolecular allylation reported by Poli and co-workers (Scheme 11).[23] Benzylamine was alkylated with freshly prepared (*Z*)-1-acetoxy-4-chloro-but-2-ene **63**, then acylated with methyl malonyl chloride to afford enamide **65**. Investigations into cyclisation conditions revealed $Pd_2(dba)_2/PPh_3$ as the most

suitable catalyst for the formation of the π-allyl-palladium complex, and potassium acetate/bis(trimethylsilyl)acetamide (BSA), the most effective base mixture for enolisation. These conditions afforded pyrrolidone **67** in good yield and solely the *anti*-diastereomer was detected in the product. The absence of a potentially competing 7-*endo*-*trig* product shows complete favour for the observed 5-*exo*-*trig* cyclisation process. Substitution of the malonyl chloride with acid chlorides bearing various electron withdrawing groups such as nitrile, acetyl and phenylsulfonyl gave analogous 2-pyrrolidones in comparable yields.



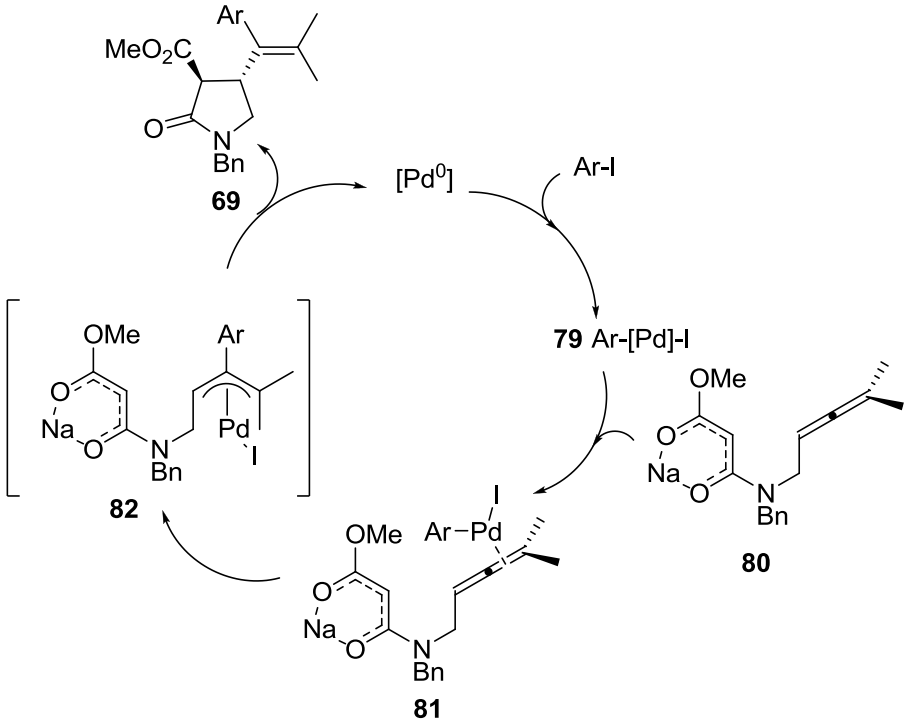
Scheme 11: Palladium catalysed intramolecular allylation

More recently, Poli and Prestat published a further refined intramolecular allylation domino reaction, allowing the synthesis of 4-styryl substituted 2-pyrrolidones (Scheme 12).[24] In this work, the allyl acetate is replaced by an allene, which undergoes carbopalladation followed by nucleophilic addition to afford compounds of the type represented by **69**. The reaction was shown to have a broad scope in terms of substituents and nature of the coupling aryl iodide, as analogues **70**–**78** illustrate. As above, the 5-*exo*-*trig* cyclisation and selectivity for the *trans*-diastereomer was displayed. The slightly unusual catalyst system using *n*-butyl lithium as an in situ reducing agent was trialled as a phosphine free alternative, and afforded improved yields. The addition of tetrabutylammonium bromide was also found to improve yields, as previously described in the literature.[25]



Scheme 12: Carbopalladation and allylic alkylation domino sequence

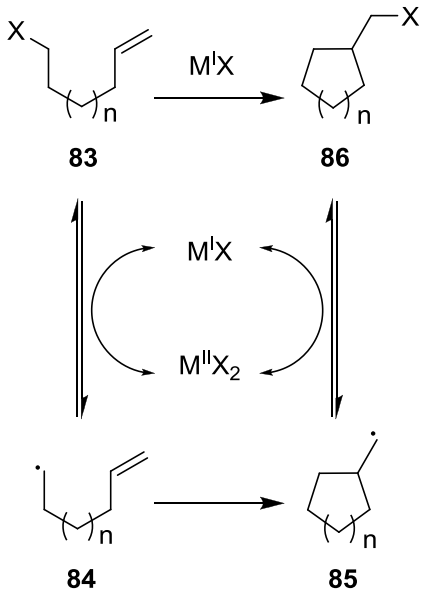
The catalytic cycle proposed by Poli and Prestat is shown below (Scheme 13). Oxidative addition of palladium(0) to the aryl iodide forms the aryl palladium species **79**. This species coordinates to the allene, which undergoes carbopalladation to form π-allyl palladium intermediate **82**. This undergoes nucleophilic attack by the deprotonated β-carbonyl amide forming the desired 2-pyrrolidone and releasing [Pd^0].



Scheme 13: Proposed mechanistic cycle for carbopalladation and allylic alkylation

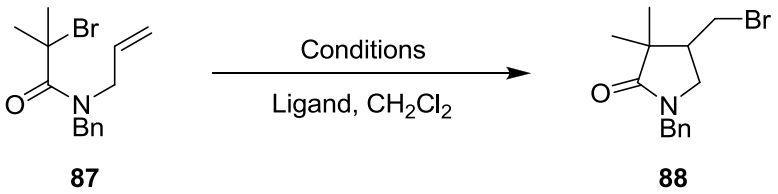
1.2.6 Radical Mediated Cyclisations

Transition metal catalysed atom transfer radical cyclisation (ATRC) reactions have recently been the subject of increased interest. Copper complexes have been most extensively investigated for these reactions, but studies into ruthenium and iron based complexes have also been published. The basic transformation is depicted in Scheme 14; transition metal mediated halogen (X) abstraction from an alkyl halide forms an alkyl radical **84**. This cyclises onto a tethered alkene (or alkyne) forming intermediate **85** and the resulting radical is quenched with the metal complexed halogen, hence atom transfer.



Scheme 14: General pathway of ATRC reactions

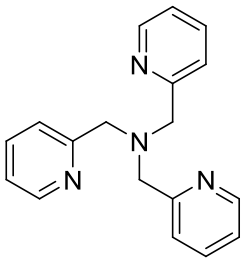
2-Pyrrolidone analogues appear to be frequently chosen as desired products in ATRC investigations. As the catalytic cycles involved are thought to be understood, further research often focuses on increasing the efficiency of reactions, with a view to better suitability for industrial processes. One such study was conducted by Clark and Wilson,[26] who noted the relatively high loadings of Cu(I) catalysts (around 30 mol%) required in some procedures, and suggested that this could be the result of a gradual oxidation to the inactive Cu(II) species throughout the reaction. While not the first investigation of reductive additives, their investigation of AIBN in the reaction mixture succinctly shows the benefits of such additives (Scheme 15). The original conditions employed to convert alkene **87** to 2-pyrrolidinone **88** used 30 mol% CuBr (with tripyridylamine ligand **89**) and gave excellent yields, but lowering the catalyst concentration to a more commercially favourable 1 mol% led to a substantial drop. Whilst increasing the temperature to 50 °C shows marginal improvement, addition of just 10 mol% of AIBN returns the yield to 100%. Additionally, the reaction ran with 1 mol% of the more stable $CuBr_2$ replacing CuBr, with equally impressive results.



87 **88**

Temp (°C)	Catalyst	Catalyst loading (mol%)	AIBN (mol%)	Yield (%)
rt	CuBr	30	-	100
rt	CuBr	1	-	5
50	CuBr	1	-	14
50	CuBr	1	10	100
50	$CuBr_2$	1	10	100

Ligand=

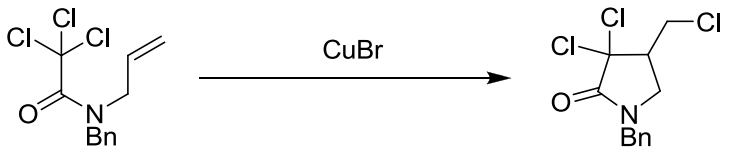


89

Scheme 15: AIBN as a reductive additive in ATRC reactions

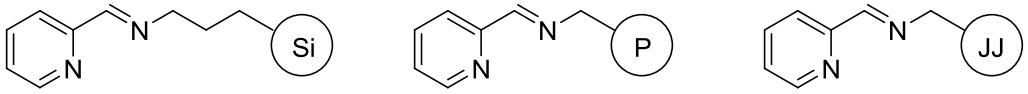
Clark also increased the industrial appeal of the Cu(I) mediated ATRC by investigating the use of solid supported ligands and catalyst.[27] A range of ligands on three types of solid support (Si – silica, P – cross-linked polystyrene and JJ – JandaJel) were investigated. The preparation of the solid support/ligand/CuBr reagent was shown by analysis to incur variation in the mmols of complex per gram of support. Having completed this analysis however, the quantity of catalyst per reaction could be kept constant at 30 mol%. Their results showed that that support type had little effect on yield (Scheme 16). For example, in Scheme 16a, using the PMI ligand on all three support types (**92**–**94**) showed minor variation in yield, and this was broadly true throughout the study. The cyclisation of **95** in Scheme 16b reveals a drawback of the heterogenous catalyst system. In comparison to the homogenous solution catalyst **97**, the solid supported variety **98** afforded no product at room temperature and required heating to afford a similar result.

a)



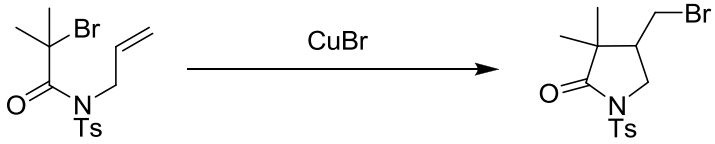
90 **91**

Resin	Time	Yield (%)
Si-PMI	3 h	92
P-PMI	3 h	98
JJ-PMI	3 h	100



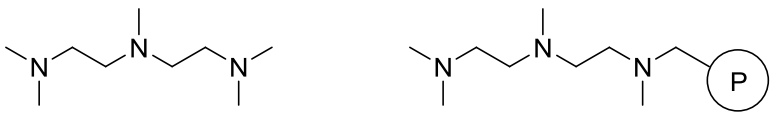
92 Si-PMI **93** P-PMI **94** JJ-PMI

b)



95 **96**

Ligand/Resin	T (°C)	Time (h)	Yield (%)
PMDETA	18	0.5	99
P-PMDETA	18	48	0
P-PMDETA	83	0.5	95



97 PMDETA **98** P-PMDETA

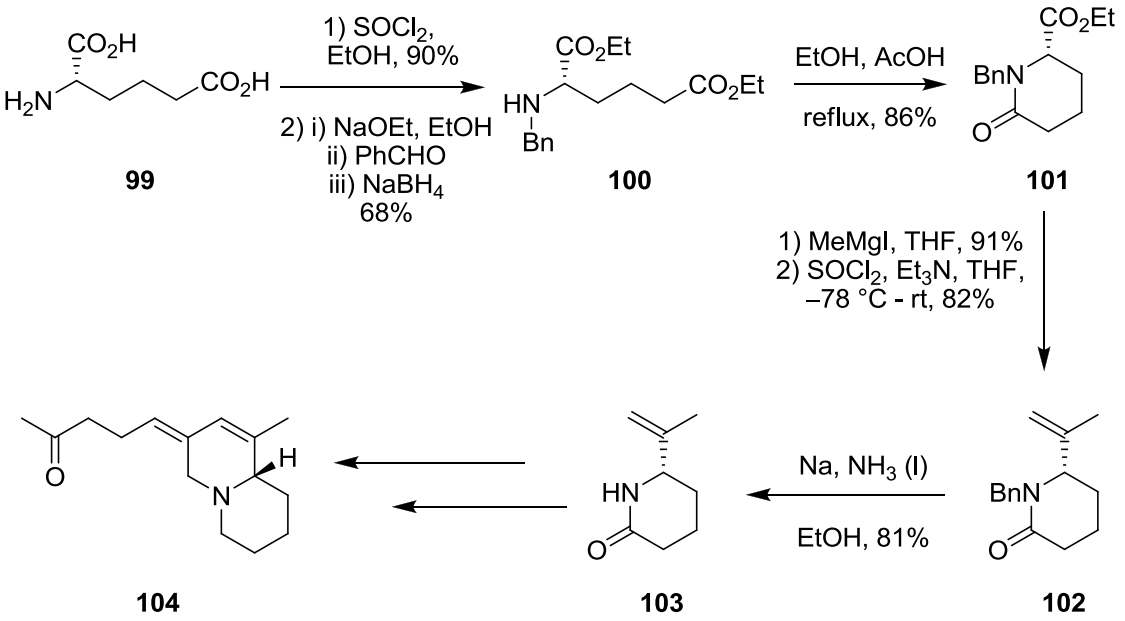
Scheme 16: Investigation of solid supported catalysts in ATRC reactions

1.3 Synthesis of 2-piperidones

1.3.1 Lactamisation

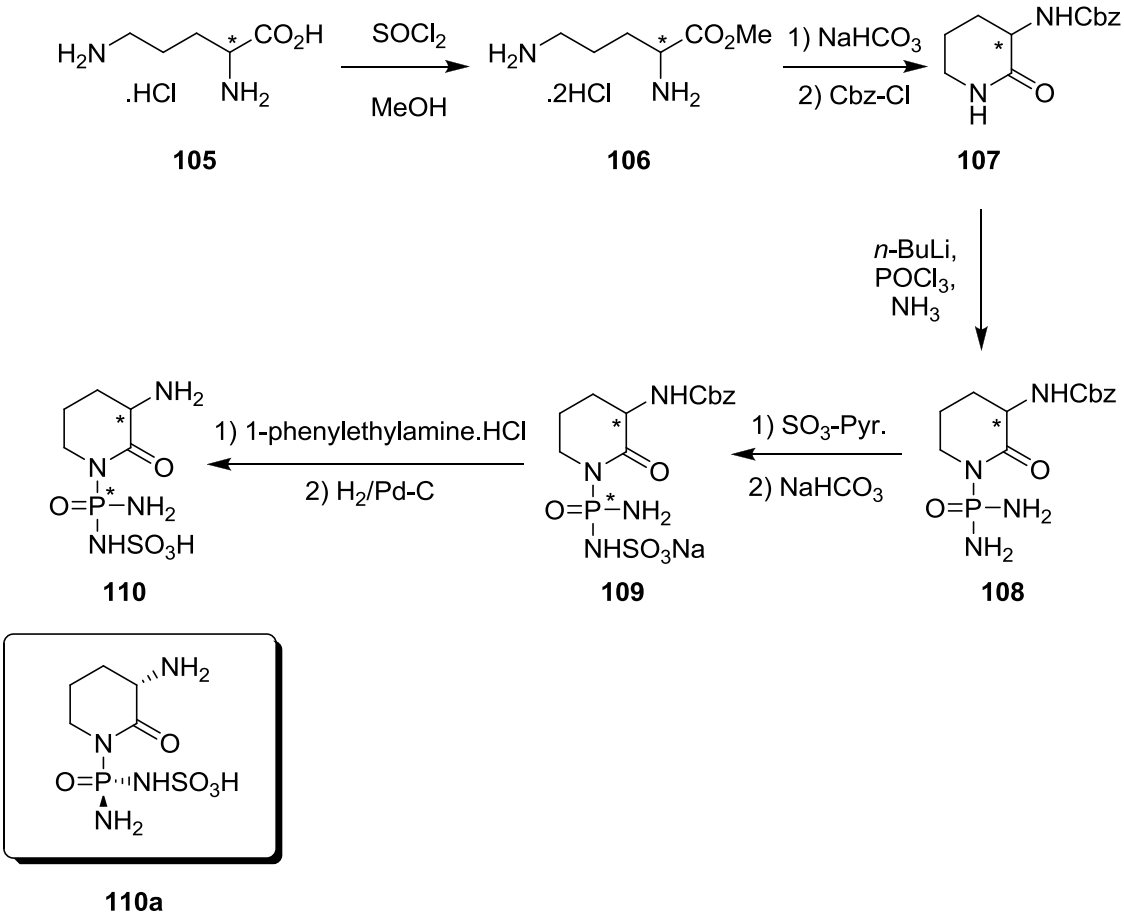
Similarly to the 2-pyrrolidones, an obvious disconnection in the retrosynthesis of 2-piperidones for the organic chemist lies in the amide bond, affording the straight α-carboxy δ-amino synthon. Indeed, a review of the literature shows that a simple lactamisation has been utilised in a variety of syntheses to afford the desired heterocycle.

An acid catalysed lactamisation was employed by Stevenson and co-workers as part of their synthesis of pumiliotoxin alkaloids, a range of related compounds originally isolated from *Dendrobates* frogs (Scheme 17).[28] Starting from the commercially available (*S*)-2-aminoadipic acid **99**, a diesterification followed by reductive amination of the amine afforded the *N*-benzyl amino diester **100**. Heating under reflux with 'a few drops' of acetic acid afforded 2-piperidone **101** after four days in 86% yield. Subsequent transformations led to 1,1-disubstituted alkene containing compound **103**, which was further functionalised and subjected to intramolecular Heck reaction, ultimately leading to homopumiliotoxin 233F (**104**). Although the piperidone was used to access the corresponding piperidine by carbonyl reduction (which, as previously mentioned, is not uncommon throughout the literature), the amide moiety was beneficial to the synthetic strategy; the group note that amines can prove problematic in palladium catalysed reactions, hence the amide functionality was deliberately chosen to help circumvent this issue.



Scheme 17: Synthesis of homopumiliotoxin 233F

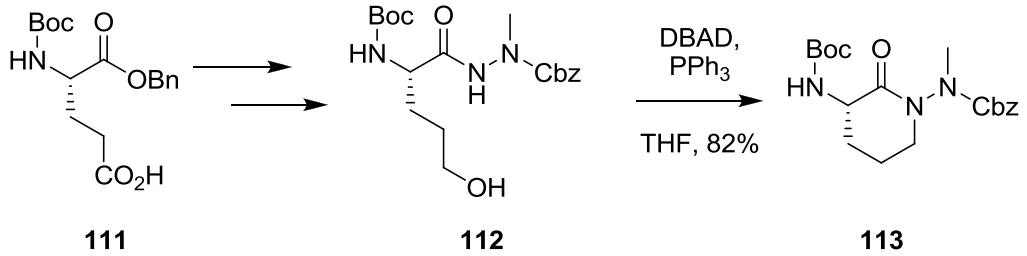
Equally as straightforward, mild basic conditions have also been used to promote lactamisation. This is demonstrated by Abe and co-workers in the first synthesis of sulphostin, which included the determination of absolute configuration.[29] Sulphostin, a compound isolated from a *Streptomyces* cultural broth, is an inhibitor of dipeptidyl peptidase IV (DPP-IV), a peptide cleavage enzyme involved in the mechanisms of diabetic and immune disorders. As the absolute configuration of naturally occurring sulphostin was unknown, all four possible stereoisomers were synthesised and their spectra and *in vitro* activity were compared with the extracted samples to determine the correct configuration (Scheme 18). Both stereoisomers of ornithine hydrochloride **105** were (individually) protected as the methyl esters, and the resulting dihydrochloride salts were treated with sodium hydrogencarbonate to effect lactamisation to both enantiomers of 2-piperidone **107**. This was followed by the protection of the primary amine with a Cbz group. Reaction with phosphorous oxychloride and ammonia afforded compounds **108**, which were reacted with sulphur trioxide-pyridine complex then sodium hydrogencarbonate to afford all four stereoisomers of **109**. Separation of each set of diastereomers by column chromatography was found to be incomplete. However, reaction with the appropriate enantiomer of 1-phenylethylamine hydrochloride allowed for complete separation of the subsequently formed salts. Hydrogenation removed the Cbz protecting group to afford each sulphostin stereoisomer. Comparison with natural compound data allowed the group to propose that the C-3-*S* and phosphorous-*R* isomer **110a** was the natural configuration.



Scheme 18: Synthesis of all four stereoisomers of sulphostin

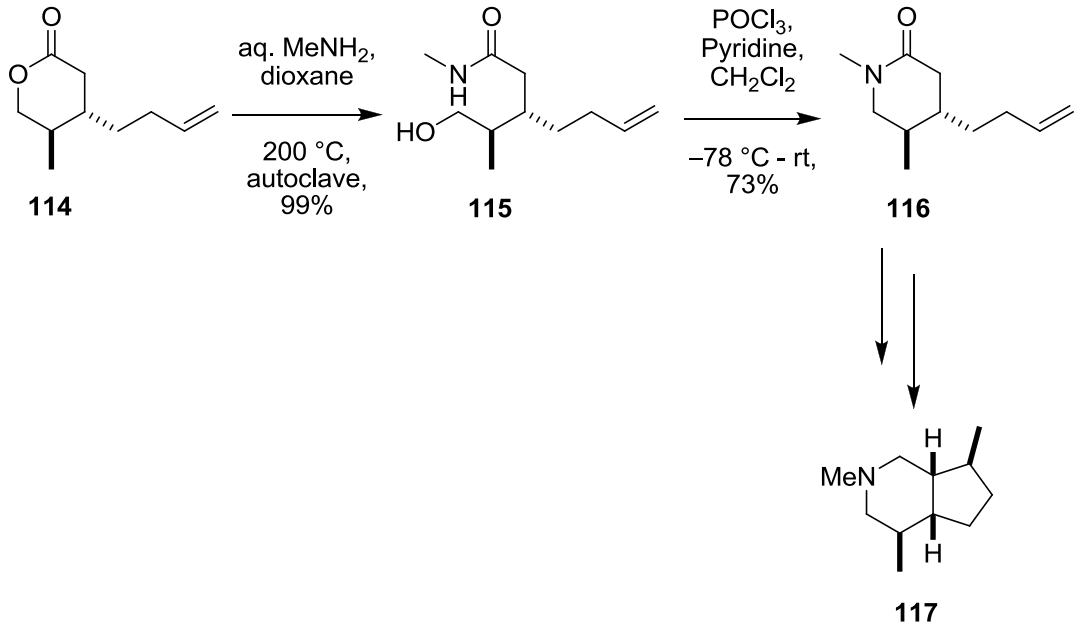
1.3.2 Intramolecular Nucleophilic Substitution

An attractive synthetic strategy for the preparation of 2-piperidones is intramolecular amide *N*-alkylation. In this approach, the presence of a hydroxyl group on the C-6 carbon of the straight chain cyclisation precursor to the 2-piperidone allows for the use of Mitsunobu-type reactions. This was demonstrated by Malachowski and co-workers in their work on a generalised synthesis towards β-, γ-, and δ-lactams for incorporation into peptidomimetic structures (Scheme 19).[30] Considering specifically the synthesis of the δ-lactam, a few high-yielding transformations starting from L-glutamic acid **111** afforded the Mitsunobu substrate **112**. Reaction of this substrate with triphenylphosphine and di-*tert*-butyl azodicarboxylate (DBAD) afforded the cyclised compound **113** in a highly satisfactory 82% yield. In addition to demonstrating a general synthesis of homologous lactams from enantiopure and relatively inexpensive starting materials, this work demonstrated the utility of the 2-piperidone motif in peptidomimetics.



Scheme 19: Synthesis of a substituted δ-lactam

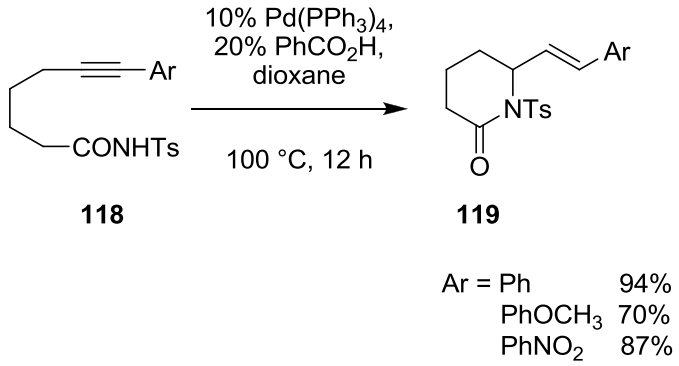
An alternative approach to amide *N*-alkylation was demonstrated by Toyota and co-workers in their diastereoselective synthesis of (±)-α-skytanthine **117** (Scheme 20).[31] Here, the 2-piperidone unit was accessed from the δ-lactone **114**. Reaction with methylamine at high temperature opened the lactone ring to afford the δ-hydroxyamide **115**. Previous work by the group had found that Mitsunobu-type conditions on this type of substrate gave unsatisfactory yields. However, use of phosphorous oxychloride led to substantial improvements, in this case affording the cyclised piperidone **116** in 73% yield.



Scheme 20: Synthesis of (±)-α-skytanthine

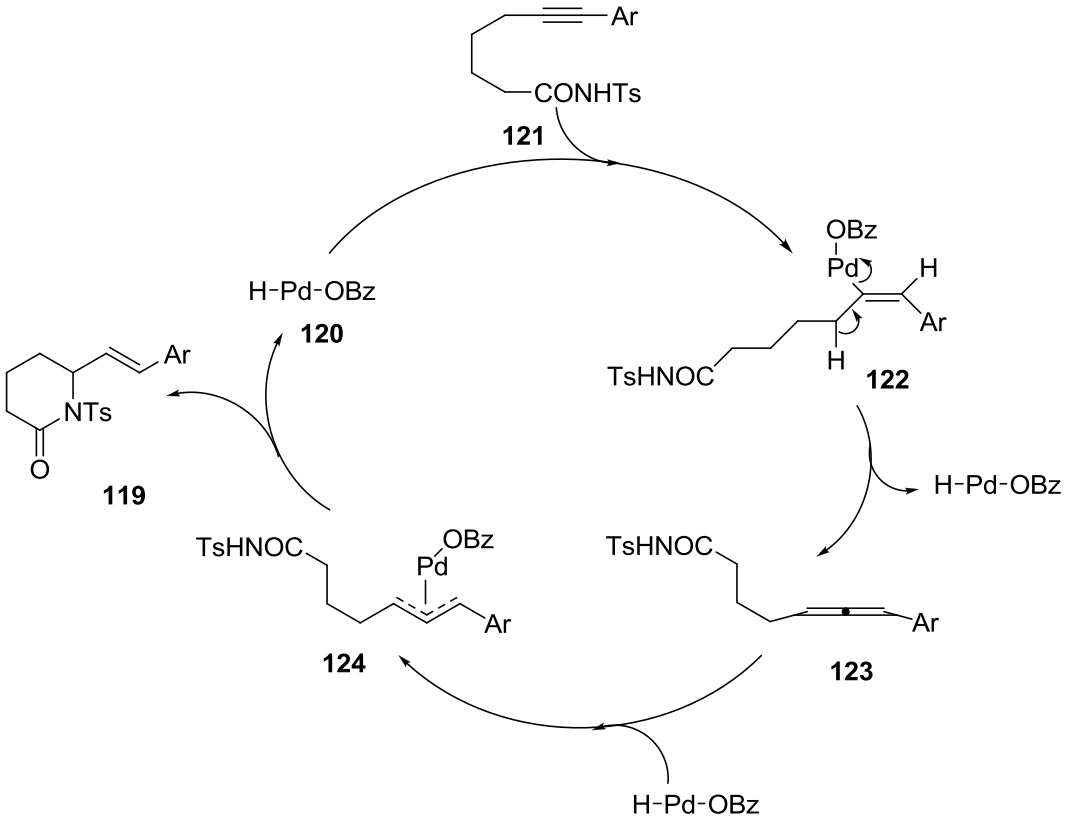
Amide alkylation need not employ leaving groups or Mitsunobu type reactions. Yamamoto demonstrated this in his work on palladium catalysed hydroamidation (Scheme 21).[32] *N*-Tosyl amides of the type represented by **118** cyclised onto aryl substituted alkynes to

afford 6-substituted 2-piperidones **119** in the presence of acid and a palladium catalyst in good yield.



Scheme 21: Hydroamidation of aryl alkynes

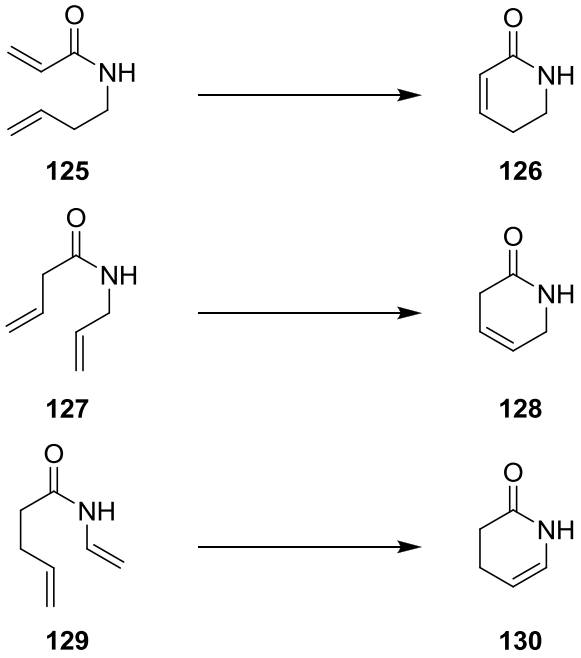
Yamamoto proposed a catalytic cycle for the hydroamidation, shown in Scheme 22. Hydridopalladium species **120** is formed by reaction of tetrakis(triphenylphosphine)palladium(0) with benzoic acid. Aryl alkyne **121** undergoes hydropalladation by the hydridopalladium catalyst, then forms an aryl allene intermediate **123** *via* β-hydride elimination. The allene undergoes hydropalladation with the expelled hydridocatalyst to form π-allylpalladium species **124**. Nucleophilic attack of the allylpalladium system by the tosylamide forms the desired piperidone and regenerates the active catalyst.



Scheme 22: Catalytic cycle of hydroamidation

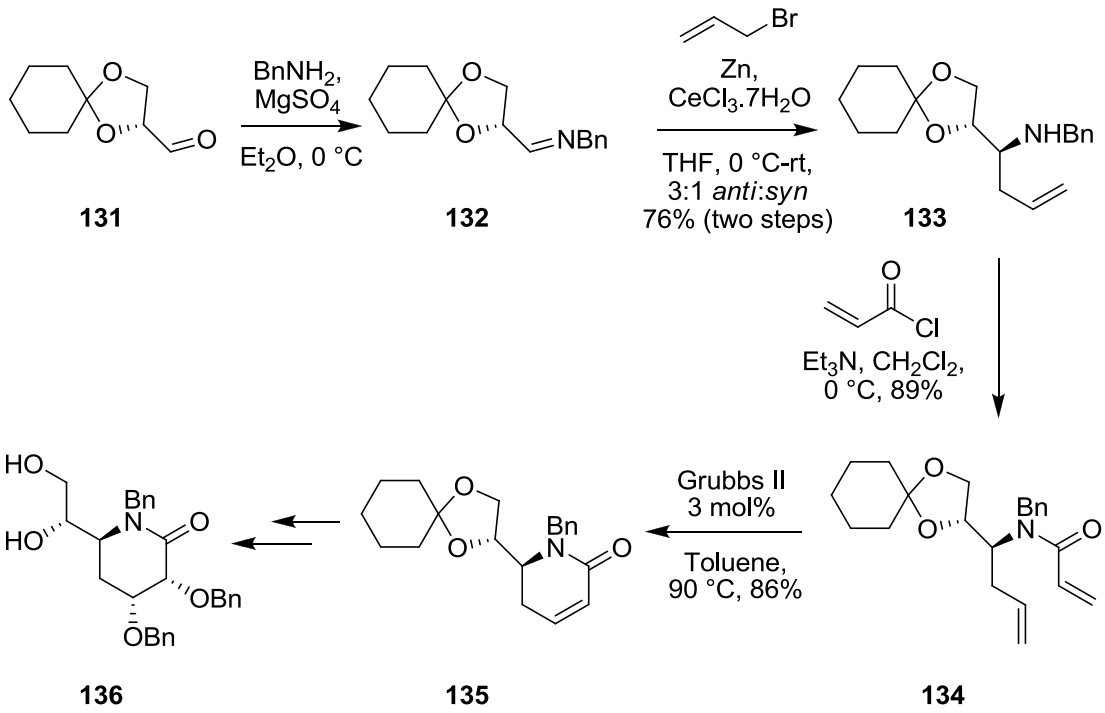
1.3.3 Ring-Closing Metathesis

Ring closing metathesis has developed into a powerful synthetic tool for the synthesis of medium and large ring sizes, and it is a viable reaction for the synthesis of 2-piperidones. Being a 6-membered ring, piperidone has three potential diene metathesis precursors leading to three unsaturated *Z*-piperidone analogues (Scheme 23).



Scheme 23: Potential diene precursors for RCM

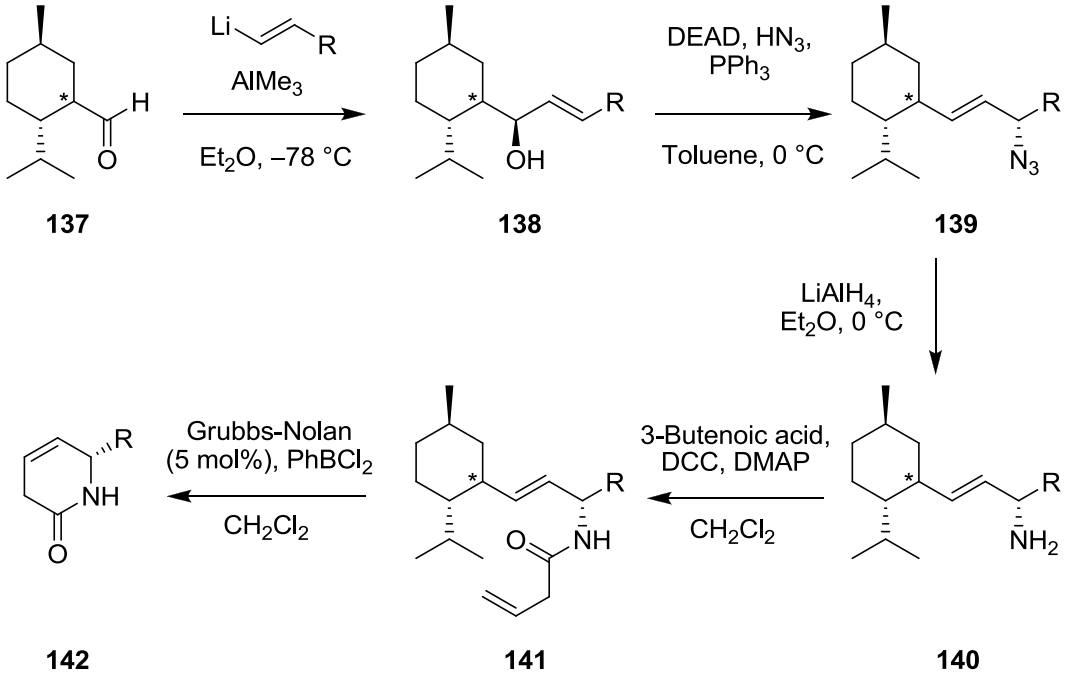
An example of the first precursor can be found in a publication by Vankar on their synthesis of azasugars and their intermediates (Scheme 24).[33] Starting with D-mannitol derived **131**, imine formation followed by a Barbier reaction with allyl bromide and zinc with a catalytic amount of cerium chloride afforded compound **133** as a separable 3:1 mixture of diastereomers. This intermediate was initially alkylated for the synthesis of piperidines, but was also acylated with acryloyl chloride to form diene **134**. Cyclisation with Grubbs 2nd generation catalyst afforded the unsaturated piperidone **135**. Following a number of transformations, intermediate **136** was generated, a compound which the authors note could be useful in the synthesis of azasugars.



Scheme 24: Synthesis of azasugar intermediate

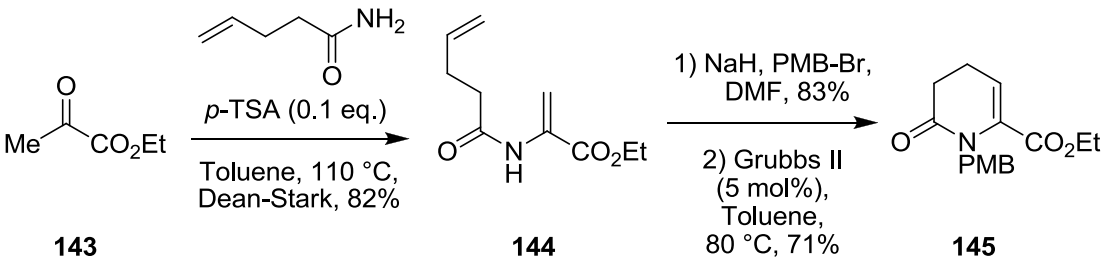
Analogues of the di-allyl substituted diene moiety were used by Spino and co-workers in the synthesis of substituted 2-piperidones alongside a variety of other heterocycles, carbocycles and amino acids (Scheme 25).[34] Their syntheses began with a common starting material, *p*-menthane-3-carboxaldehyde **137**, which can be synthesised as either enantiomer from commercially available menthone. The menthane moiety acts as a chiral auxillary for the stereoselective attack of the aldehyde by a variety of vinyllithium analogues in the presence of trimethylaluminium to form allylic alcohols **138**. Diastereomeric ratios for the allylic alcohol products varied depending on the R group from 19:1 to 200:1. Trimethylaluminium was found essential to maintaining reasonable stereoselectivity, as analogues reacted in its absence gave diastereomer ratios of between 2:1 and 6:1. The allylic alcohols were subjected to Mitsunobu conditions using hydrazoic acid as the nucleophile. Stereospecific S_N2 displacement followed by an in situ stereoselective 3,3-sigmatropic rearrangement of the allylic azide afforded compounds **139**. The authors note that while they believe the majority of the compound reacted *via* this mechanism, it was possible that it was in competition with a S_N2' mechanism. Either way, the rearranged allylic azides were formed in generally excellent diastereoselectivities. Lithium aluminium hydride reduction of azides **139** afforded amines **140**, which were acylated with 3-butenoic acid to form dienes **141**. Ring closing metathesis with Grubbs-Nolan catalyst afforded the cyclised piperidones in good yield with removal of the

menthone moiety. However, the reactions would not proceed without the presence of a Lewis acid, in this case $PhBCl_2$. This was believed to be due to the coordination of the amide oxygen to the ruthenium carbene intermediate.



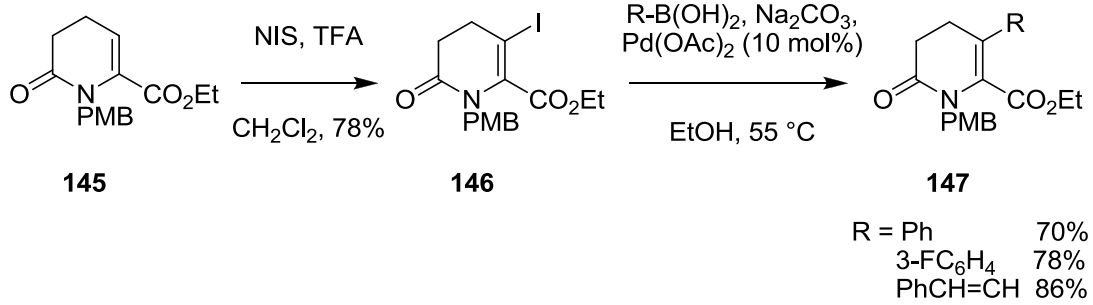
Scheme 25: Synthesis of substituted 2-piperidones

Finally, the use of the *N*-vinyl amide in ring closing metathesis appeared in a methodology study of piperidone synthesis by Rutjes and co-workers (Scheme 26).[35] Unsaturated amides were generated by reaction of the acid chloride precursor with ammonia. Reaction of the amide with ethyl pyruvate **143** under Dean Stark conditions afforded the dehydroamino ester **144**, which was *N*-alkylated with *p*-methoxybenzyl bromide. Ring closing metathesis was effected by Grubbs 2nd generation catalyst, affording the cyclised product **145** in good yield.



Scheme 26: Synthesis of unsaturated 2-piperidones

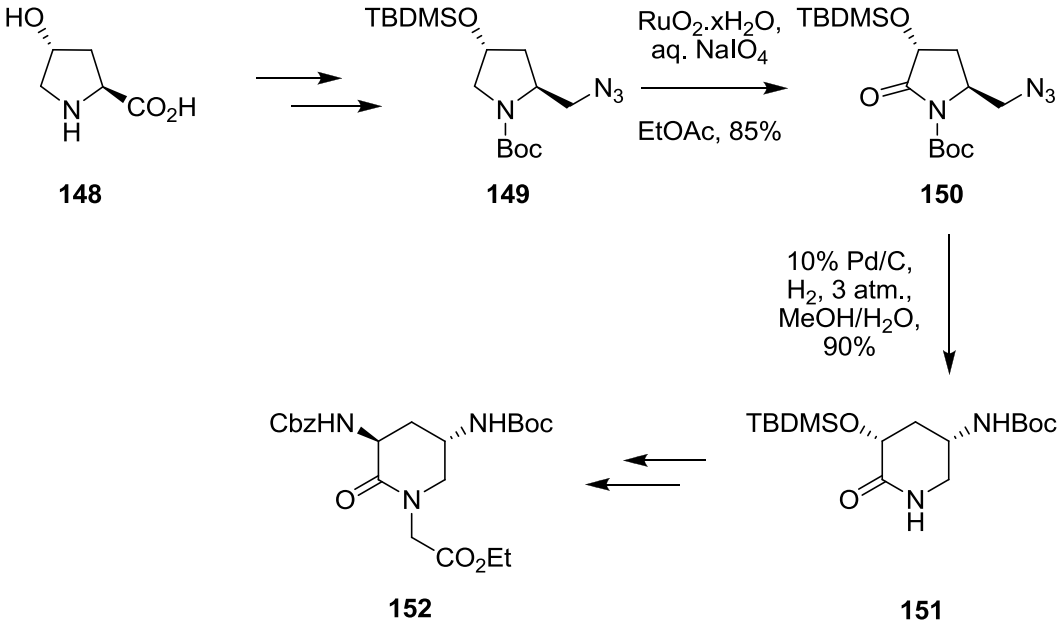
Additionally, enantiomerically pure substituted amides were generated in several steps from pentose-based lactones, which were used in the aforementioned synthetic pathway to generate substituted piperidones in moderate to good yields. The utility of the *endo* double bond was illustrated with the conversion to the iodinated enamide **146** and subsequent palladium catalysed coupling with a variety of coupling partners (Scheme 27).



Scheme 27: Iodination and coupling of 2-piperidone derivatives

1.3.4 Ring Expansion

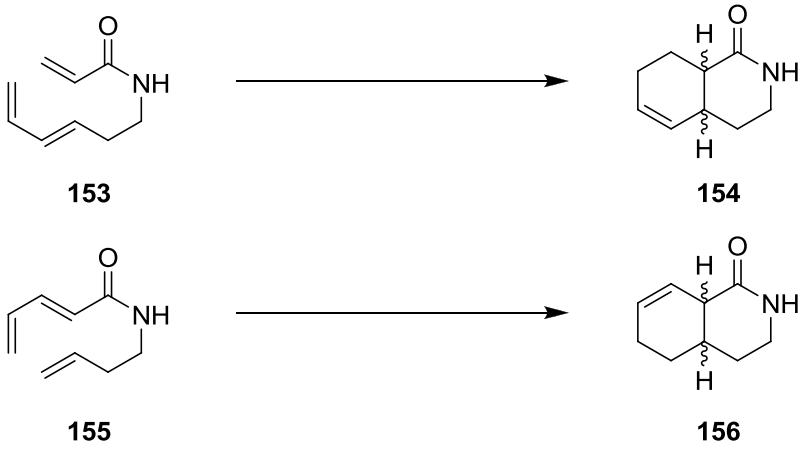
Ring rearrangement/expansion of γ-lactams was used by Tanaka in the synthesis of peptidomimetic 2-piperidones (Scheme 28).[36] A literature procedure was used for the conversion of commercially available *trans*-4-hydroxy-L-proline **148** to the protected pyrrolidine azide **149**. Oxidation with ruthenium oxide afforded the γ-lactam **150**. Subsequent hydrogenation of the azide functionality to the free amine initiated the transamidation/ring expansion to form the substituted 2-piperidone **151**, and further transformations led to the Dab-Gly surrogate peptidomimetic **152**.



Scheme 28: Synthesis of Dab-Gly peptidomimetic

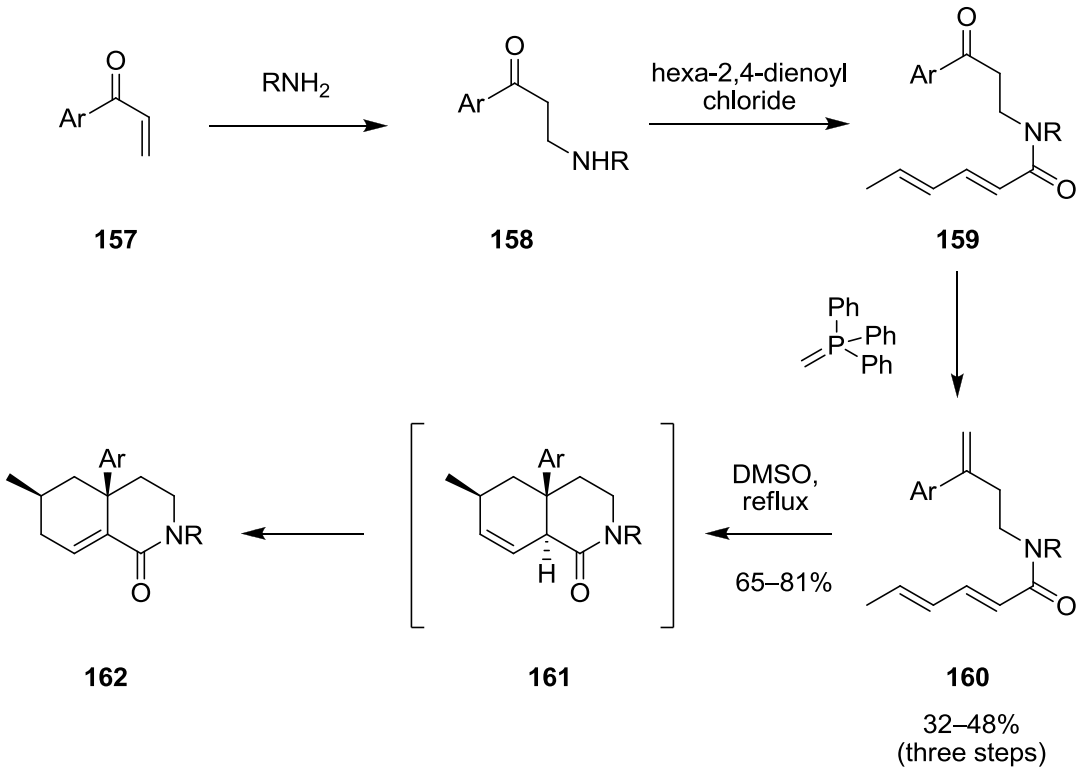
1.3.5 Pericyclic Reactions

The Diels-Alder reaction has received attention in the synthesis of 2-piperidones. This is commonly in the synthesis of fused bicyclic lactams, where the Diels-Alder reaction forms a carbocyclic ring in addition to completing the piperidone ring itself. In this synthetic strategy, it is possible to visualise two potential triene precursors types; those of the type exemplified by **153** with the diene unit attached to the nitrogen side, and those like **155**, where it is attached to the carbonyl side (Scheme 29).



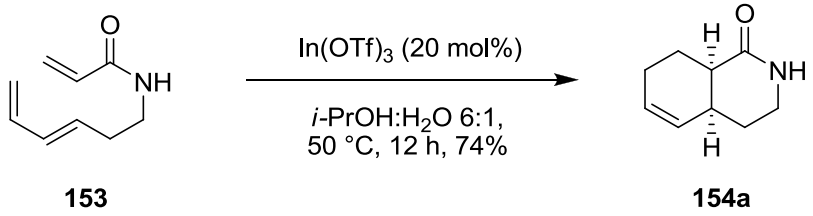
Scheme 29: Potential triene precursors for bicyclic lactam sythesis

Jones and co-workers investigated the use of the Diels-Alder reaction in the synthesis of bicyclic fragments of the morphine structure (Scheme 30).[37] Synthesis of the Diels-Alder precursor was facile; conjugate addition to an aryl vinyl ketone afforded secondary amines **158**. Amine acylation with hexa-2,4-dienoyl chloride installed the diene moiety, while Wittig reaction of the ketone with methylenetriphenylphosphorane afforded the alkene dienophile. With the trienes in hand, the Diels-Alder reaction was able to proceed in good yield to afford the single diastereomer **162** after isomerisation of the initial Diels-Alder adduct **161**. After determination of the relative stereochemistries of the C-4 aryl and C-6 methyl groups by X-ray crystallography, and with the knowledge that the *E*,*E*- geometry of the diene was set, it was deduced that the reaction had proceeded solely *via* the *endo* transition state.



Scheme 30: Synthesis of bicyclic lactam morphine fragments

The alternative strategy of employing a diene alkylated nitrogen as in compound **153** has been used by Taguchi and co-workers (Scheme 31).[38] Their work focused on the development of the synthesis of bicyclic lactones via an indium(III) trifluoromethanesulfonate catalysed Diels-Alder reaction in aqueous media. This gave the Diels-Alder adduct in higher yield and selectivity than previous reaction conditions.[39]

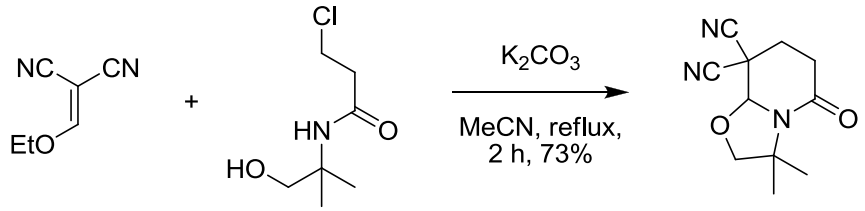


153 **154a**

Scheme 31: Indium triflate catalysed Diels-Alder reaction

1.3.6 Domino Reactions

Domino reactions are powerful tools for the synthetic chemist, and reactions can be designed to form multiple bonds and increase chemical complexity in a single step. Comesse and co-workers used a domino reaction in the formation of bicyclic lactams such as **165**.[40] Although the majority of examples were based on pyrrolidones, they also demonstrated the formation of fused bicyclic 2-piperidones (Scheme 32). The reaction of ethoxy methylene derivatives such as **163** with *N*-hydroxyalkyl haloamides like **164** in the presence of base resulted in the formation of three bonds in a single step.



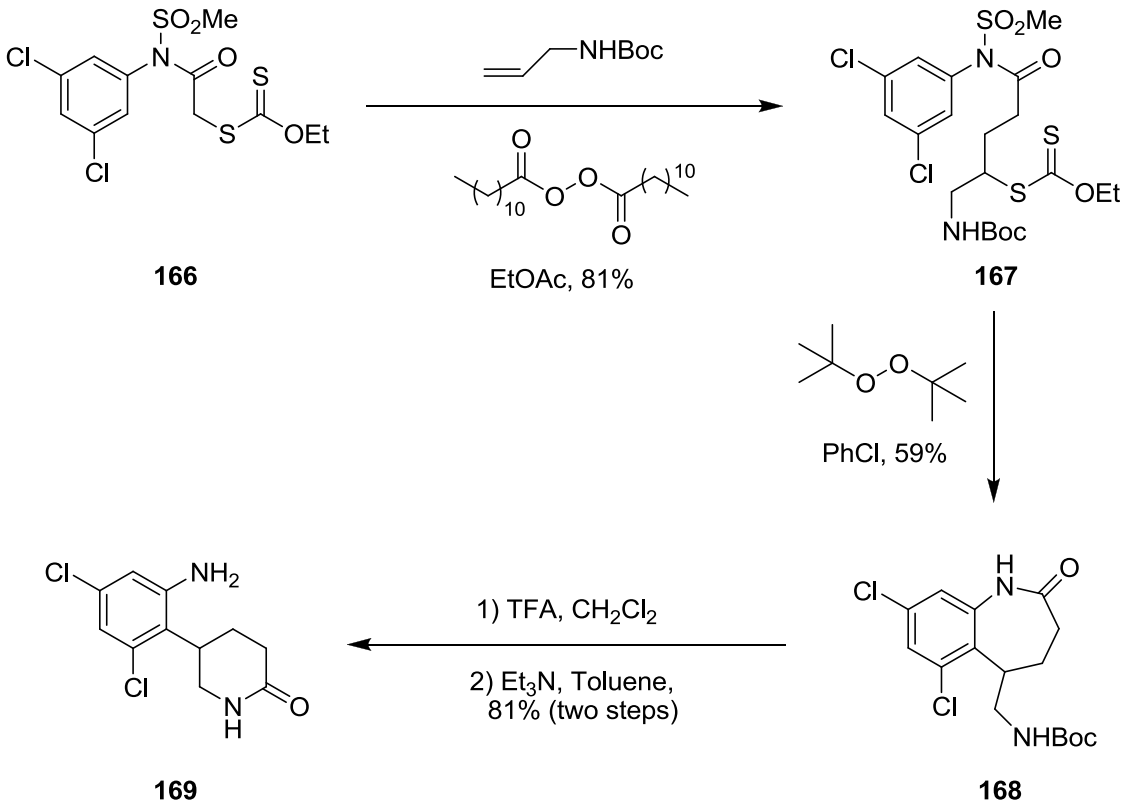
163 **164** **165**

Scheme 32: Domino reactions in the synthesis of bicyclic lactams

1.3.7 Radical-Mediated Reactions

Syntheses of substituted heterocycles that are efficient and broad in scope are highly desirable in the pharmaceutical and agrochemical industries. Modern organic chemistry often focuses on the ability to rapidly synthesise a library of compounds containing substituents suitable for further elaboration. Zard and co-workers demonstrated the synthesis of 4-aryl-2-piperidones using radical cyclisation and transamidation (Scheme 33).[41] A range of xanthate esters, exemplified by dichloro compound **166**, was readily prepared from substituted anilines. Extension of the alkyl chain with *N*-Boc allylamine was catalysed by dilauroyl peroxide (DLP). Radical cyclisation to form benzazepinone **168** was

initiated by di-*tert*-butyl peroxide (DTBP). This step also resulted in the loss of the methanesulfonamide protecting group, but this was not found to have a detrimental effect on the subsequent reactions. Trifluoroacetic acid removal of the Boc-group followed by cyclisation in the presence of base afforded the desired substituted 2-piperidone **169**. Iodo- and bromo-substituted analogues were also synthesised and have potential utility in coupling reactions, while Zard indicates that the benzazepinones are also a much studied pharmacaphore in their own right.



Scheme 33: Synthesis of 4-aryl-2-piperidones

1.4 Summary

The synthesis of 2-pyrrolidones and 2-piperidones has received substantial literature attention, inidicative of the utility of these molecules in various areas of industry and research. It is perhaps as a result of, rather than in spite of, the relative simplicity of these molecules that has allowed the use of a broad range of chemistries for their synthesis. For both 2-pyrrolidones and 2-piperidones, the most straightforward transformation is lactamisation from linear chain γ- and δ-amino carboxylic acids and their derivatives. A variety of methods such as acid catalysed, based catalysed or simple heating make this a flexible approach.

Ring closing metathesis reactions are an effective method for heterocycle formation, and as discussed above, the synthesis of diene precursors via amine acylation endow these methodologies with great flexibility over the ring size of target products. Although more commonly employed for the synthesis of 2-piperidones, pericyclic reactions such as the Diels-Alder reaction are powerful tools for constructing cyclic system in an often highly stereoselective fashion. Finally, the carbocyclic portion of the 2-piperidone and 2-pyrrolidone rings provides ample room for the investigation of various intramolecular alkylations, couplings etc., of which it is hoped the above discussion provides an interesting selection of examples.

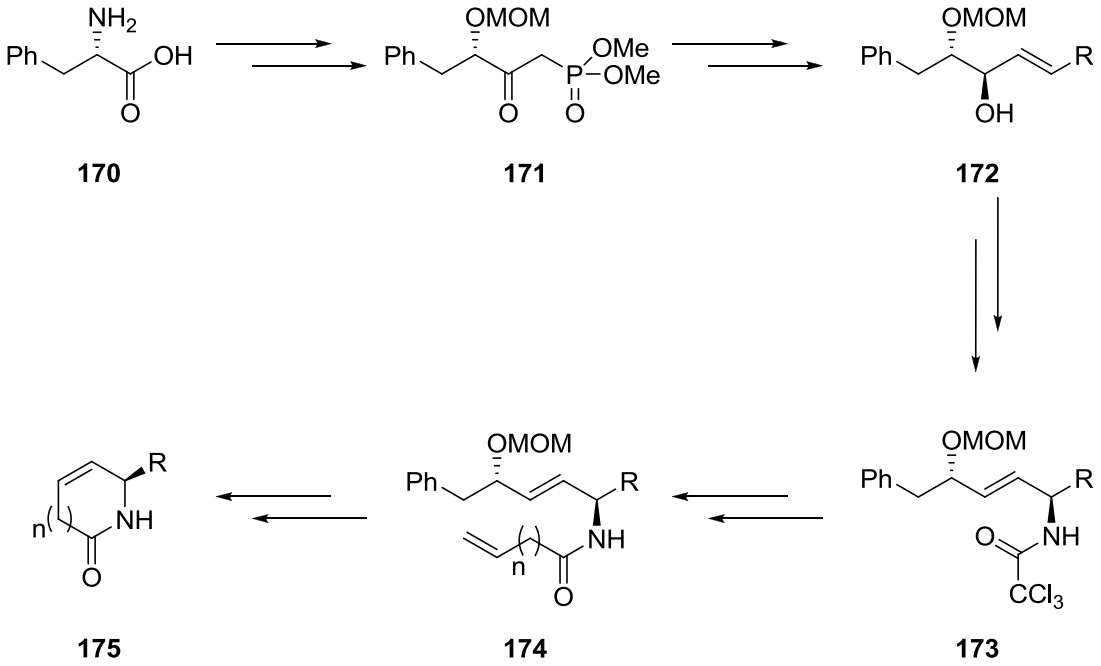
2 Results and Discussion

2.1 Synthesis of 2-Pyrrolidones and 2-Piperidones

2.1.1 Introduction

As previously discussed, the 2-pyrrolidone and 2-piperidone motifs are important in various fields of chemistry, and numerous routes have been developed towards their synthesis. However, with any synthetic route, critical consideration can reveal drawbacks. To make a legitimate contribution to this area of chemistry, it was important that a novel synthesis address some of these issues. In modern organic chemistry there is a trend towards highly stereoselective reactions and syntheses. This is understandable given, for example, the requirements of the pharmaceutical industry, where opposing enantiomers may have different effects. One example of this is methamphetamine; the dextromethamphetamine enantiomer is a prescription psychological stimulant, whilst levomethamphetamine is sold as an over the counter nasal spray and affects the peripheral nervous system with little psychological effect.[42]

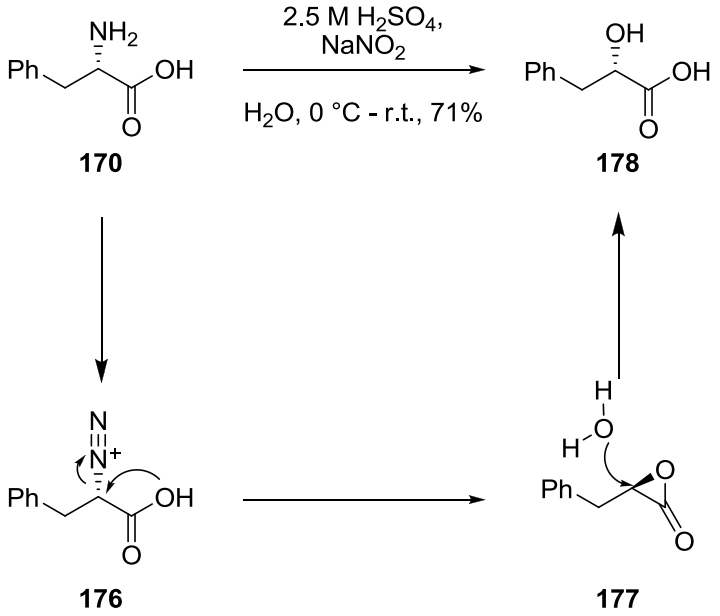
The aim of the following project was to develop a flexible synthesis of 2-pyrrolidones and 2-piperidones, which allowed for the incorporation of a variety of substituents, and the ability to generate both ring sizes from a common intermediate. The key transformations of this methodology are illustrated in Scheme 34. The starting material chosen was L-phenylalanine **170**, an inexpensive and enantiopure compound. A number of facile transformations lead to phosphonate ester **171**. Following a Horner-Wadsworth-Emmons (HWE) protocol, this intermediate reacts with a variety of aldehydes to form α,β-unsaturated ketones, which are subsequently stereoselectively reduced to form allylic alcohols. This is followed by a key step of the synthesis, the Overman rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides **173**, which results in a highly selective transfer of stereochemistry. Hydrolysis of the trichloroacetamide affords a primary amine common intermediate, which is acylated with homologous carboxylic acid derivatives to form dienes **174**. The final, critical step is the ring closing metathesis (RCM) of dienes **174** to form unsaturated heterocycles **175**, the double bond of which allows for further elaboration. Overall, the proposed methodology affords substituted, chiral 2-pyrrolidones and 2-piperidones in a highly flexible manner from an inexpensive starting material.



Scheme 34: Key intermediates in proposed synthesis

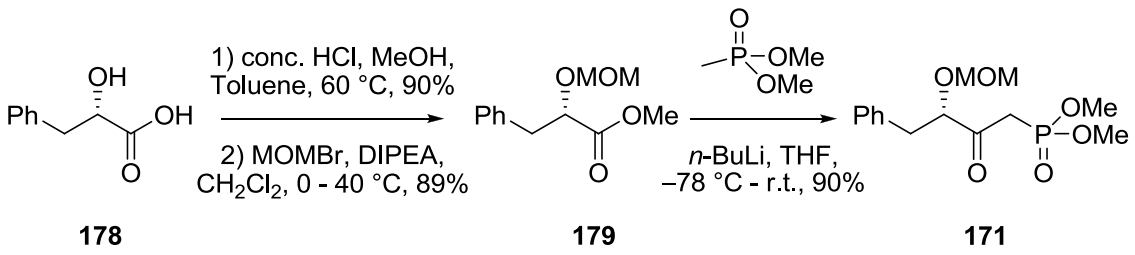
2.1.2 Synthesis of α,β-Unsaturated Ketones

The synthesis began as previously mentioned with the α-amino acid, L-phenylalanine **170**. Treatment under acidic conditions with sodium nitrite afforded the α-hydroxy acid **178** in 71% yield with retention of stereochemistry.[43] The stereochemical outcome can be explained by examination of the proposed reaction mechanism; following formation of the diazonium salt **176**, nitrogen is displaced by the intramolecular attack of the carboxylic acid forming the α-lactone **177**. Nucleophilic ring-opening of the lactone by water, analogous to an epoxide ring-opening, affords the α-hydroxy acid with overall retention of stereochemistry.



Scheme 35: Diazotization of L-phenylalanine

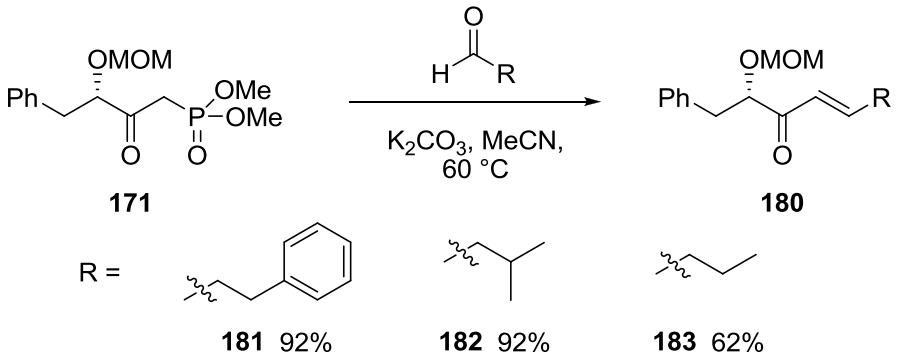
Protection of the α-hydroxy acid then followed (Scheme 36). Methyl esterification proceeded in excellent yield, as did hydroxyl protection with the methoxymethyl ether (MOM) group. Regarding the choice of hydroxyl protecting group, the MOM group is primarily suitable due to its stability to the proposed reaction conditions later in the synthesis. It has also been successfully employed in previous group work as a palladium coordinating moiety in asymmetric Overman rearrangements, affording increased flexibility to investigate alternative routes.[44] Formation of the phosphonate ester **171** by reaction of methyl ester **179** with the dimethyl methylphosphonate ester anion proved facile.[45]



Scheme 36: Synthesis of phosphonate ester

The phosphonate ester intermediate marks the first divergent point of the synthesis, as the choice of the aldehyde reagent for the HWE reaction determines the nature of the substituent in the final product. Regarding the selection of aldehydes, it was necessary to

consider the subsequent Overman rearrangement that would later be employed to transfer stereochemistry; it has been reported that the Overman rearrangement proceeds in improved yields with electron rich substituents on the terminal carbon of the allylic system, and reduced or even zero yields for electron withdrawing groups.[46] For this reason, a small range of aliphatic aldehydes was chosen to participate in the HWE reaction. Due to the position of the stereocentre directly adjacent to the carbonyl functionality, it was thought prudent to avoid strong bases in the HWE reaction, lest racemisation is induced. To this end, the mild Masamune-Roush conditions of 1,8-diazabicycloundec-7-ene (DBU) and lithium chloride were investigated.[47] The addition of lithium chloride increases the acidity of the α-methylene protons, and allows the use of a milder base such as DBU. Unfortunately, despite investigation of elevated temperatures and extended reaction times, no reaction was observed using the Masamune-Roush protocol. A successful alternative was found in conditions developed by Lubell, employing potassium carbonate in acetonitrile.[48] HWE reactions using these conditions afforded the desired α,β-unsaturated ketones with the general structure of compound **180**, with various alkyl side chains **181**–**183** in moderate to high yields. Observation of alkene proton coupling in the region of 16 Hz, and the absence of significant by-products, suggests the HWE reaction is entirely selective for the *E*-isomers of the α,β-unsaturated ketones.



Scheme 37: Horner-Wadsworth-Emmons reaction

2.1.3 Stereoselective Ketone Reduction

The strategy of employing the Overman rearrangement required the conversion of the α,β-unsaturated ketones to chiral allylic alcohols. Rather than employ chiral, stereoselective reducing agents, the stereocentre already present in the molecule allowed for the investigation of a chelation controlled reduction. Zinc borohydride is readily prepared from

zinc chloride and sodium borohydride, and has previously been employed in the chelation controlled, stereoselective reduction of β-hydroxy ketones.[49] Figure 3 depicts the proposed chelated intermediate that results in a stereoselective reduction. The zinc cation is thought to coordinate to the carbonyl oxygen and at least one of the MOM-protected hydroxyl oxygens. The Newman projection demonstrates the steric bias provided by the benzyl moiety.

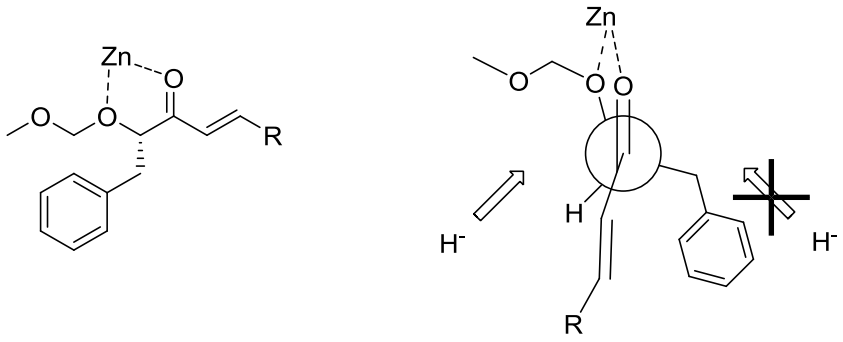
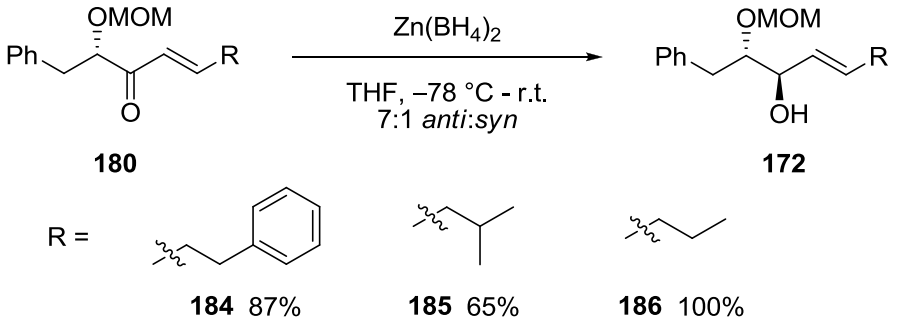


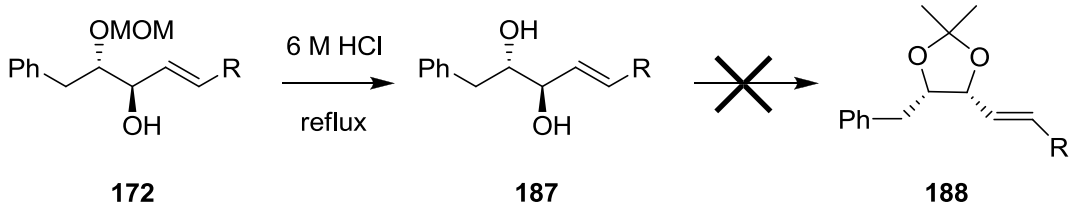
Figure 3: Felkin-Anh representation of chelation controlled reduction

These reactions consistently afforded a 7:1 mixture of diastereomers in favour of the desired *anti* isomer illustrated by structure **172**, a satisfactory outcome for a reaction that does not employ a chiral reducing agent. Other reagents trialled in this reaction confirm the suitability of zinc borohydride; sodium borohydride and lithium borohydride were shown by ^{1}H NMR spectroscopy to afford 2:3 and 1:3 *anti*:*syn* diastereomer ratios, respectively. These results are hardly surprising, however, as the 2+ charge affords a greater likelihood of bidentate coordination. Unfortunately, column chromatography conditions for satisfactory separation of the diastereomers proved elusive. It was found that separation was considerably easier at a later stage in the synthesis, as detailed below.



Scheme 38: Zinc borohydride reduction of enones

A question remained over the outcome of the ketone reduction; how was it possible to determine that the theoretically preferable *anti* diastereomer was in reality the major product? To investigate the stereochemistry, the removal of the MOM protecting group followed by cyclic acetal formation with the two free hydroxyl groups to afford structure **188** was proposed (Scheme 39). It was thought that this may lead to improved separation of diastereomers by column chromatography, but perhaps more importantly the constrained cyclic structure would allow the use of NOESY techniques for stereochemical determination. In practice this was not as straightforward as envisaged. The MOM protecting group appeared quite robust in the face of acidic conditions, and while extended reaction times and heating did afford some of the desired diol, it also incurred the formation of multiple by-products. Unfortunately, the formation of the cyclic acetal proved difficult under the conditions trialled. Despite a number of attempts, only starting material was returned, and NOESY confirmation of stereochemistry was not conducted. It was therefore necessary to devise an alternative method for the validation of the proposed stereochemistry. A number of the pyrrolidone and piperidone final products or their enantiomers are known literature compounds. The ^{1}H NMR spectra and $[\alpha]_D$ values obtained from these compounds compare favourably with those found in the literature, so it is possible to confidently state that the structure of these compounds is as reported.[50–54] Hypothetically, to arrive at the correct target compounds from the *syn* allylic alcohol diastereomer would infer that the stereochemical outcome of another step in the synthesis, likely the Overman rearrangement, was also not as expected. The likelihood of both the reduction and the Overman rearrangement proceeding with theoretically disfavoured stereochemical outcomes is thought to be very low. Thus, it is inferred that as the target products are of the correct configuration, the intermediates are also.



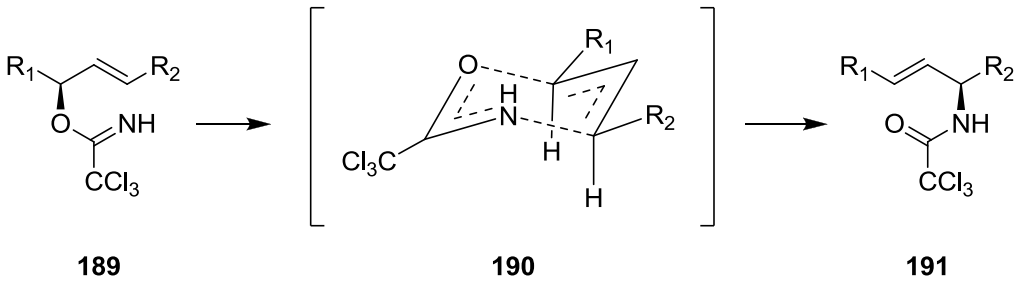
172 **187** **188**

Scheme 39: Attempted acetal formation for NOESY analysis

2.1.4 Trichloroacetimidate Synthesis and Overman Rearrangement

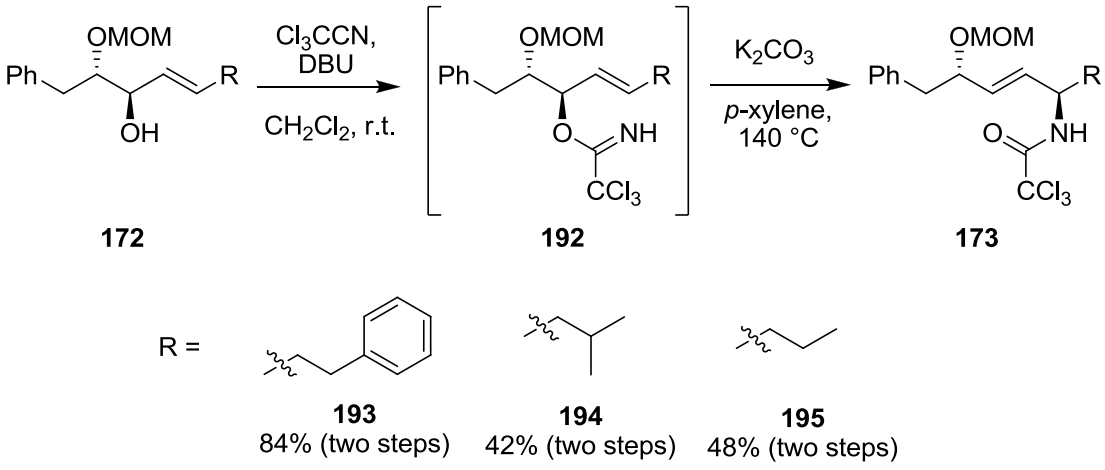
In preparation for the Overman rearrangement, the alcohol was treated with trichloroacetonitrile to form an allylic trichloroacetimidate. Previous research in the group has utilised this reaction, and typical conditions employed DBU (0.5 equiv.) and trichloroacetonitrile. However, under the aforementioned conditions, the desired allylic trichloroacetimidate was observed in a modest 30–40% conversion after 24 hours. This is possibly due to the increased substitution of compounds **184**–**186** when compared to previous allylic alcohol intermediates prepared in the group, as greater steric hindrance surrounding the hydroxyl group may lead to lower reaction rates. In an attempt to accelerate the reaction, stronger bases were suggested, the hypothesis being that an increased proportion of alkoxide present in the reaction would lead to greater conversion and shorter reaction times. Initially *n*-butyl lithium was trialled, but despite some evidence of alkoxide formation (reaction mixture changing from colourless to deep red upon reagent addition), no trichloroacetimidate formation was observed by ^{1}H NMR spectroscopy. Substituting *n*-butyl lithium for sodium hydride led to improved results; using an excess of sodium hydride afforded 70% conversion to trichloroacetimidate after 2.5 hours. However, extension of reaction times did not lead to an increase in conversion, but to a gradual increase in by-product formation. Ultimately it was found that increasing the quantity of DBU to 1.2 equivalents and lengthening the reaction time to 48–60 hours led to conversions of over 80% with minimal by-product formation. Allylic trichloroacetimidates are sensitive to column chromatography. Hence, rapid filtration of the crude product through a short silica plug was necessary to remove DBU, and the product present in the filtrate was used without further purification.

Subsequent to the formation of the allylic trichloroacetimidates is the Overman rearrangement, which yields allylic trichloroacetamides.[55] This is a key step in the synthesis, as it involves the conversion of an sp^2 hybridised carbon to the tertiary stereocentre of the final compounds in a stereoselective fashion. The Overman rearrangement is a [3,3]-sigmatropic rearrangement. It can be initiated thermally or with the use of palladium(II) or mercury(II) catalysts.[46] The rearrangement preferentially proceeds through chair-like transition state **190**, which in conjunction with the concerted nature of the thermal rearrangement leads to the highly selective transfer of stereochemistry from acetimidiate to acetamide (Scheme 40).



Scheme 40: Preferred chair-like transition state of the Overman rearrangement

The investigation of the Overman rearrangement began with the exploration of the thermally promoted method, which involves reaction of the allylic trichloroacetimidate in *p*-xylene at 140 °C for 18–24 hours. While the energy costs of maintaining this temperature for extended periods cannot be ignored, it was reasoned that economically and environmentally it would be preferable to employ thermal initiation if possible, as opposed to transition metal catalysts. In practice, the thermal Overman rearrangement proved to be very effective (Scheme 41). Yields over two steps from the allylic alcohol were in the range of 42–62%. The addition of a substoichiometric quantity of potassium carbonate to the reaction mixture has been shown to improve the yield of rearrangements.[56] It is not believed to participate directly in the rearrangement mechanism, rather it neutralises the trichloroacetic acid by-product that can be formed as a result of allylic trichloroacetamide hydrolysis, and therefore reduces the amount of acid catalysed trichloroacetimidate decomposition.



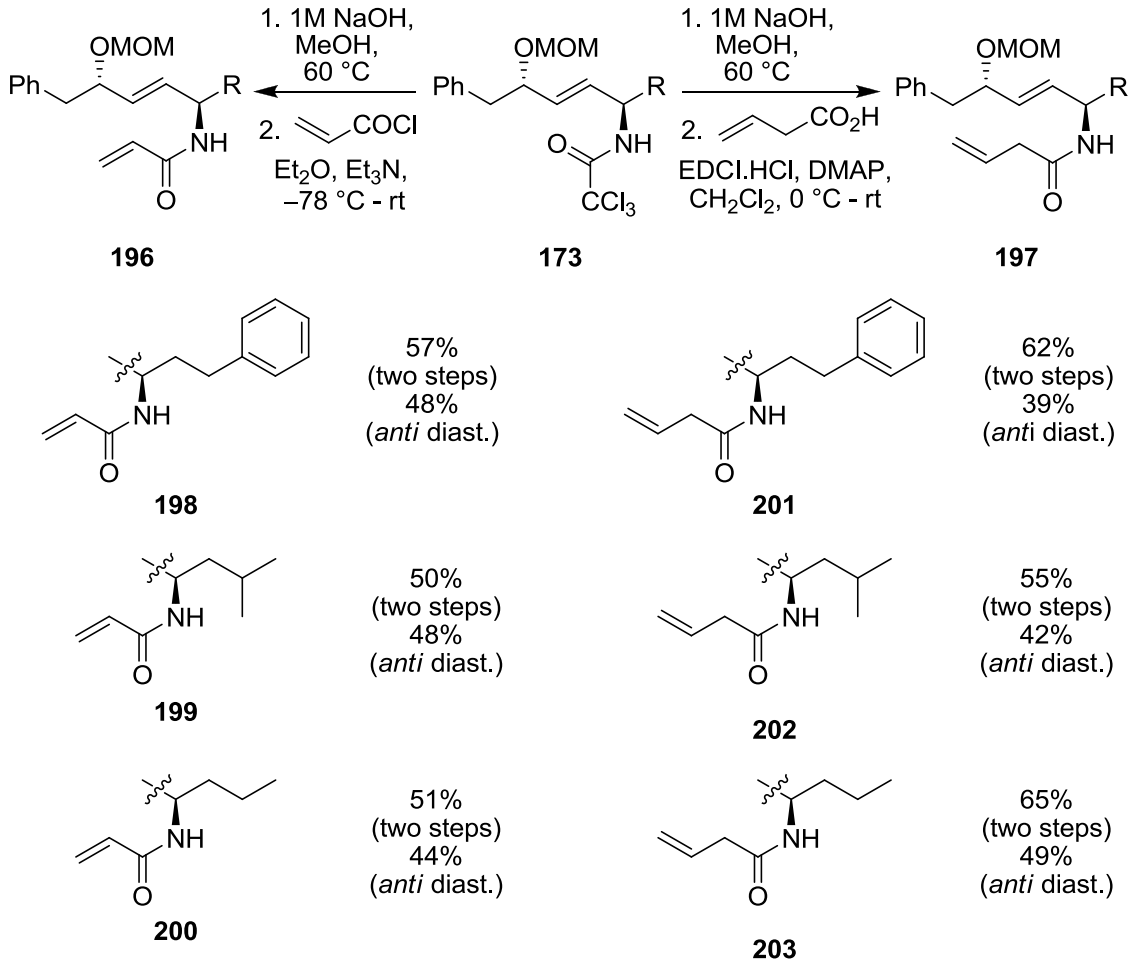
Scheme 41: Acetimidate formation and Overman rearrangement

Unfortunately, an area of ambiguity was the diastereomeric outcome of the rearrangement. While the diastereomers of the allylic alcohol were distinguishable by ^{1}H NMR spectroscopy, no such distinction could be made for the allylic trichloroacetamide. Fortunately, at a later stage in the synthesis the diastereomers could again be distinguished, and from these results it appears that stereochemical integrity was maintained during the Overman rearrangement, with diastereomer ratios being identical to those found in the allylic alcohols. Given the results afforded by the thermal rearrangement, it was not deemed necessary to investigate metal catalysed methods.

2.1.5 Trichloroacetamide Hydrolysis, Acylation and Ring-Closing Metathesis

Hydrolysis of the trichloroacetamides to primary amines proved facile. Treatment with sodium hydroxide was sufficient to effect complete hydrolysis after 18 hours, and after analysis of the ^{1}H NMR spectra of the crude product, purification was deemed unnecessary. The primary amine is a key intermediate in the synthesis, as choice of acylating reagent determines ring size of the final compound; acylation with an acryloyl unit leads to 2-pyrrolidone structures, while the 3-butenoyl unit leads to 2-piperidones. Acryloyl chloride and triethylamine in dichloromethane at 0 °C were found to be suitable acylating conditions. While initial yields were reasonable at around 40% over two steps, previous literature work suggested diethyl ether in place of dichloromethane, and conducting the reaction at −78 °C followed by warming to room temperature.[57] This protocol led to an increase in yields over the two steps to 50–57%. Pleasingly, it was found that not only were the *syn* and *anti* diastereomers distinguishable by ^{1}H NMR spectroscopy post acylation, they were easily seperable by column chromatography. Thus the *anti* diastereomer was isolated in yields of 44–48%.

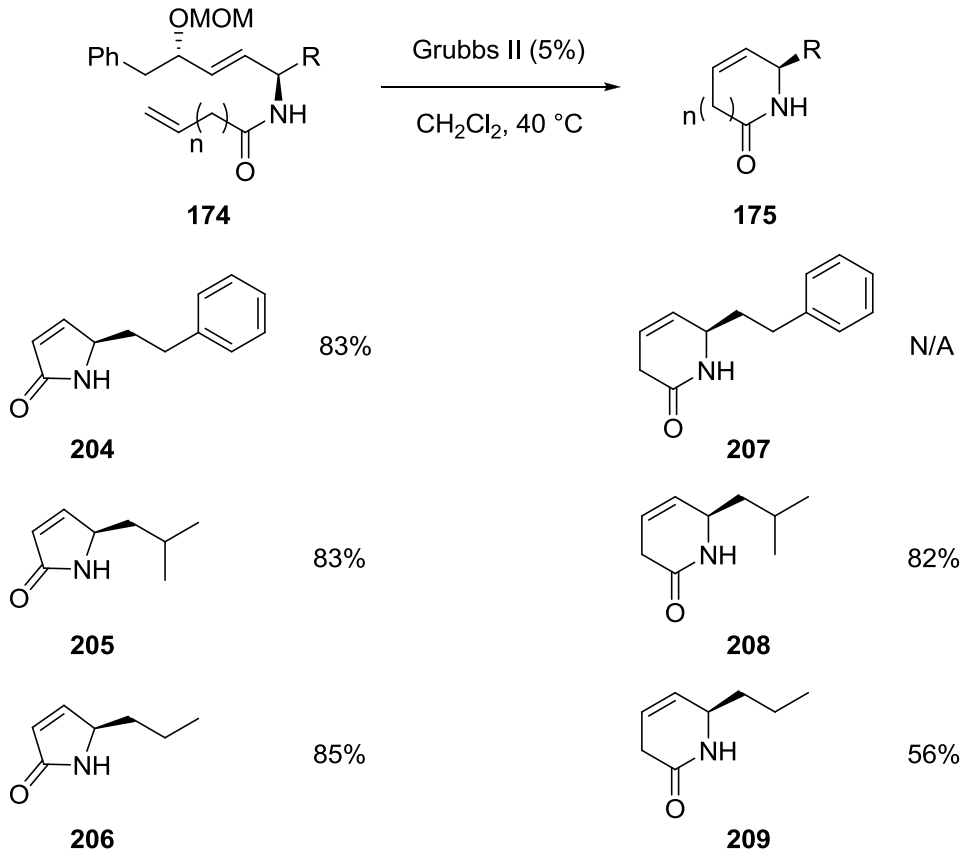
Acylation employing the 3-butenoyl unit was then investigated. 3-Butenoyl chloride was not commercially available, which was unsurprising as it was believed attempts to synthesise this reagent from, for example, 3-butenoic acid and thionyl chloride, would result in isomerisation to crotyloyl chloride under the acidic conditions. Thus, it was decided to investigate an amide coupling reaction involving 3-butenoic acid and EDCI hydrochloride. Overall yields were comparable to those of the acryloyl acylation at 55–62%, and similarly it was found that the diastereomers were again separable by column chromatography, affording the *anti* diastereomer in yields of 39–49% over two steps.



Scheme 42: Trichloroamide hydrolysis and primary amine acylation

Attention next turned to the ring closing metathesis of the dienes, perhaps the most critical step of the synthesis. Fortunately, using Grubbs 2nd generation catalyst, all dienes cyclised smoothly to the corresponding unsaturated 2-pyrrolidones and 2-piperidones in very good yields (Scheme 43). One exception to this was the synthesis of (6*R*)-6-phenethyl-1,6-dihydropyridin-2-one **207**. While the ring closing metathesis proceeded well, the product was slightly unstable, appearing to isomerise to what was thought to be the α,β-unsaturated system. Column chromatography only served to increase the rate of isomerisation, and the two isomers were inseparable. As a result of this instability, (6*R*)-6-phenethyl-1,6-dihydropyridin-2-one **207** was taken directly through to the hydrogenation stage. What caused the instability of this particular analogue and not others is unclear. Having successfully completed the cyclisation of all analogues, it was felt necessary to determine the enantiopurity of these compounds. Thus, (5*R*)-5-phenethyl-1,5-dihydropyrrol-2-one **204** underwent chiral HPLC analysis, and was found to have an enantiomeric excess of 93%. This is a highly satisfactory result for a synthesis that begins with an inexpensive

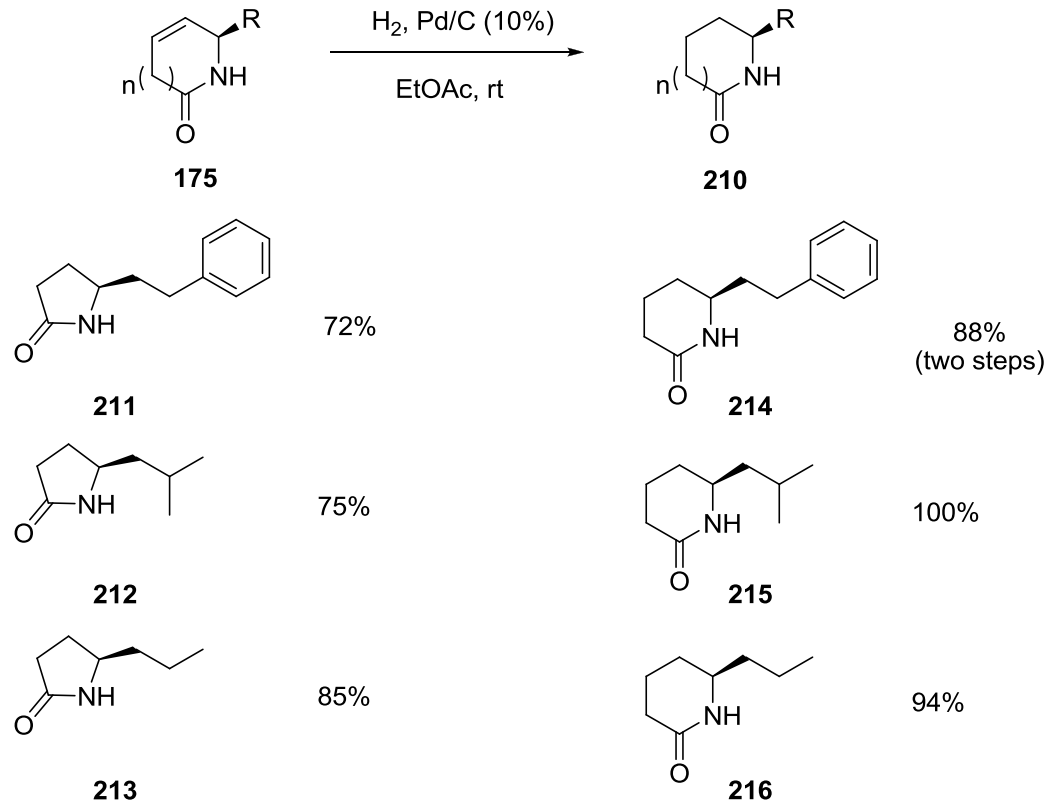
chiral pool source and does not utilise chiral reagents or chiral chromatographic techniques.



Scheme 43: Ring closing metathesis of dienes

2.1.6 Hydrogenation and Synthesis of *N*-Boc Coniine

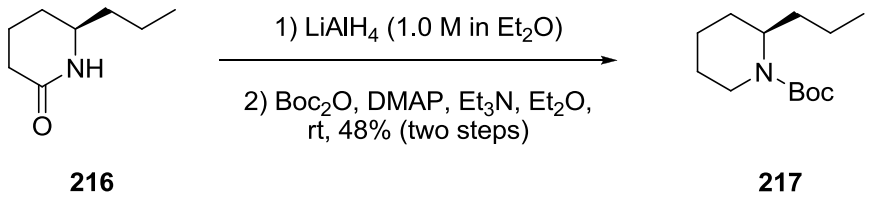
Ultimately, the small library of compounds was subjected to hydrogenation, forming the target 2-pyrrolidones and 2-piperidones. Elevated gas pressure was not required, and the reactions proceeded at room temperature. Without exception, these hydrogenations proceeded in good yield and in a very clean fashion (Scheme 44).



Scheme 44: Hydrogenation to saturated heterocycles

As noted above, some of the target products had previously been reported in the literature, and the analytical data collected compared favorably with literature values. As discussed previously, the 2-pyrrolidones and 2-piperidones are sometimes used to access pyrrolidines and piperidines. To demonstrate this, amide reduction of the (6*S*)-6-propylpiperidin-2-one analogue **216** was investigated. This reduction would afford the known natural compound (+)-coniine, a toxic alkaloid produced by the poison hemlock family of plants.[58] There was literature precedence for the in situ Boc-protection of the piperidine; coniine is known to be volatile, an undesirable characteristic given its toxicity, and the hydrochloride salt is known to be highly hygroscopic.[59] Therefore, 2-piperidone **216** underwent lithium aluminium hydride reduction to its piperidine derivative followed by Boc protection as a

one-pot process (Scheme 45). *N*-Boc-(+)-coniine **217** was isolated in 48% yield over two steps, and analytical data was consistent with that reported in the literature.



216 **217**

Scheme 45: Synthesis of *N*-Boc-(+)-coniine

2.1.7 Summary

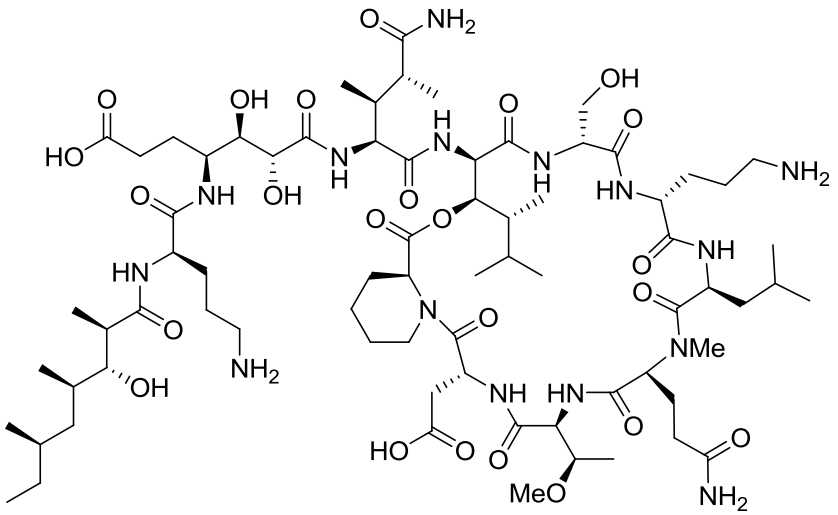
In summary, this project achieved the aims proposed at the outset. Three key transformations can be identified in this synthesis. First, a chelation controlled zinc borohydride reduction of α,β-unsaturated ketones was employed to produce allylic alcohols with good stereoselectivity. By utilising the stereocentre present in the ketone substrate, the requirement for a chiral reducing reagent was removed. Second, the Overman rearrangement was utilised to transfer stereochemistry from the allylic alcohol to the tertiary stereocentre present in the target compounds. The concerted nature of the [3,3]-sigmatropic rearrangement with the proposed chair-like transition state led to an excellent retention of stereochemical integrity. Third, the ring-closing metathesis reaction was a critical step in the formation of the cyclised products, and presented little in the way of difficulties.

In this synthesis, the unsaturated pyrrolidones and piperidones were hydrogenated to their corresponding saturated lactams. However, the presence of the alkene affords opportunities for further functionalisation. For example, epoxidation,[60] dihydroxylation[61] and fluorination[62] are potential elaborations of the core structure. The α,β-unsaturated system of the pyrrolidones allows for the investigation of 1,4-conjugate additions with organometallic reagents.[63] Finally, as exemplified by the synthesis of *N*-Boc-coniine discussed above, amide reduction gives facile access to the corresponding pyrrolidine and piperidine derivatives.

2.2 Synthesis of 4-Oxopipecolic Acid Derivatives

2.2.1 Introduction

Pipecolic acid is a cyclic, non-proteinogenic amino acid found in a variety of biological systems, including plants and mammals. It has been reported as the product of lysine metabolism.[64] More specifically, it has been detected in various physiological fluids in humans, including blood plasma, urine and cerebrospinal fluid.[65, 66] Interestingly, it was also identified as one of a variety of organic compounds found in the Murchison meteorite, a meteorite that landed in Murchison, Australia in 1969.[67] The pipecolic acid motif can be found in a variety of biologically active compounds. Homophymine A **218** is a natural product isolated from the marine sponge *Homophymia* sp. which has demonstrated anti-HIV activity (Figure 3).[68]



218 Homophymine A

Figure 3: Natural product Homophymine A

Compounds L-366,682 **219** and L-366,948 **220** are oxytocin antagonists which each contain two pipecolic acid motifs (Figure 4). Oxytocin is a peptide that induces and maintains uterine contractions during labour.[69] The inhibition of oxytocin function is thought to have potential therapeutic value in the prevention of premature births.

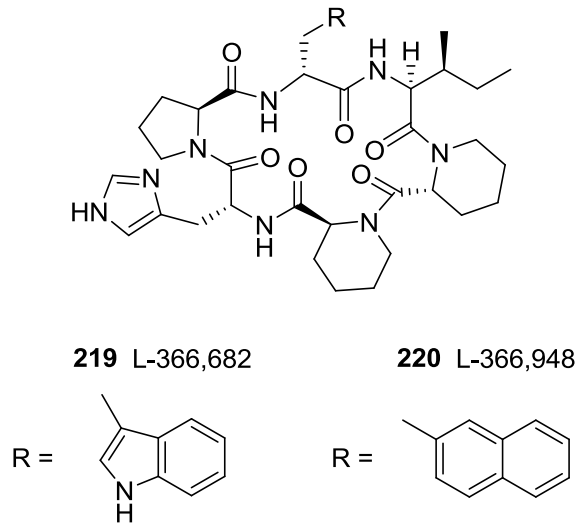
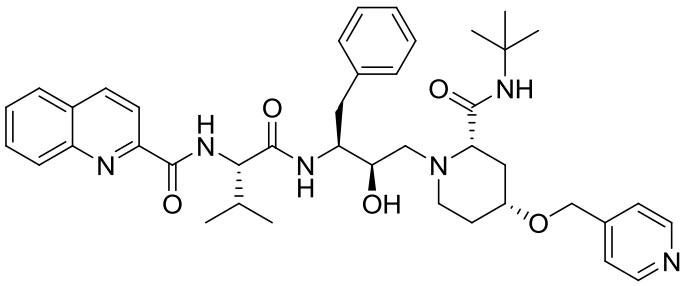
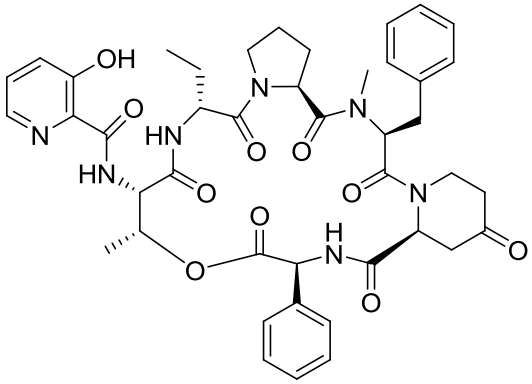


Figure 4: Oxytocin inhibitors

Modified analogues of the pipecolic acid motif, for example 4-oxygenated derivatives, also feature in biologically relevant compounds (Figure 5). Palinavir **221** is a potent inhibitor of HIV protease, and contains the 4-hydroxy-pipecolic acid motif.[70] Virginiamycin S_1 **222** is a component of the commercial antibiotic virginiamycin.[71] It contains the 4-oxopipecolic acid motif, and is used in the treatment of infections in agricultural livestock.



221 Palinavir



222 Virginiamycin S_1

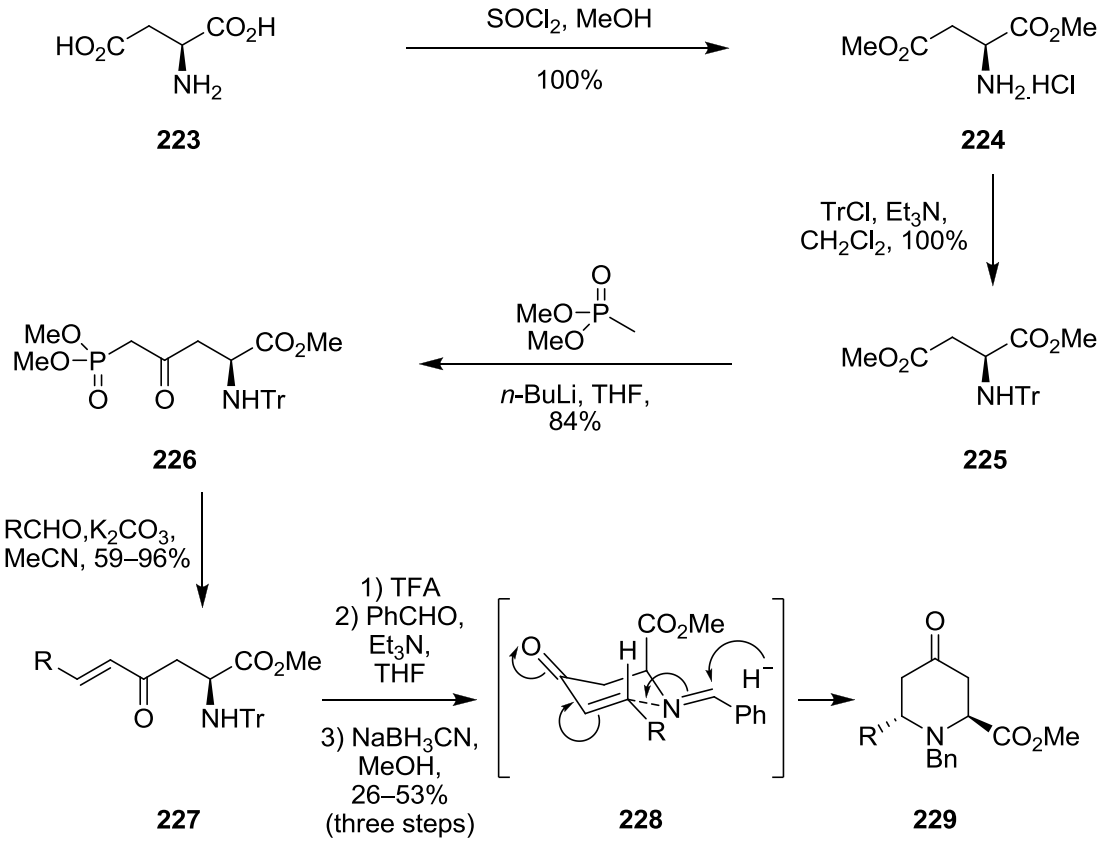
Figure 5: 4-oxo and 4-hydroxypipecolic acid derivatives

It is clear that compounds bearing the pipecolic acid motif display interesting biological activities, and in order to exploit these properties, it is important that novel and efficient syntheses are developed.[72] Indeed, previous group work led to a novel synthesis of 4-oxo and 4-hydroxy-6-substituted pipecolic acid derivatives.[73] It is this work that forms the basis of the novel methodology discussed here.

2.2.2 Previous Synthesis and Proposed Novel Synthesis

The previous route developed within the group began with enantiopure, commercially available L-aspartic acid **223**, which was treated with thionyl chloride to form the dimethyl ester hydrochloride salt **224** (Scheme 46). The amino group was then protected with trityl chloride. Reaction with the anion of dimethyl methylphosphonate at the least hindered, 4-position methyl ester afforded phosphonate ester **226**. This was reacted with a variety of aldehydes to form α,β-unsaturated ketones **227**. These compounds are themselves of interest, as de-tritylation and ester hydrolysis afforded a variety of unnatural amino acids, some of which displayed fluorescent properties.[74] The possibility of a 6-*endo*-*trig*

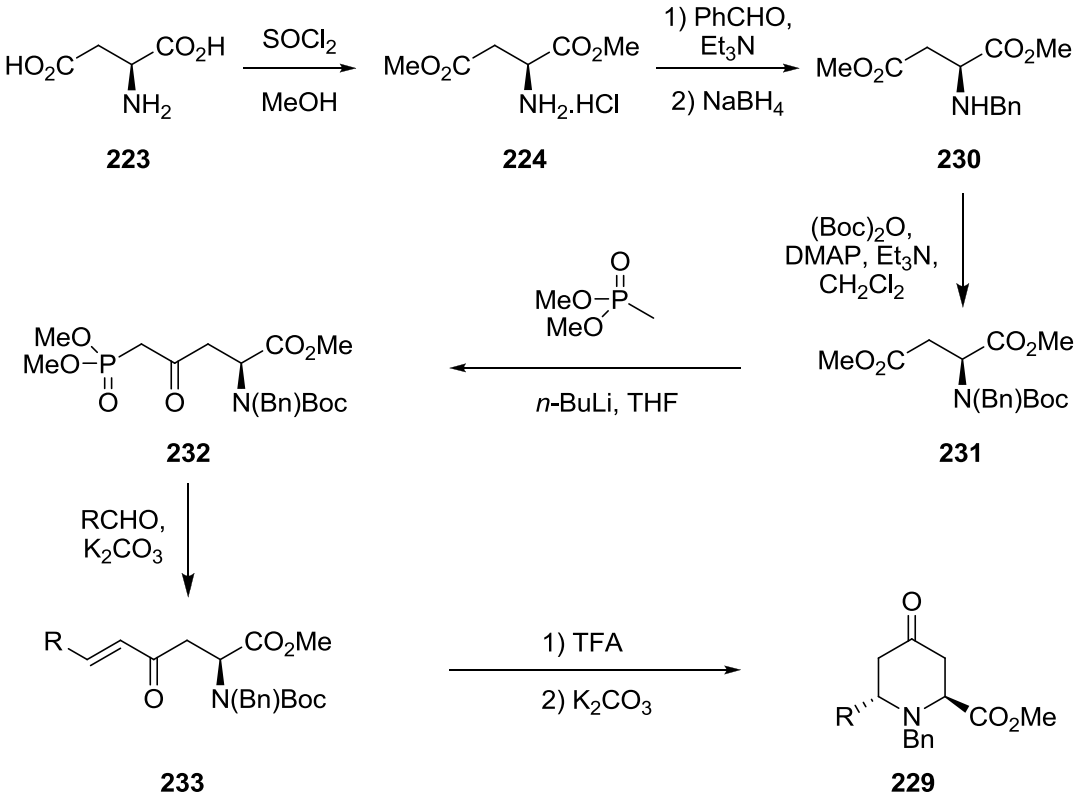
cyclisation of these compounds was investigated, and after various conditions were examined, the following strategy was found to be most effective; post acidic de-tritylation, reaction of the amine trifluoroacetic acid salt with benzaldehyde in the presence of base afforded the benzyl imine. Hydride reduction of the imine initiated a 6-*endo*-*trig* cyclisation, postulated to proceed via transition state **228**, to form the 2,6-*trans*-disubstituted 4-oxopipecolic product **229** in 26–53% yield over the three steps.



Scheme 46: Previous synthesis of 4-oxopipecolic acid deivatives

Whilst the cyclisation afforded access to the desired 4-oxo-pipecolic acids, there were aspects of this synthesis which could be improved. The yields of the cyclisation, being in the region of 26–53%, were considered to be generally low. It was proposed that this was due to competing ketone reduction during the one-pot process. After attaining very good yields for the majority of the synthesis, it was unfortunate that the reaction conditions in the final step should lead to only moderate yields. Therefore, in order to improve on this aspect, a synthesis which did not require the use of hydride reducing agents during cyclisation was proposed (Scheme 47). The starting material for this synthesis was, again, L-aspartic acid, which was to be converted to the dimethyl ester as before. However, instead of the trityl protecting group, the primary amine would undergo benzylation via

reductive amination, followed by orthogonal protection with the Boc group. Diester **231** could then undergo substitution with dimethyl methylphosphonate to form phosphonate ester **232**, the precursor for HWE reactions with a variety of aldehydes, affording α,β-unsaturated ketones **233**. The Boc group would then be removed under acidic conditions, and the cyclisation of the *N*-benzyl amine in the presence of a base, such as sodium carbonate, would be investigated. In summary, the aim of this project was to improve upon the yields of the cyclisations observed in previous group work to give 2,6-*trans*-disubstituted 4-oxopipecolic acid derivatives **229** more efficiently.

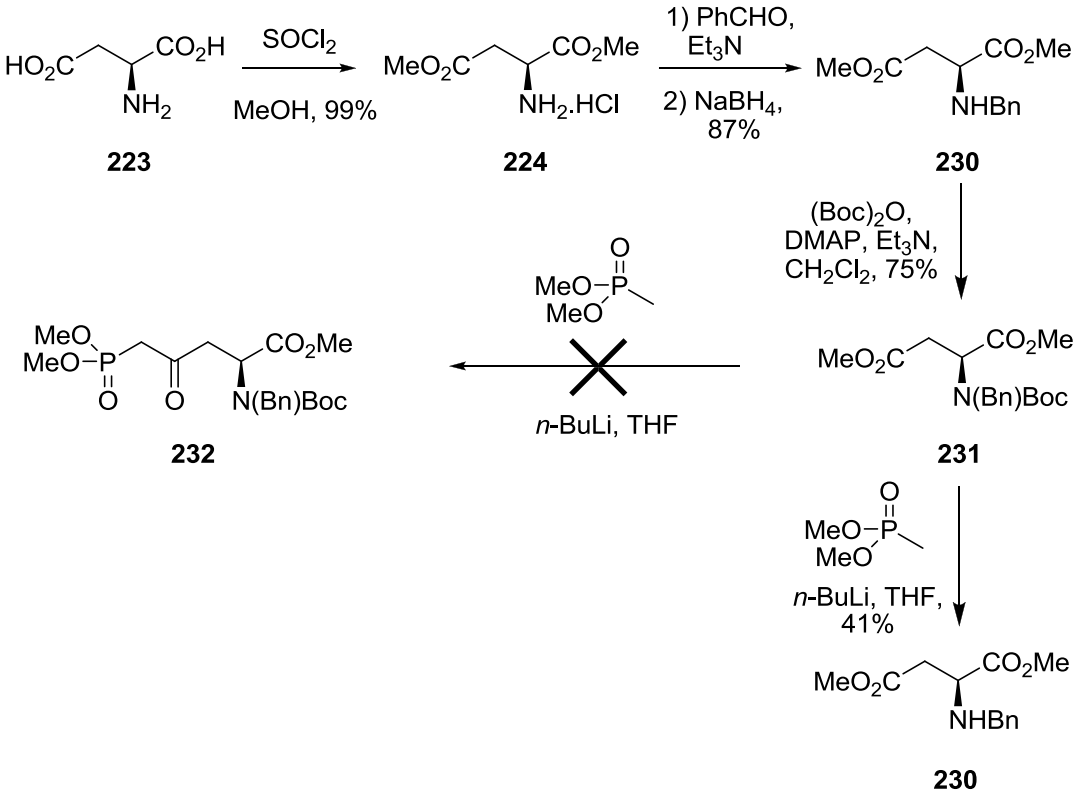


Scheme 47: Proposed synthesis of 4-oxopipecolic acids

2.2.3 Attempted Synthesis of Phosphonate Ester Intermediate

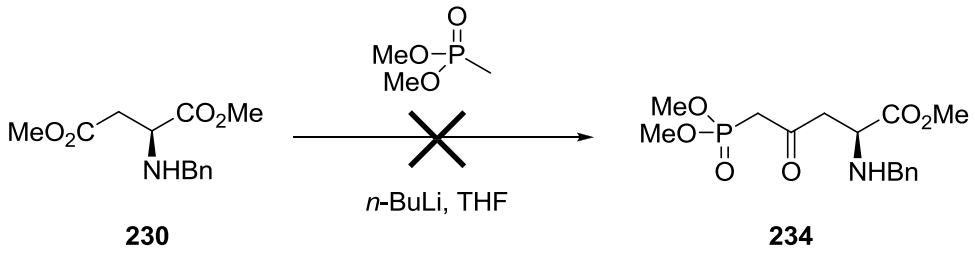
The synthesis began with a number of rudimentary protections that were unproblematic (Scheme 48). Diesterification proceeded in near quantitative yield. Reductive amination afforded benzyl protected amine **230** in good yield, and avoided issues of quaternisation that can be observed with the use of benzyl halides. Boc protection furnished the compound with steric bulk around the amine, which was intended to perform a similar function to the trityl group by favouring attack of the distal ester by the phosphonate

reagent. Unfortunately, substitution at this distal ester with dimethyl methylphosphonate did not proceed as planned. Rather than attack the carbonyl of the methyl ester, the phosphonate ester anion preferentially attacked the carbonyl of the Boc carbamate, resulting in the loss of the Boc group. Only the *N*-benzyl compound **230** was isolated from the reaction mixture.



Scheme 48: Attempted synthesis of β-keto phosphonate ester **232**

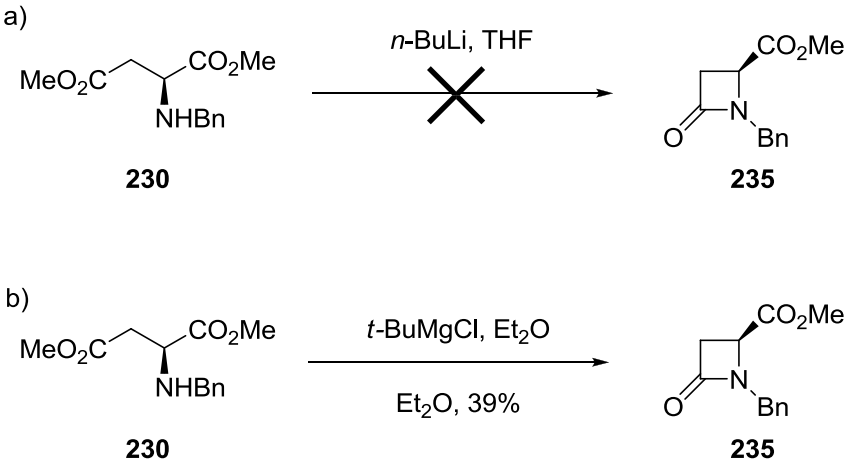
As the *N*-benzyl compound **230** was already in hand, it was decided to attempt the formation of the phosphonate intermediate **234** without protection from the Boc group (Scheme 49). It was hypothesised that a mixture of products from phosphonate substitution at the 4-carbonyl, the 1-carbonyl, and a combination of both may be observed. In practice, however, the desired reaction was not observed, only a minor amount of decomposition to unknown by-products. The reason for this is not clear. It was suggested that one equivalent of the phosphonate reagent may act as a base rather than a nucleophile, removing the amine hydrogen atom. To compensate for this, two equivalents of the dimethyl methylphosphonate anion were added to the reaction mixture. Despite this, the reaction outcome was similar to that previously observed. One hypothesis is that electronic repulsion may exist between the anionic amine, and the excess anionic phosphonate reagent.



230 **234**

Scheme 49: Unsuccessful β-keto phosphonate ester synthesis

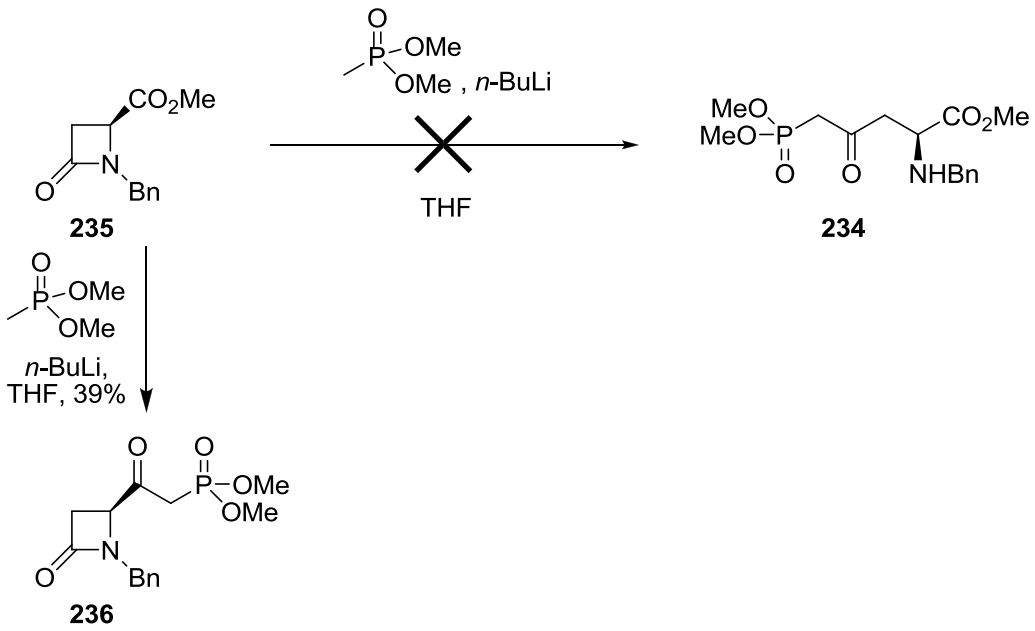
The above experimental results suggested that di-protection of the amino group was necessary. An interesting approach, which would not require additional protecting groups, would be to form β-lactam **235** from *N*-benzyl diester **230** (Scheme 50). This would mask the NH functionality, and there is literature precedence for the ring opening of β-lactams with anionic carbonucleophiles, for which it was intended to use the phosphonate reagent.[75] The first challenge was to form the β-lactam, which in itself was not entirely trivial. The first attempt employed *n*-butyl lithium as a base, which would deprotonate the secondary amine and facilitate cyclisation. Unfortunately, no cyclisation was observed. ^{1}H NMR spectroscopy of the crude product mixture suggested that *n*-butyl lithium had acted as a nucleophile towards the ester moieties. However, literature precedence was found for the formation of β-lactams using Grignard reagents as a base.[76] Using these conditions, the β-lactam was isolated in 39% yield.



Scheme 50: Synthesis of β-lactam **236**

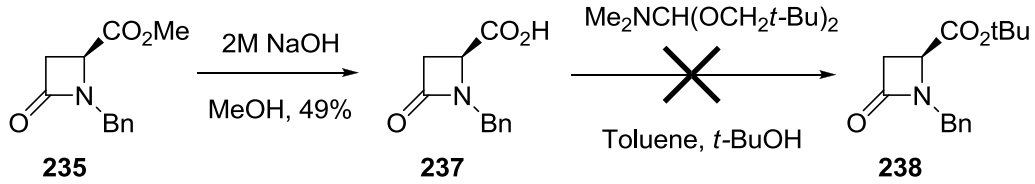
Having formed the β-lactam, the ring opening using the original conditions for phosphonate ester formation was attempted. Disappointingly, these conditions did not

effect ring opening (Scheme 51). However, the phosphonate reagent successfully attacked the methyl ester group, affording phosphonate ester **236** in 39% yield.



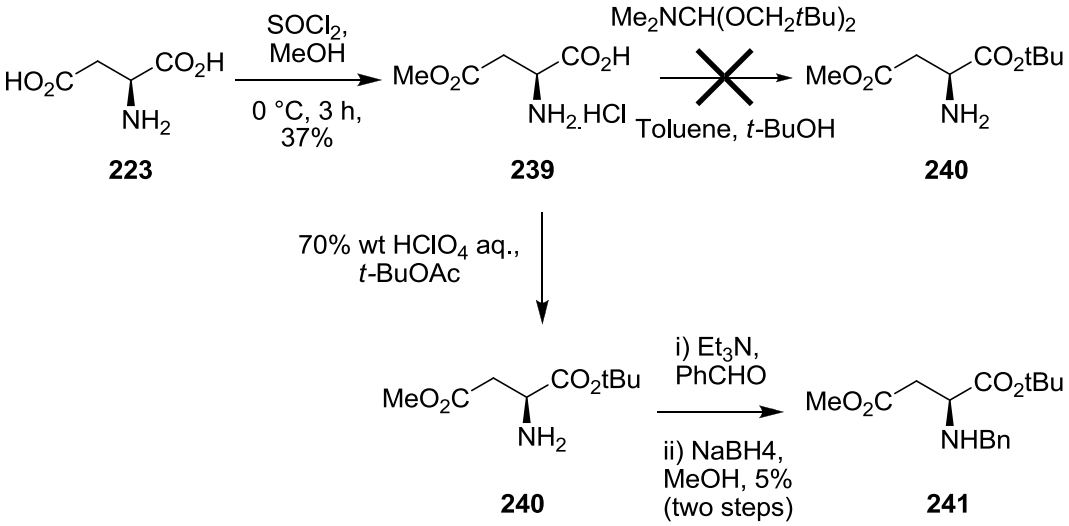
Scheme 51: Attempted synthesis of β-keto phosphonate ester **234**

Despite the setback, it was believed that this approach merited further attention. A review of similar ring opening reactions revealed that success was more likely using a bulkier ester group.[77] Whilst it was not explicitly stated that this was to avoid unwanted reaction of the ester, it was inferred that a bulkier ester functionality may allow selective ring opening. It was decided to attempt the formation of the *exo tert*-butyl ester using β-lactam compound **235** (Scheme 52). Methyl ester **235** was hydrolysed to carboxylic acid **237** under basic conditions in modest yield. The formation of a *tert*-butyl ester is often non-trivial. In addition, a literature review of *tert*-butyl esterification methods revealed that the majority of these employed acidic conditions. As the β-lactam structure is known to be acid sensitive, this restricted the options. One suitable reaction employed *N*,*N*-dimethylformamide dineopentyl acetal.[77] Unfortunately, despite several attempts, the *tert*-butyl ester **238** could not be generated from β-lactam acid **237** using these conditions.



Scheme 52: Ester hydrolysis and attempted ester formation

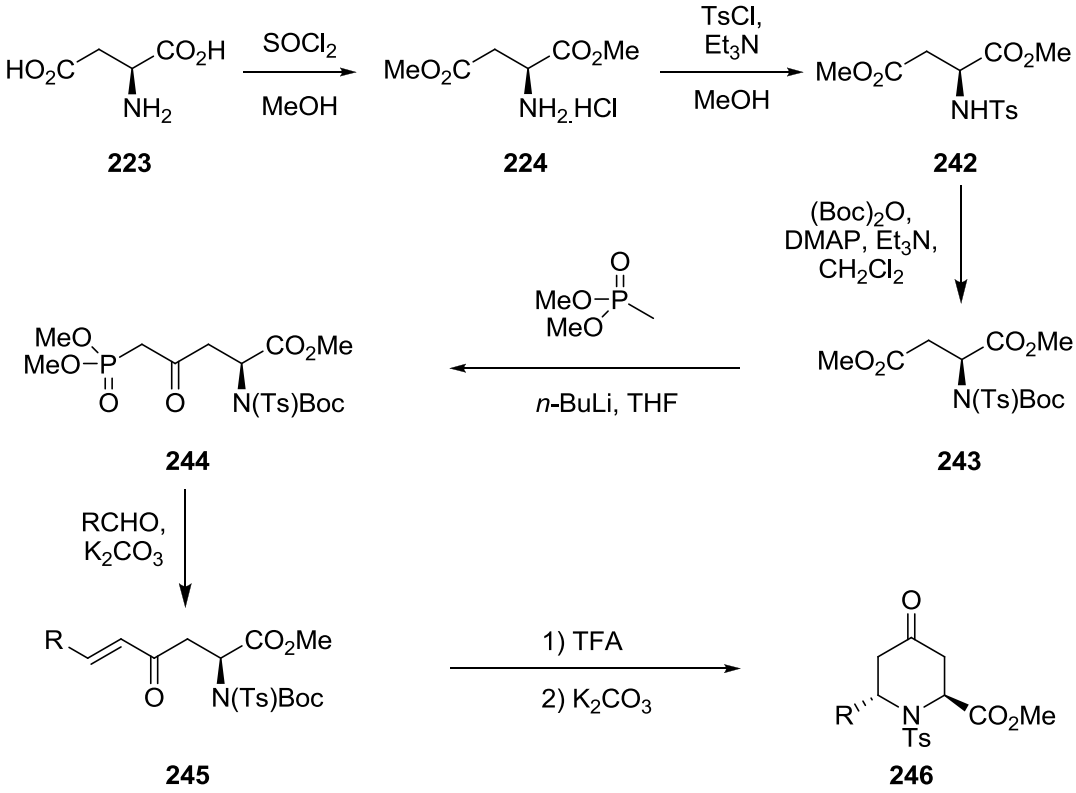
An alternative approach was next investigated, installing the *tert*-butyl ester at an earlier stage of the β-lactam synthesis. Thus, installation of the *tert*-butyl group before lactamisation of the aspartic acid derivative was attempted (Scheme 53). The synthesis was revised, and using modification of a literature procedure,[78] it was possible to isolate monoesterified product **239** in a modest yield of 37% by reaction of aspartic acid with thionyl chloride at 0 °C in methanol. The challenge, then, was to form the *tert*-butyl ester at the 1-position. The previous approach using *N*,*N*-dimethylformamide dineopentyl acetal was trialled, but again, no reaction was observed using this reagent. The absence of the β-lactam unit widened the scope of possible reaction conditions, and allowed for the use of 70% wt. perchloric acid in *tert*-butyl acetate.[79] It was observed from the ^{1}H NMR spectra of the crude product that some *tert*-butyl ester **240** had been formed. It was decided that the crude material was sufficiently clean to use without further purification. Thus, the crude material was subjected to a reductive amination using benzaldehyde and sodium borohydride, which gave the benzyl amine **241** in a 5% yield. This necessitated a reassessment of strategy; the first three steps of the synthesis had afforded markedly poor yields, and would likely require substantial time and effort in order to improve them. In addition, it was not certain whether deprotonated dimethyl methylphosphonate would effect ring opening of the proposed β-lactam. Also, it was possible that the bulky ester group could have a negative impact on subsequent reactions, particularly the proposed cyclisation. Regrettably, it was decided to abandon efforts towards this strategy, with the aim of developing a process more akin to the original synthesis.



Scheme 53: Synthesis of *tert*-butyl ester **241**

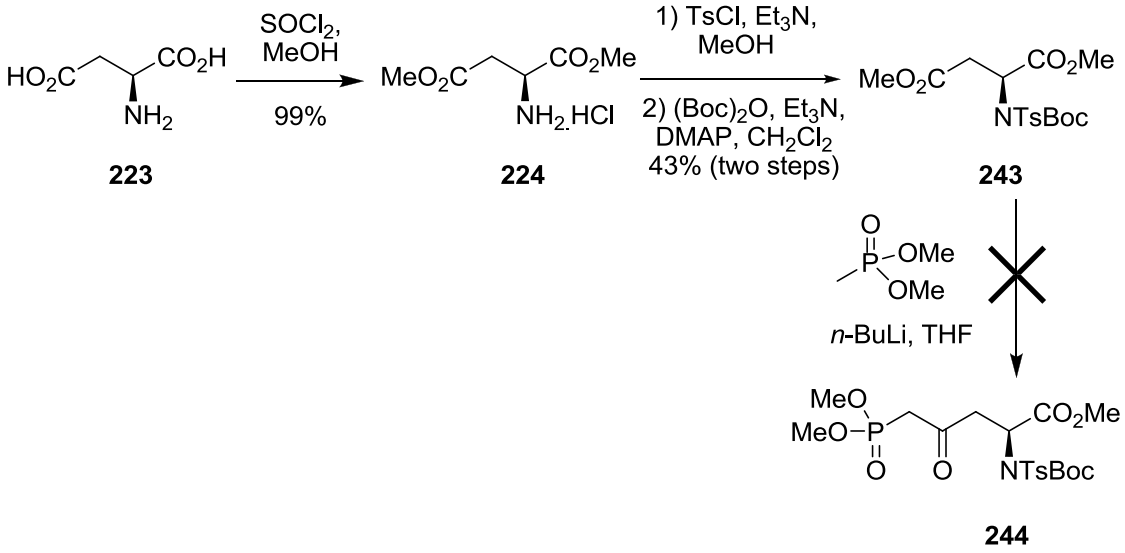
2.2.4 Revised Synthesis of 4-Oxopipecolic Acid Derivatives

The revised synthesis is shown in Scheme 54. It is broadly similar to the original synthesis with a simple variation in protecting group, exchanging the *N*-benzyl moiety for *N*-tosyl. There were two main reasons for this exchange; firstly, it was proposed that by varying the electronics and sterics of the protecting group, the phosphonate ester formation may proceed without eliminating the Boc group or performing other unwanted reactions. Secondly, at the cyclisation stage, the electron withdrawing effects of the sulfonamide group may facilitate cyclisation with a weak base.



Scheme 53: Revised synthesis of 4-oxopipecolic acid derivatives **246**

Preparation of the di-protected amine **243** proved facile (Scheme 55). Following diesterification using previously mentioned conditions, amine protection using *p*-toluenesulfonyl chloride followed by Boc anhydride afforded glutamic acid derivative **243** in good yield. However, the subsequent phosphonate ester formation was unsuccessful. Whilst the Boc protecting group remained intact, no reaction at either ester was observed. Despite several attempts using an excess of the phosphonate ester anion, only starting material was isolated.

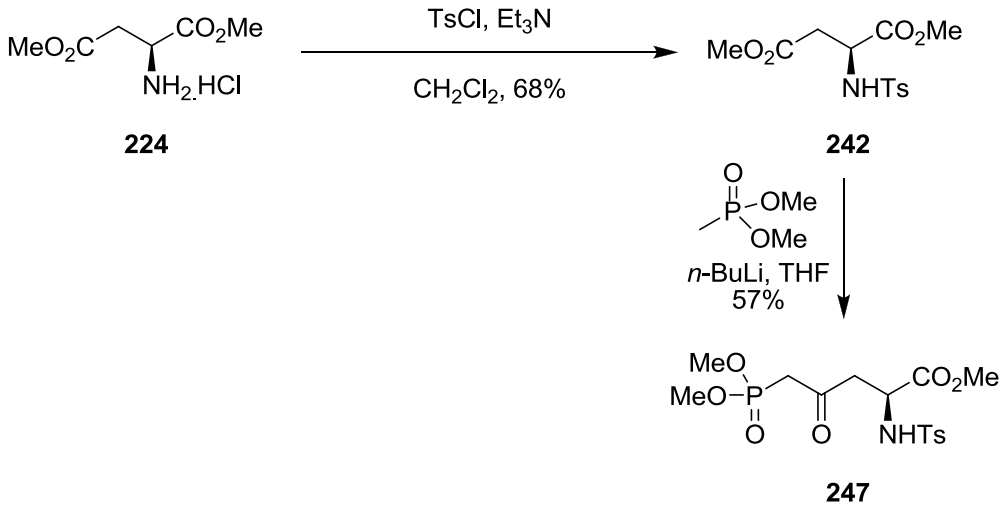


223 **224** **243** **244**

Scheme 55: Attempted synthesis of phosphonate ester **244**

By comparing the outcomes of the attempted syntheses of *N*,*N*-benzylBoc phosphonate ester **232** and *N*,*N*-tosylBoc phosphonate ester **244**, it appeared that the nature of the protecting groups can have a significant impact on the reactivity of the substrate; in the case of **232**, the Boc group was removed, whilst in the case of **244**, no reaction was observed. Thus, it was reasoned that an attempt to form the mono-protected *N*-tosyl compound **247** would be a worthwhile investigation (Scheme 56). As expected, the formation of *N*-tosyl compound **242** presented no problems. In addition, it was found that in the presence of 2.5 equivalents of the dimethyl methylphosphonate anion, the phosphonate ester **247** was formed in 57% yield. The di-phosphonate ester and the 1-phosphonate ester were not observed in the ^{1}H NMR spectra of the crude product, suggesting regioselective addition had occurred. It had been previously observed that the *N*-benzyl compound **230** did not form the desired phosphonate ester when treated with the deprotonated phosphonate reagent, and it was proposed that the formation of an anionic amino species was hindering the reaction, possibly by electronic repulsion. However, the presence of the sulfonamide moiety in compound **242** is likely to lower the pKa of the amine NH relative to that of compound **230**. In other words, the formation of a deprotonated, anionic amino derivative of **242** is of greater likelihood. That this should lead to the desired phosphonate ester does not correlate with the previous hypothesis. It has therefore been proposed that the following occurs: in the case of *N*-benzyl compound **230**, the secondary amine is deprotonated, but as it is not able to disperse this charge through conjugating groups it is relatively reactive and quickly quenched with acidic protons abstracted from other modified aspartic acid molecules. The regenerated secondary amine

is able to react again, and hence the phosphonate reagent is rapidly quenched before it is able to react with the methyl ester. Whilst the *N*-tosyl amine **243** is more acidic, the anion formed is stabilised through conjugation with the sulfonamide group. It is therefore less likely to re-protonate, and will spectate while the remaining phosphonate reagent reacts with the distal methyl ester. With the successful synthesis of **248**, progress to the Horner-Wadsworth-Emmons reaction was then studied.

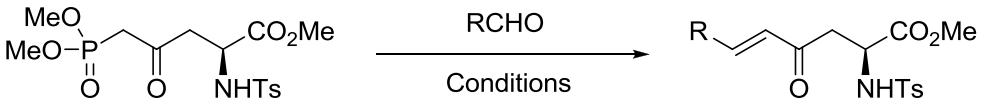


Scheme 56: Synthesis of *N*-tosyl phosphonate ester **247**

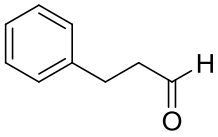
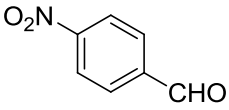
2.2.5 The Horner-Wadsworth-Emmons Reaction

The previously successful HWE conditions of potassium carbonate in acetonitrile were trialled using hydrocinnamaldehyde as an aldehyde substrate (Scheme 57, entry 1).[80] Despite several attempts, the maximum yield obtained using these conditions was 11%. Monitoring by TLC showed very slow progress, and the gradual increase in undesirable by-products over the course of the reaction led to the conclusion that extending reaction times would not be an effective solution. A screening of a small range of conditions was therefore initiated. Again using hydrocinnamaldehyde, the mild Masamune-Roush protocol of lithium chloride and DBU was trialled, but only starting material was isolated (entry 2).[47] The same result was observed when using the stronger base sodium hydride (entry 3), where an extra equivalent of hydride was added to compensate for the acidity of the sulfonamide NH. After these poor results, it was proposed that a more reactive aldehyde such as *p*-nitrobenzaldehyde may afford a better outcome. No reaction at all was observed using the previously successful potassium carbonate with *p*-nitrobenzaldehyde (entry 4). The Masamune-Roush protocol was attempted again, but as before, only starting material

was reclaimed (entry 5). A change of strategy was then proposed, where stronger bases at lower temperatures may allow the deprotonation of both the sulfonamide NH, and the β-keto phosphonate methylene carbon, without excessive side reactions or degradation. Thus, lithium hexamethyldisilazide at −78 °C was trialled, but again, no reaction was observed (entry 6). As an alternative, lithium diisopropylamide at −78 °C was trialled (entry 7). While this did not afford the desired α,β-unsaturated ketone, the reaction did produce a substantial quantity of *p*-nitrobenzyl alcohol as a side product; the propensity of lithium dialkyl amides to act as reducing agents for carbonyl compounds has previously been reported and exploited by Férézou and co-workers.[81]



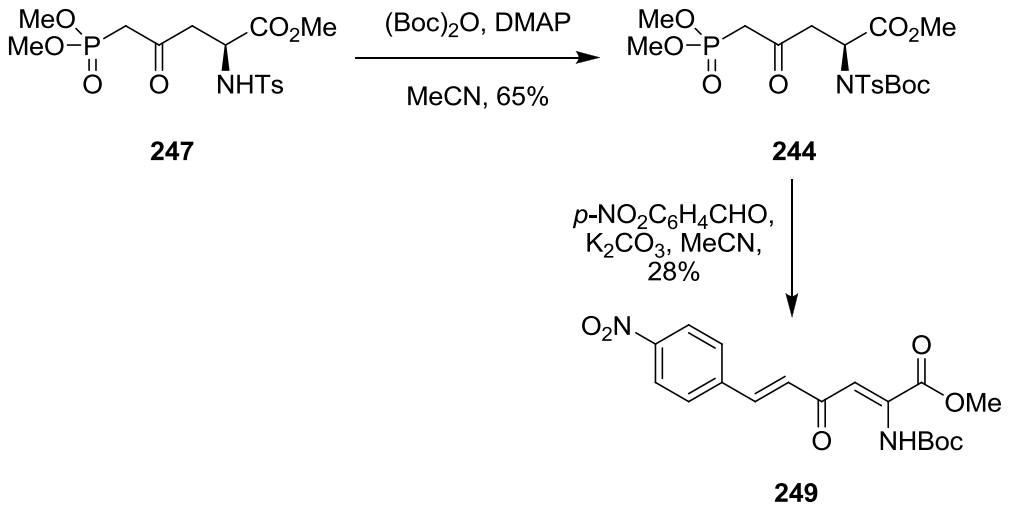
247 **248**

Entry	Aldehyde	Conditions	Yield
1		K_2CO_3, MeCN, 50 °C	11%
2	"	LiCl, DBU, MeCN, 60 °C	SM
3	"	NaH, THF, 0 °C - rt	SM
4		K_2CO_3, MeCN, 50 °C	SM
5	"	LiCl, DBU, MeCN, 60 °C	SM
6	"	LiHMDS, THF, −78 °C	SM
7	"	LDA, THF, −78 °C	SM and *p*-nitrobenzyl alcohol

Scheme 57: Horner-Wadsworth-Emmons conditions screen

Having considered the results using aliphatic and aromatic aldehydes, and a mixture of inorganic and organic, strong and mild bases in the proposed HWE reaction, the conclusion that the phosphonate ester may be the source of the problem was reached. More specifically, it was suspected that the acidic NH of the sulfonamide may be detrimental to

reaction progress. Di-protection of the nitrogen was thought to be necessary, and as the use of the Boc group was originally proposed in the previous iteration of the synthesis, it seemed logical to utilise this protecting group. Treatment of **247** with Boc-anhydride gave **244** in 65% yield, allowing the reinvestigation of the HWE reaction (Scheme 58). As the potassium carbonate conditions had given the only positive result in the previous conditions screen, they were deemed the most suitable choice. It was decided to continue with the use of *p*-nitrobenzaldehyde as it was believed that its increased electrophilicity gave the best chance of success. These conditions afforded somewhat mixed results. It appeared that the HWE reaction had proceeded and the α,β-unsaturated ketone had been formed. Unfortunately, the reaction did not stop at this point, and under the basic conditions, the tosyl moiety acted as a leaving group. Whilst it was not possible to obtain a sample clean enough for full analysis, ^{1}H and ^{13}C NMR spectra strongly suggested the formation of conjugated species **249**. In forming the α,β-unsaturated system, the key stereocentre had inadvertently been lost.

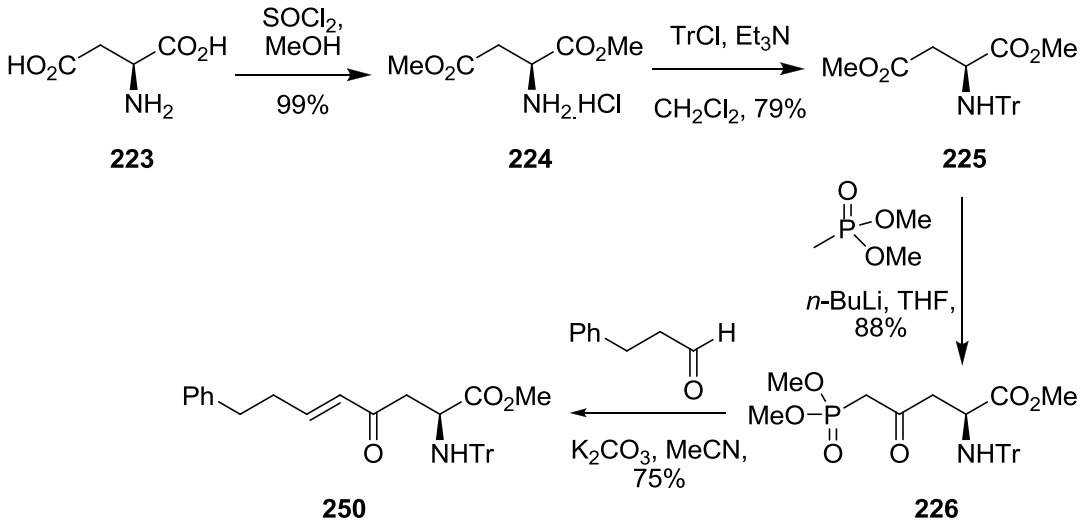


Scheme 58: Attempted Horner-Wadsworth-Emmons procedure

2.2.6 Synthesis of *N*-Trityl α,β-Unsaturated Ketone

These results prompted another reappraisal of the strategy. The main objective was to obtain a cyclisation precursor containing the α,β-unsaturated ketone and an *N*-tosyl moiety appended to a stereocentre. In the interest of time and efficiency, it was proposed that the route previously developed by our group should be followed to form the *N*-trityl α,β-unsaturated ketone,[73] followed by investigation of trityl removal, tosylation, and cyclisation. This seemed logical as the majority of the route was well developed, and

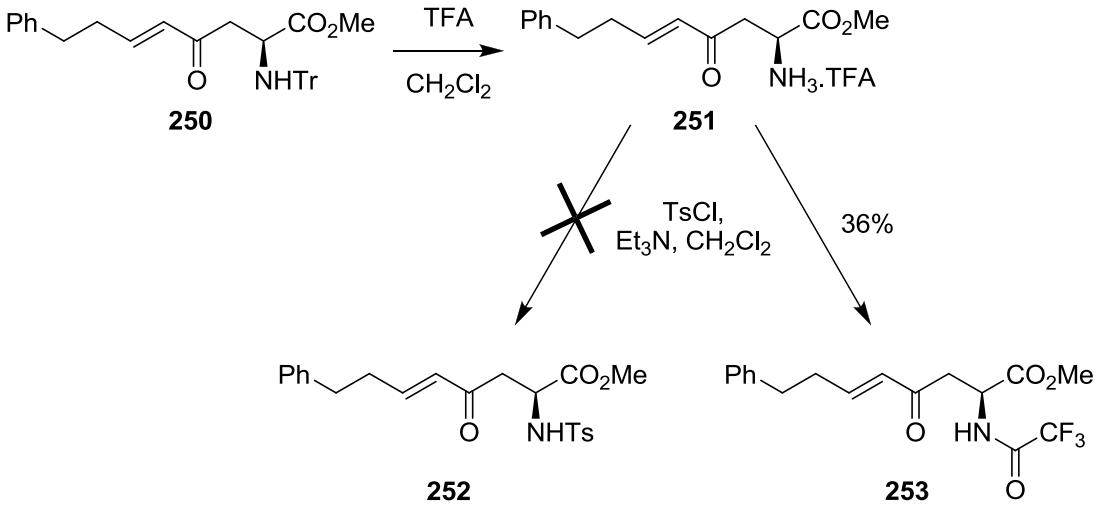
theoretically the detritylation and tosylation should prove facile, allowing attention to be focused on the critical cyclisation step. The route began with the diesterification of L-aspartic acid, followed by high yielding tritylation and phosphonate ester formation steps (Scheme 59). Hydrocinnamaldehyde was chosen as a model substrate, and unsurprisingly, the HWE reaction afforded ketone **250** in good yield. The considerable steric bulk of the trityl moiety hinders unwanted side reactions that may occur as a result of the reactivity of the secondary amine.



Scheme 59: Synthesis of α,β-unsaturated ketone **250**

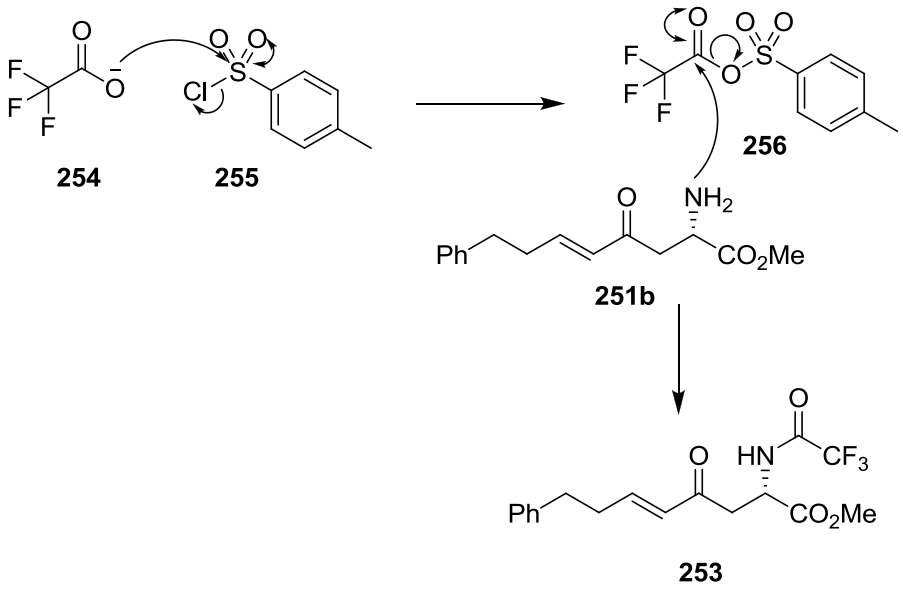
2.2.7 Detritylation and Tosylation

Having formed *N*-trityl ketone **250**, attention focused on its detritylation and subsequent tosylation. The previously published synthesis had achieved detritylation using trifluoroacetic acid, and therefore this was the reagent of choice. Deprotection was effected cleanly and quickly, and the trifluoroacetic acid salt of the primary amine **251** was isolated without requiring purification (Scheme 60). Standard conditions for tosylation were then employed, using *p*-toluenesulfonyl chloride and triethylamine. Surprisingly, however, the ^{1}H and ^{13}C NMR spectra of the isolated product showed the formation of trifluoroacetamide **253**.



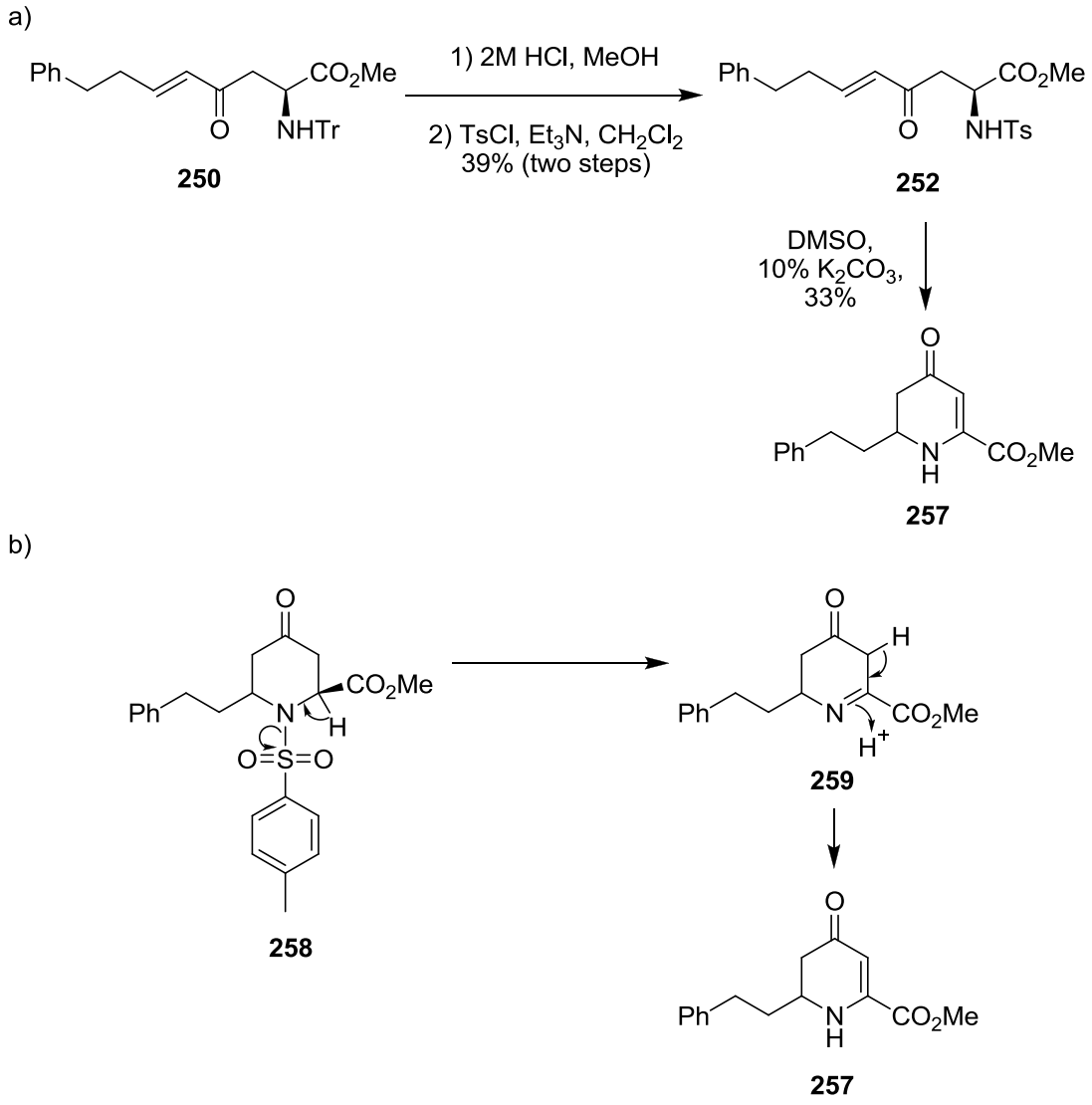
Scheme 60: Unexpected trifluoroacetamide synthesis

This was an unexpected result, but a plausible mechanism may hold the explanation after-the-fact (Scheme 61). It was believed that the trifluoroacetate anion **254** is more nucleophilic towards *p*-toluenesulfonyl chloride than either the amine TFA salt **251** or the primary amine **251b**. It therefore forms intermediate **256** *in situ*, which likely displays similar reactivity characteristics to an acid anhydride. It is this species that reacts with the primary amine, which preferentially attacks the carbonyl component of the anhydride over the sulfone, leading to the formation of the trifluoroacetic amide **253**.



Scheme 61: Proposed mechanism of trifluoroacetic amide synthesis

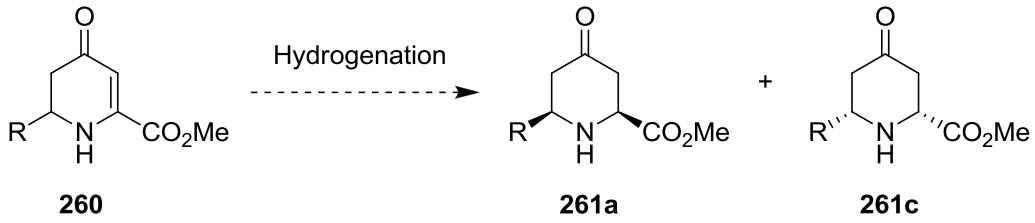
Undeterred by this unexpected result, trifluoroacetic acid was exchanged for 2 M hydrochloric acid in the detritylation step, and these conditions were found to be equally as effective, affording the amine hydrochloride salt cleanly. This was followed by standard tosylation conditions, and the *N*-tosyl amine **252** was isolated in 39% yield over two steps (Scheme 62a). Finally, it was possible to investigate the crucial cyclisation procedure, and literature precedence had been found for the similar cyclisation of simple *N*-tosyl amines by employing potassium carbonate as a base.[82] These conditions were applied to substrate **252**. It appeared that the cyclisation of the amine had proceeded as planned. Unfortunately, the reaction did not stop at this point. In a similar fashion to the unexpected synthesis of **249**, the tosyl moiety was able to act as a leaving group under the basic conditions, forming imine **259**, which tautomerised to the more stable, conjugated product **257** (Scheme 62b). Whilst cyclisation had been achieved, a stereocentre had been lost, and it was not possible to determine the stereochemical outcome of the cyclisation. The reaction was repeated in acetonitrile as it was proposed that a slightly less polar solvent may lead to lower solubility of potassium carbonate and therefore decrease the chance of the unwanted tosyl elimination occurring. However, despite a reaction time of several days, only starting material with some evidence of decomposition was isolated from this mixture.



Scheme 62: Synthesis of unsaturated pipecolic acid derivative **257** and possible cyclisation mechanism

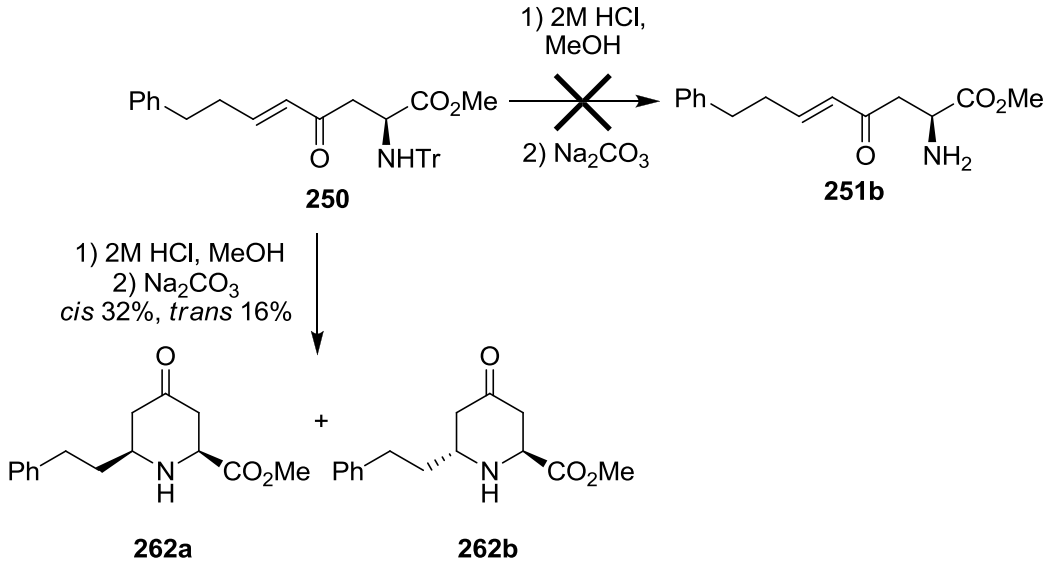
2.2.8 Detritylation and Cyclisation

It was proposed that the issues of cyclisation could be overcome by further elaboration of product **257**. Were this pattern of detosylation to continue with different analogues, hydrogenation of the alkenes may be facially directed by the presence of the tertiary stereocentres present in the unsaturated intermediates **260** (Scheme 63). On the assumption that the cyclisation had not proceeded in a highly stereoselective fashion, this would give both *cis* enantiomers of the initial target compounds.



Scheme 63: Proposed selective hydrogenation

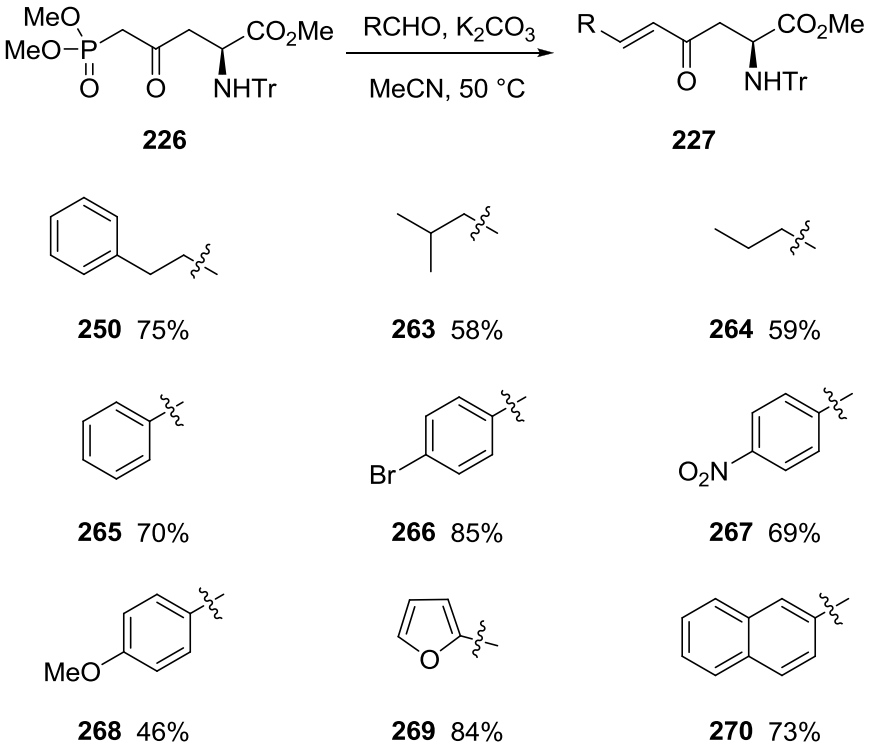
Before work could begin on this new strategy and the hydrogenation investigated, further quantities of *N*-tosyl amine **252** had to be synthesised. One area where it was felt that optimisation was necessary was the detritylation and tosylation procedure, with a previous yield of only 39% over two steps. It was proposed that neutralisation of the hydrochloride salt to form the primary amine before tosylation was attempted could afford higher yields. The detritylation was conducted as before with 2 M hydrochloric acid. After 1 hour, the reaction was treated with sodium carbonate. After extraction of the reaction mixture and ^{1}H NMR analysis of the product, it was found that the product of neutralisation was in fact the cyclised products **262a** and **262b**. The 2:1 *cis*:*trans* mixture of diastereomers proved easy to separate by column chromatography, and were isolated in an unoptimised 48% overall yield over the two steps.



Scheme 64: Formation of 4-oxopipecolic acid derivatives **262a** and **262b**

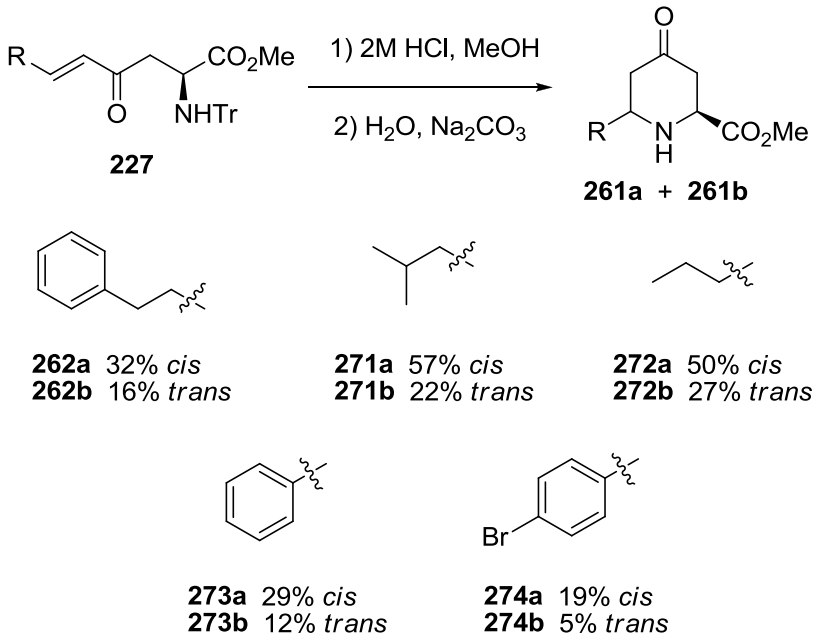
With a promising cyclisation procedure in place, the scope of the reaction was investigated with a variety of analogues. This began with the synthesis of a variety of α,β-unsaturated

ketones *via* the HWE reaction. A variety of aliphatic and aromatic substituents were included. With the exception of the *p*-methoxyphenyl derivative, which reacted slowly and in moderate yield, the HWE reactions proceeded in good yield and with complete *E*-selectivity (Scheme 65).



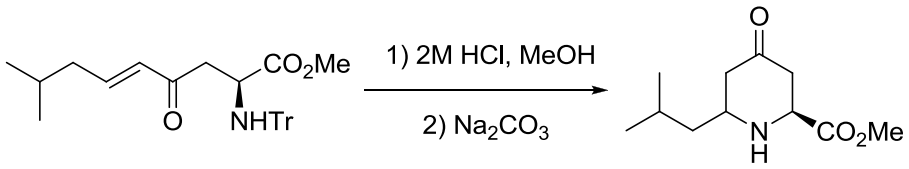
Scheme 65: Synthesis of α,β-unsaturated ketone analogues

With a variety of α,β-unsaturated ketones in hand, attention was turned to the cyclisation step. Using the serendipitous procedure of acidic detritylation, dilution with water and treatment with sodium carbonate, a variety of analogues were successfully cyclised (Scheme 66). The diastereomeric ratios were in the range of between 2:1 and 3:1 *cis*:*trans*, and the stereoisomers were separable by column chromatography. However, it was proposed that the cyclisation conditions should be investigated for optimisation; the diastereomeric ratios obtained thus far were not exceptional. Also, whilst some analogues had cyclised in respectable yields, others were far more modest.



Scheme 66: Sodium carbonate mediated cyclisation

In an effort to increase the diastereomeric ratios of the product mixtures, it was proposed that a reduction in reaction temperature might lead to improved ratios. This was experimentally proven to be correct (Scheme 67). However, it was ultimately not felt beneficial to adopt low temperatures as part of the cyclisation for two reasons. Firstly, the improved ratio from 2.5:1 to 3.3:1 *cis*:*trans* was not as substantial as had been hoped. Secondly, the reduced temperatures slowed the reaction markedly; whilst the room temperature trial had proceeded to completion over the reaction period, the reaction conducted at −20 °C had only converted around 10% of starting material to product in the same time. The conclusion was reached that the practical complications of maintaining the reaction at −20 °C for extended periods outweighed the minor benefits observed with regards to stereochemistry.

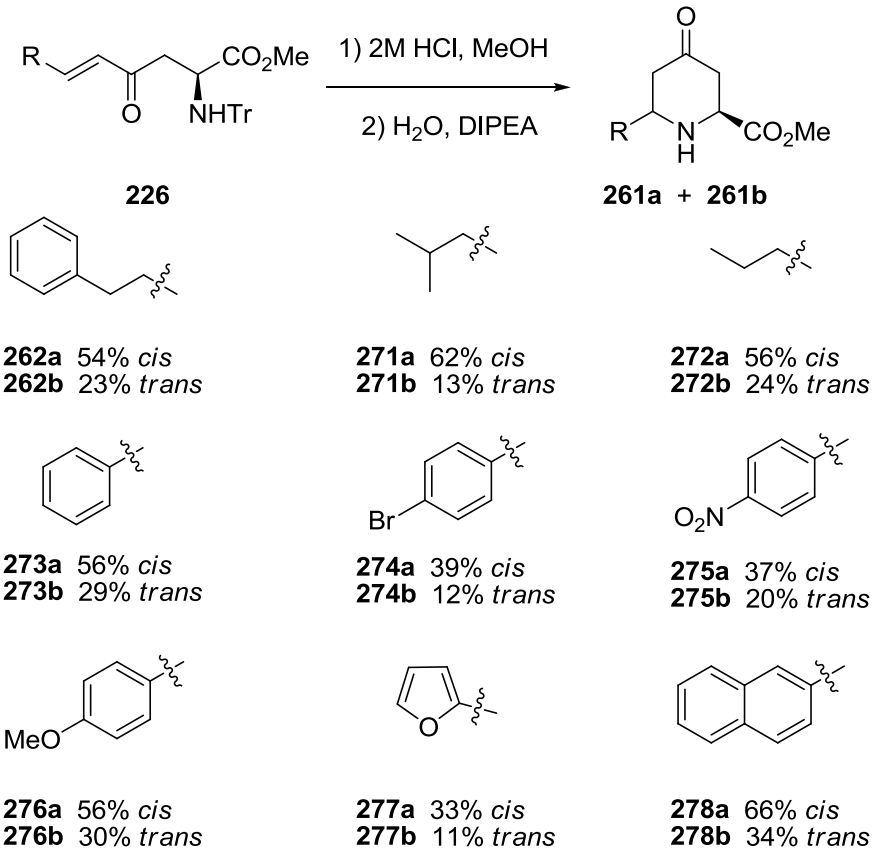


263 **271a + 271b**

Temp (°C)	*cis*:*trans* ratio
25	2.5 : 1
0	2.8 : 1
–20	3.3 : 1

Scheme 67: Effect of temperature on cyclisation

In parallel, investigations to improve the overall yields of the cyclisation were also conducted. It had been noted that under the original conditions, despite the dilution of the reaction mixture with water, a visible quantity of sodium carbonate was left undissolved at the bottom of the reaction vessel. It was proposed that faster reactions and higher yields might be achieved with the use of a fully soluble, homogenous base. To this end, *N*-ethyldiisopropylamine was substituted for sodium carbonate, which led to a substantial increase in yields. (Scheme 68). Using these optimised conditions, it was possible to cyclise the entire library of the *N*-trityl amine analogues in good overall yield and with a consistent preference for the *cis* diastereomer.



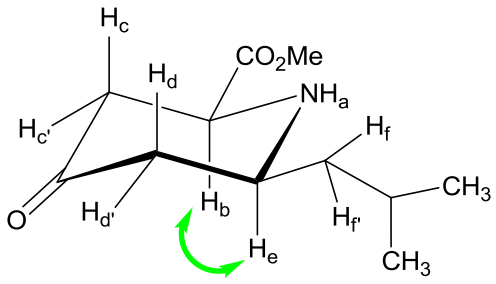
Scheme 68: *N*-Ethyldiisopropylamine mediated cyclisation

2.2.9 Determination of Stereochemistry by nuclear Overhauser effect Spectroscopy (4-Oxo Derivatives)

It has been noted above that the cyclisation affords the *cis*-diastereomer as the major component, and spectroscopic data supports this claim. Inspection of ^{1}H NMR data for the 2-H and 6-H protons of the major products displays a consistent trend for coupling constants in the region of 10-12 Hz. This strongly suggests that both of these protons are adopting axial positions, from which can be inferred a *cis*-relationship of the substituents in the equatorial 2- and 6-positions. This is in contrast to the ^{1}H NMR data obtained for the minor products; the 2-H protons consistently afford coupling constants in the region of 6-7 Hz. These constants are too small for axial-axial couplings, yet too large for axial-equatorial or equatorial-equatorial. Instead, this suggests the occurrence of ring-flipping between chair conformations of the minor products leading to an averaged coupling constant between the two possible conformations. This observation lends itself to the assignment of a *trans*-product, as the energy difference between both chair conformations

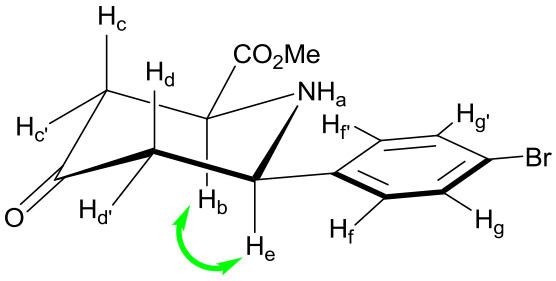
of said *trans*-product is likely to be lower in comparison to that found in the *cis*-product as a result of sterics.

Although the 1H NMR data of the cyclised products provided valuable information for stereochemical assignment, it was felt necessary to supplement this with further analysis. For this purpose, selective nOe (nuclear Overhauser effect) spectroscopy experiments were conducted on all of the cyclised products. Upon irradiating the hydrogen atoms at the 2-position of the *trans*-diastereomers, no enhancement of the 6-position hydrogen peaks was observed. However, this result in itself was not sufficient. Between the 2-H and 6-H atoms lies the nitrogen atom, which contains a quadrupolar nucleus. It is known that the nuclear Overhauser effect may be curtailed by quadrupolar relaxation through heteroatoms. Therefore, it was the results of the selective nOe experiments on the *cis*-diastereomers that allowed for the confident assignment of relative stereochemistry. In the selected examples below, irradiation of H_b induced enhancement of the H_e signal, and vice versa. In addition, as the reaction conditions employed in this synthesis are unlikely to induce either complete or partial racemisation of the 2-position stereocentres, it can be stated with confidence that the absolute stereochemistry is as described.



Saturation	% nOe
2.93 ppm (H_e)	1.2 (H_b) 0.5 ($H_{d'}$) 0.2 (H_f) 0.9 ($H_{f'}$)
3.67 ppm (H_b)	1.2 (H_e) 0.9 ($H_{c'}$/H_a)

Figure 6: Key nOe couplings for isobutyl derivative **271a**



Saturation	% nOe
3.94 ppm (H_e)	1.6 (H_b) 2.0 ($H_{d'}$) 1.4 (H_f/$H_{f'}$)
3.77 ppm (H_b)	1.7 (H_e) 0.7 ($H_{c'}$)

Figure 7: Key nOe couplings for *p*-bromophenyl derivative **274a**

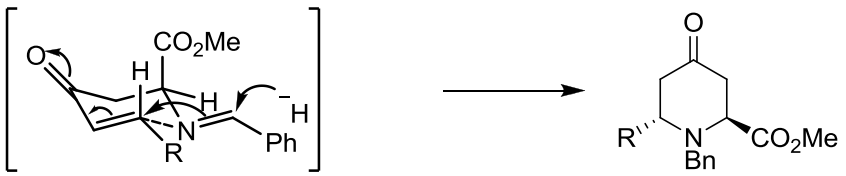
2.2.10 Rationale of Stereochemical Outcome

One aspect of the cyclisation that required consideration was the theoretical reasoning behind the observed stereochemical outcome. As demonstrated in Scheme 46, the diastereomeric outcome of the cyclisation previously investigated in the group had shown a consistent preference for the *trans*-diastereomer. Why should the current cyclisation predominantly produce the *cis*-diastereomer? The rationale behind the previous work's outcome is demonstrated in Scheme 69a. Prior to bond formation, the *N*-benzyl imine is proposed to adopt a 6-membered chair-like transition state **228**. It is thought to be sterically more favourable for the benzyl imine moiety to adopt a pseudo-equatorial position. This is also true for the R group, which also orients in a pseudo-equatorial fashion. Imine reduction then leads to the formation of the *trans*-diastereomer. Whilst the methyl ester group adopting a pseudo-axial position may be unfavourable in terms of sterics, it could conceivably be necessary to allow the access of the hydride equivalent to one face of the imine group.

In the case of the current cyclisation, the benzyl moiety on the amine is not present. This allows for the possibility of primary amine **279** adopting a chair-like transition state with both the R group and methyl ester in pseudo-equatorial positions, leading to *cis*-diastereomer **261a** (Scheme 69b). However, as can be seen in Scheme 69c, it is also possible for the primary amine to adopt transition state **280**. Whilst this configuration with its pseudo-axial methyl ester is likely disfavoured over **279** with both substituents pseudo-equatorial, the steric bulk of the ester is less discriminating. Hence, the primary amine can adopt this configuration without incurring significant steric hindrance, and this is perhaps why the selectivity of the cyclisation is not particularly high. However, this does leave scope to investigate the cyclisation with bulkier ester groups, which may lead to improved selectivity.

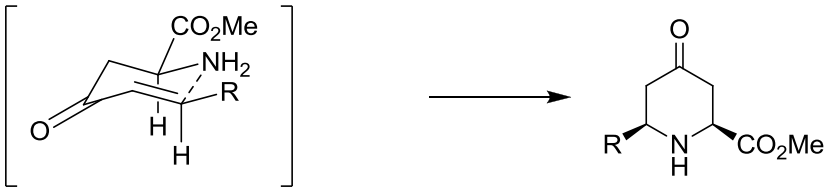
As an additional note on this matter, whilst the chair conformations of Scheme 69 provide a convenient explanation of the observed outcomes, in reality the intermediates may be flatter than those depicted to allow more effective orbital overlap in the conjugated α,β-unsaturated ketone system. Modelling studies may provide further information on the true nature of these reactions.

a)



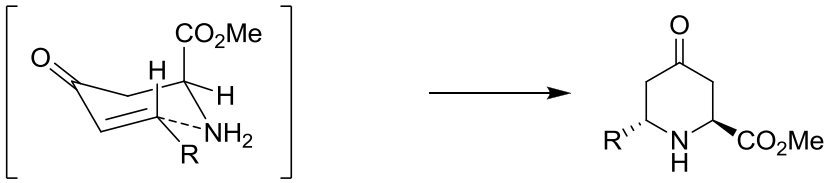
228 **229**

b)



279 **261a**

c)

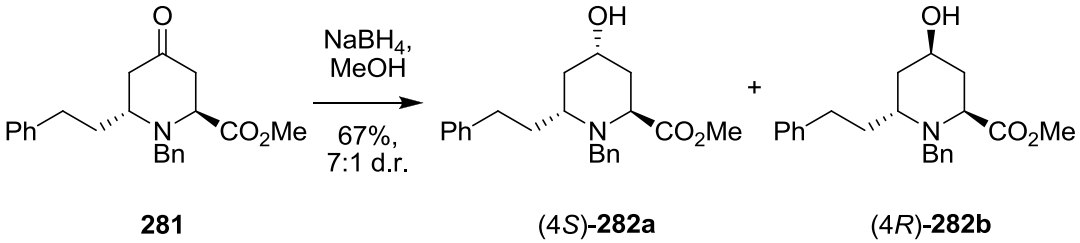


280 **261b**

Scheme 69: Rationale of stereochemical outcome

2.2.11 Synthesis of 4-Hydroxy Derivatives

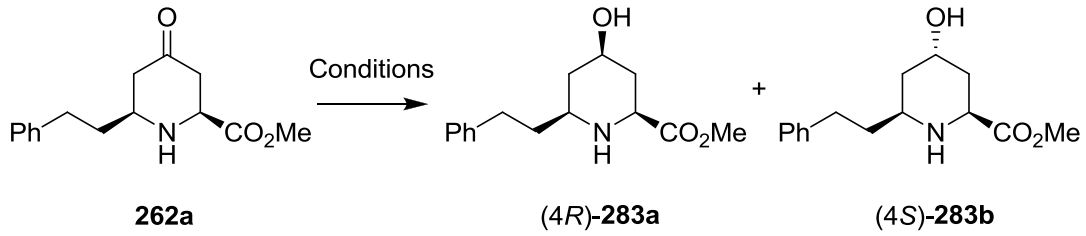
As stated, the major diastereomer obtained from the cyclisation reaction was the *cis*-isomer. Previous work on the synthesis of *trans*-4-oxopipecolic acids had been extended with a stereoselective carbonyl reduction to form 4-hydroxypipecolic acid derivatives.[73] Using sodium borohydride, the predominant *trans*-diastereomers, exemplified by analogue **281**, were reduced to the 4-hydroxy derivatives with a preference for the (4*S*)- isomer **282a** in ratios ranging from 2:1 to 7:1 (Scheme 70). It was therefore proposed that an investigation into the reduction of the *cis*-diastereomer would make an interesting comparison.



Scheme 70: Previous 4-oxopipecolic acid reduction

The reduction of model substrate **262a** was trialled with a small range of reducing agents (Scheme 71a). L-Selectride proved entirely ineffective, with no reduction observed. Sodium borohydride afforded the desired products in modest yield. However, the diastereomeric ratio of 13:1 was an improvement over the ratios observed in the reduction of the *trans*-diastereomer in previous group work. Sodium cyanoborohydride afforded a modest improvement in yield, but a decrease in stereoselectivity. The most effective reagent in this trial was proven to be sodium triacetoxyborohydride, offering good selectivity and a very good yield. These conditions were applied to a further two analogues, producing 4-hydoxypipecolic acid derivatives in further improved yields and selectivities (Scheme 71b). In comparison with the reduction of the *trans*-diastereomers, the reduction of the *cis*-isomers appears to proceed with greater diastereoselectivity.

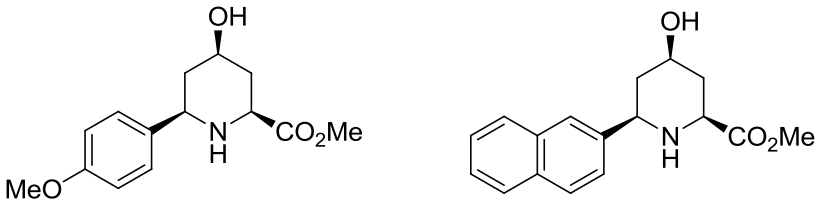
a)



262a (4*R*)-**283a** (4*S*)-**283b**

Conditions	d.r. (4*R*):(4*S*)	Yield (%)
L-Selectride (1 M), THF, –78 °C - r.t.	n/a	0
$NaBH_4$, MeOH, 0 °C - r.t.	13:1	52
$NaBH_3CN$, MeOH, 0 °C - r.t.	10:1	60
$NaBH(OAc)_3$, THF, 0 °C - r.t.	13:1	87

b)



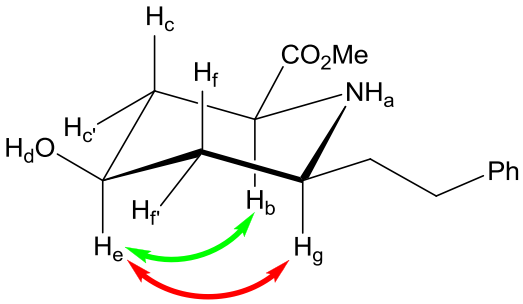
(4*R*)-**284a** (4*R*)-**285a**

96%, 23:1 (4*R*):(4*S*) 100%, 17:1 (4*R*):(4*S*)

Scheme 71: Reduction to 4-hydroxypipecolic acid derivatives

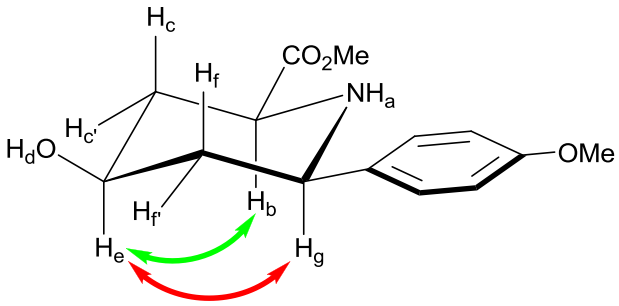
2.2.12 Determination of Stereochemistry by nuclear Overhauser effect Spectroscopy (4-Hydroxy Derivatives)

Determination of the stereochemistry of the 4-hydroxy compound was achieved using selective nOe experiments. As shown in Figures 8-10, irradiation of the H_e peak produced an enhancement of the H_b and H_g signals, confirming formation of the (4*R*)-isomer. This suggests a preference for axial attack, which is often observed with small nucleophiles despite being the more sterically congested approach. The origin of this axial selective effect is thought to be the relief of torsional strain. In the ketone starting material, the carbonyl group is close to an eclipsed position with the C-H bonds of the C-3 and C-5 carbons. Equatorial attack would force the C-O bond through a fully eclipsed position, while axial attack relieves torsional strain, and is therefore the preferred approach.



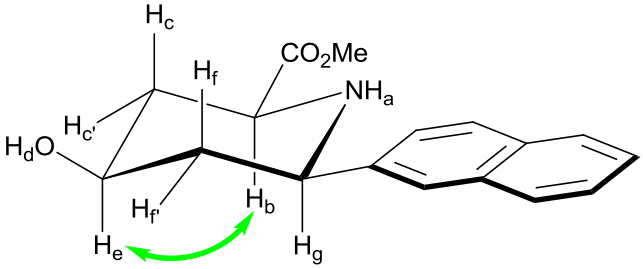
Saturation	% nOe
3.39 ppm (H_b)	1.1 (H_e) 1.5 (H_g) 0.9 ($H_{c'}$)
3.74 ppm (H_e)	0.6 (H_b) 0.7 (H_g) 0.8 ($H_{c'}$) 0.9 ($H_{f'}$)

Figure 8: Key nOe couplings for phenethyl derivative **283a**



Saturation	% nOe
3.85 ppm (H_e)	0.9 (H_b) 0.8 (H_g) 1.1 ($H_{f'}$) 1.3 ($H_{c'}$)

Figure 9: Key nOe couplings for *p*-methoxyphenyl derivative **284a**

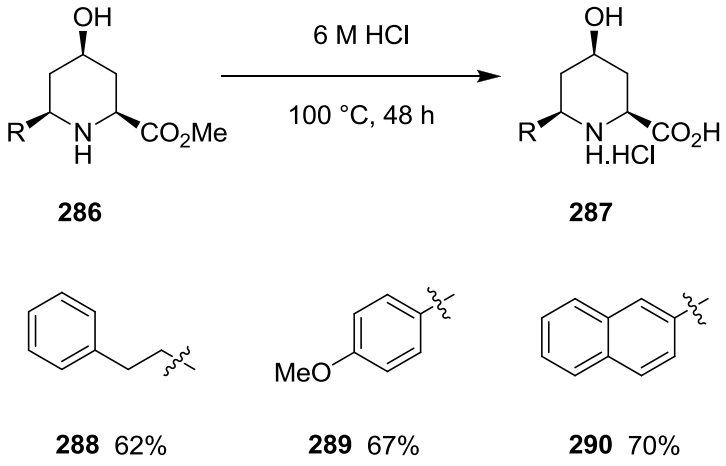


Saturation	% nOe
3.91 ppm (H_e)	1.2 (H_b) 1.3 ($H_{f'}$) 1.6 ($H_{c'}$)

Figure 10: Key nOe couplings for naphthyl derivative **285a**

2.2.13 Ester Hydrolysis

The core structure of the compounds synthesised in this project is the pipecolic acid moiety. It seemed logical to hydrolyse the methyl ester to the carboxylic acid for completeness, at least for the three 4-hydroxy analogues (Scheme 72). Using 6 M hydrochloric acid this proved facile, with carboxylic acid hydrochloride salts **288**–**290** formed in good yield.



Scheme 72: Hydrolysis of methyl esters

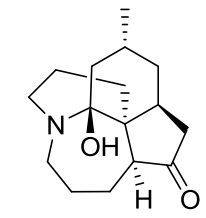
2.2.14 Summary

In summary, this project achieved the aims proposed at the outset. The serendipitous discovery of a cyclisation that did not require the use of hydride reducing agents afforded a library of 4-oxopipecolic acid derivatives. The novel cyclisation offers improved yields, fewer synthetic manipulations, and compared to sodium cyanoborohydride used in previous work, *N*-ethyldiisopropylamine is advantageous in terms of economy and toxicity. The diastereoselectivity of the novel cyclisation is admittedly poorer than the original methodology, but due to higher overall yields, the amount of the major diastereomers isolated are greatly improved for the novel procedure. There is also scope to investigate the cyclisation with a bulkier ester moiety. In addition, the *cis*-relationship of the 2,6-substituents contributes to the higher selectivity of the 4-oxo reduction. However, as the major diastereomers of each procedure are opposing, these two methods can be considered as complementary.

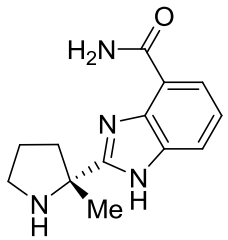
2.3 Synthesis of Quaternary Substituted Heterocycles

2.3.1 Introduction

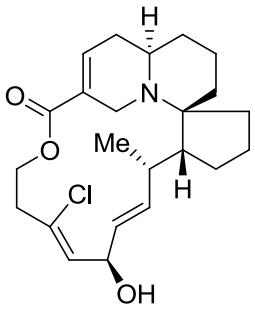
The enantioselective synthesis of quaternary stereocenters presents the synthetic chemist with a significant challenge that has been well noted within the literature.[83–85] However, the prevalence of quaternary stereocenters in biologically relevant compounds provides a compelling impetus for the development of novel methodologies towards their synthesis. Of particular relevance to this project are quaternary substituted nitrogen containing heterocycles, examples of which are illustrated below (Figure 11). Fawcettimine **291** is one of a group of alkaloids isolated from the *Lycopodium* genus of plants which have been shown to possess acetylcholinesterase activity.[86] Veliparib (ABT-888) **292** is a poly(ADP-ribose) polymerase inhibitor, which shows potential as an anti-cancer treatment and is currently in clinical trials.[87] Halichlorine **293** is a marine alkaloid isolated from the sponge *Halichondria okadai* and has potential in treatment for inflammatory diseases as an inhibitor of the vascular cell adhesion molecule 1 (VCAM-1) protein.[88]



291 Fawcettimine



292 Veliparib

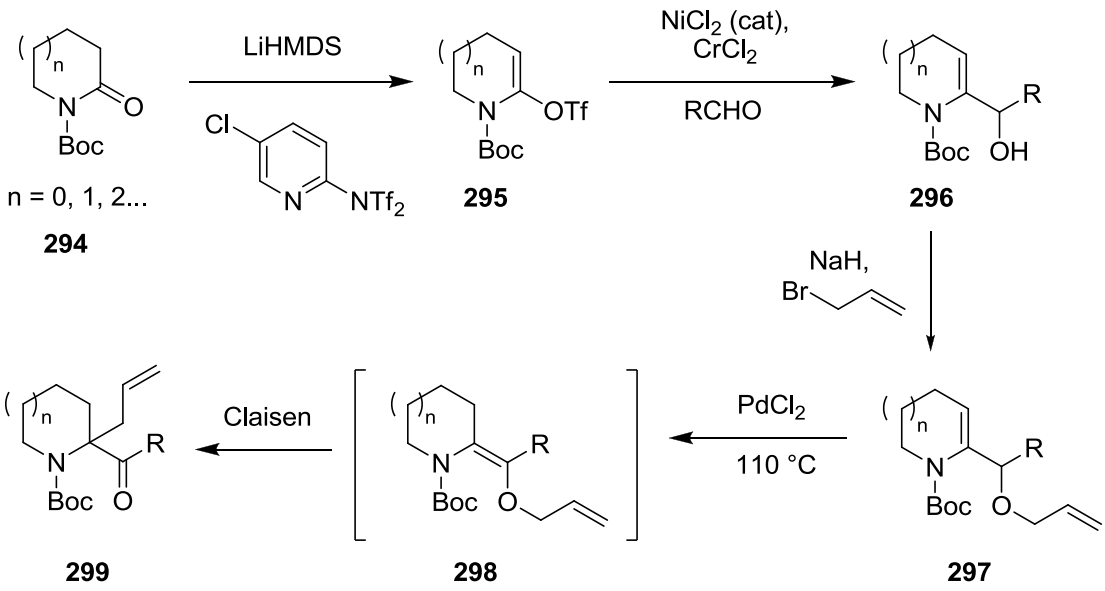


293 Halichlorine

Figure 11: Selected quaternary substituted *N*-heterocycles

As many natural products contain a 2,2-disubstituted *N*-heterocyclic motif, the aim of this project was to develop methodology that would allow access to these systems with a

flexibility that would accommodate variable ring sizes. The proposed synthesis was to begin with with *N*-Boc lactams of various sizes, which form the core of the heterocycles (Scheme 73). Following deprotonation with lithium hexamethyldisilazide, the resulting enolate would be trapped with Comins' triflating reagent, affording enol triflate **295**. A nickel and chromium based catalytic system would then be employed to effect the coupling of the enol triflate and a variety of aldehydes, affording allylic alcohol **296**. The alcohol would be alkylated under basic conditions to afford ether **297**. A one pot, palladium catalysed isomerisation-rearrangement process would first promote the tautomerisation to allyl-vinyl ether intermediate **298**,[89] followed by the Claisen rearrangement to afford tertiary substituted lactam **299**. It was proposed that the route should initially be trialled achirally, forming a racemic mixture of tertiary enantiomers. However, if the core methodology proved successful it could be modified to produce a stereoselective outcome, perhaps with the use of a chiral palladium source, or by the integration of a set stereocentre within the original lactam ring.

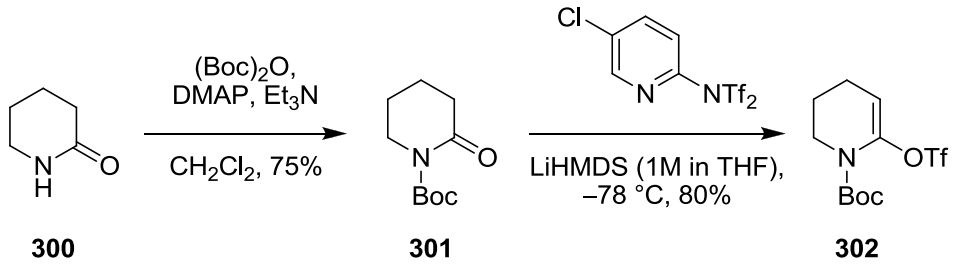


Scheme 73: Proposed synthesis of tertiary substituted *N*-heterocycles

2.3.2 Synthesis of Enol Triflates

To begin the synthesis it was necessary to produce an *N*-Boc lactam. The 6-membered 2-piperidone **300** was chosen as the starting material, and Boc protection was effected in good yield under standard conditions (Scheme 74). The Boc group was chosen as other potentially suitable groups (Cbz, Tf etc.) have been shown to cause stability issues with the

subsequently formed enol triflates.[90] The protected lactam **301** was then subjected to a low temperature deprotonation to afford the enolate species, achieved using lithium hexamethyldisilazide at –78 °C. To trap the enolate, a triflating reagent is required. The most prominent triflating reagent is arguably triflic anhydride. However, this reagent is reported as affording, at best, moderate yields upon reaction with enol triflates in tetrahydrofuran. Improved yields were reported by McMurray with the use of *N*-phenyltrifluoromethanesulfonimide.[91] However, reaction times were slow, which is particularly undesirable when using an unstable enolate, or when using a regioselectively deprotonated enolate that may equilibriate. This led to the development of the *N*-(5-chloro-2-pyridyl)trifluoromethanesulfonimide reagent by Comins, which, due to the electronegative properties of the chloropyridyl ring, displayed improved reactivity towards enolates.[92] For this reason, Comins' reagent was utilised in this synthesis. Indeed, monitoring of reaction progress by TLC and analysis of the crude product by ^{1}H NMR spectroscopy suggested that the reagent had been very effective. However, after purification, the yields afforded were disappointingly low. After several repetitions of the reaction with similar results, it was proposed that the enol triflate product **302** may be unstable under silica based column chromatography conditions. It was found that with the addition of 1% triethylamine to the eluent system, yields improved markedly to 80%, indicating that the enol triflate was indeed sensitive to mildly acidic media.

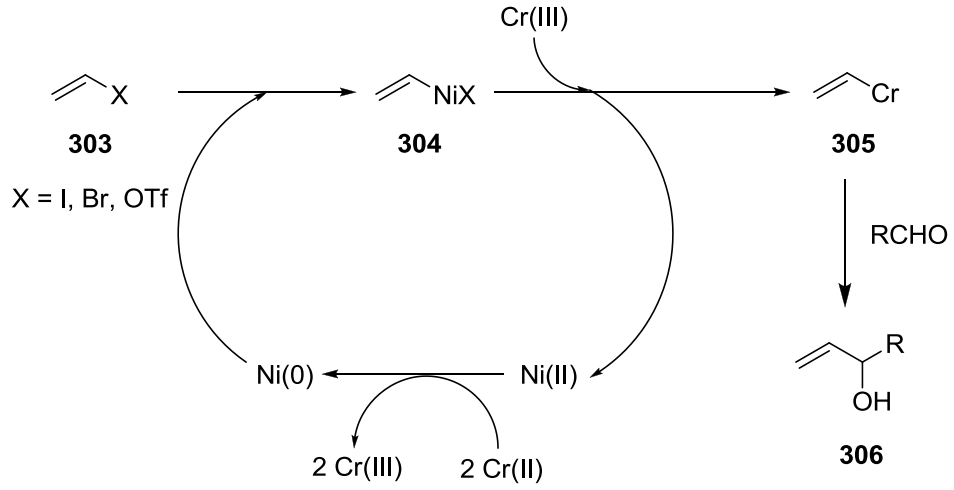


Scheme 74: Synthesis of *N*-Boc enol triflate **302**

2.3.3 Chromium and Nickel Mediated Coupling of Enol Triflate and Aldehydes

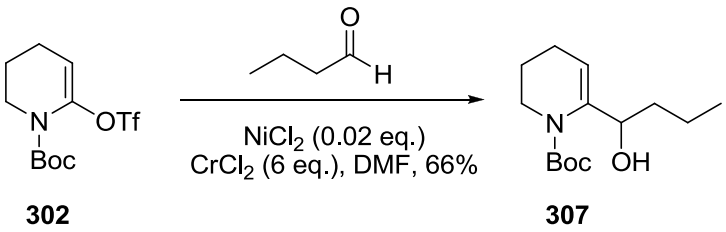
The next step for investigation was the chromium and nickel mediated coupling with various aldehydes. The oxidative insertion of metals into carbon-halide or carbon-triflate bonds to form a reactive organometallic species is by no means uncommon. However, the proposed mechanisms of the chromium-nickel catalytic system are probably sufficiently

unfamiliar to most to warrant further discussion. The insertion of chromium species into carbon-halide bonds has been known and investigated for several decades.[93] However, it was the groups of Kishi and Nozaki who discovered (independently) in 1986 that nickel contaminants in the chromium source had a catalytic effect on the formation of organochromium species.[94, 95] The protocol developed from these observations has since been termed the Nozaki-Hiyama-Kishi (NHK) reaction. The mechanisms of this process were proposed by Nozaki and co-workers (Scheme 75). Chromium(II), which is employed in excess, reduces catalytic nickel(II) to nickel(0). Nickel(0) oxidatively inserts into the carbon-halide or carbon-triflate bond of a substituted vinyl species **303**, forming an organonickel reagent **304**. Transmetallation affords the organochromium species **305** which undergoes nucleophilic addition with the corresponding aldehyde to form allylic alcohol **306**, whilst also releasing nickel(II) to participate in further catalytic cycles.



Scheme 75: Proposed mechanism of NHK coupling

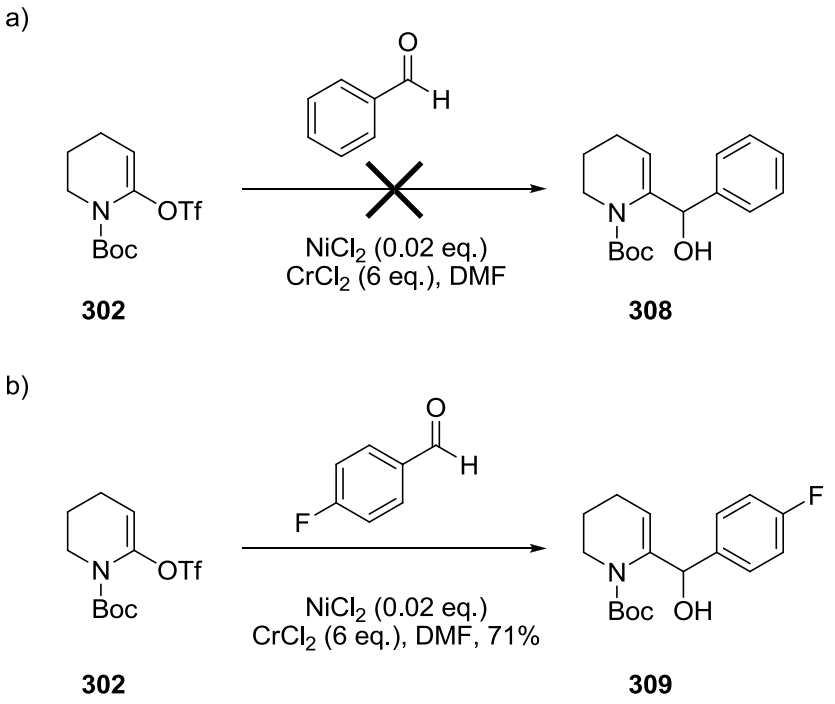
In practice, the NHK reaction requires the rigorous use of anhydrous techniques due to the sensitivity of the nickel and chromium species to water and oxygen. The nickel(II) chloride and chromium(II) chloride employed in this synthesis are highly hygroscopic, and are oven dried before use. The solvent, dimethylformamide, is dried by distillation and stored over molecular sieves, then degassed with argon before use. Whilst nickel(II) chloride is used in 2 mol% amounts, 6 equivalents of chromium(II) chloride are employed relative to the enol triflate. This is unfortunate and not ideal when viewed from a 'green' chemistry perspective, however, fewer equivalents of chromium(II) have been shown to markedly reduce yields.[89] Using these conditions, reaction of enol triflate **302** with butyraldehyde afforded alcohol **307** in a yield of 66% (Scheme 76).



302 **307**

Scheme 76: NHK coupling reaction with butyraldehyde

Whilst this yield is reasonable, the reaction was temperamental, affording inconsistent yields. On one occasion, despite the previously successful conditions being employed, no reaction was observed. In order to determine the scope of the reaction, investigations into coupling with aromatic aldehydes were initiated. Benzaldehyde was reacted under the standard conditions several times, and also at an elevated temperature of 50 °C, without success; only starting materials were isolated from each reaction (Scheme 77a). It was proposed that an electron deficient aldehyde may prove more successful, and to this end, *p*-fluorobenzaldehyde was employed under the standard conditions (Scheme 77b). This resulted in the isolation of alcohol **309** in 71% yield. However, this result proved to be irreproducible. Despite several attempts and maintaining rigorously anhydrous conditions, subsequent reactions returned only starting materials.



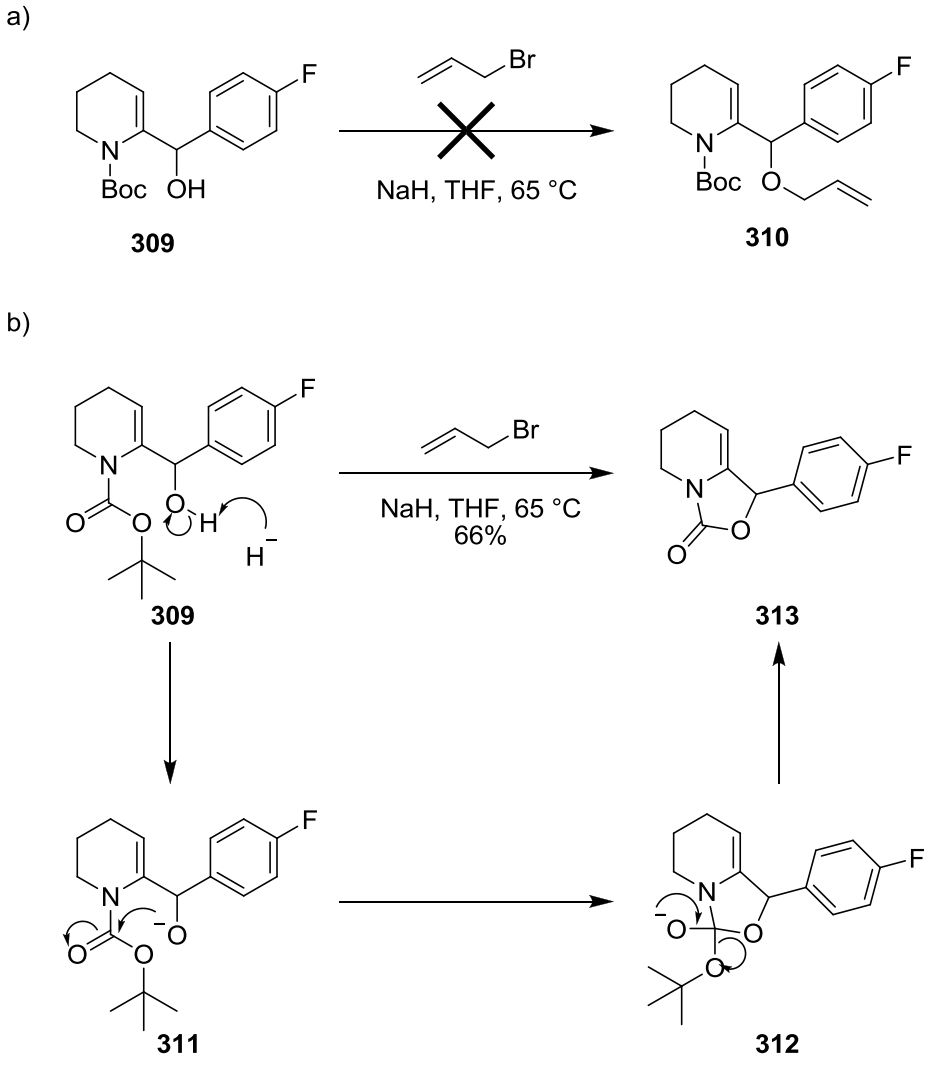
302 **308**

302 **309**

Scheme 77: NHK coupling reactions

2.3.4 Alkylation of Allylic Alcohol

In spite of the issues surrounding the NHK coupling, it was thought pertinent to progress the project. This involved the deprotonation of the alcohol with sodium hydride and alkylation with allyl bromide with the intention of forming di-allyl ether **310** (Scheme 78a). Unfortunately, the reaction did not proceed as expected. After purification and analysis of the major reaction product, it appears that the alkoxide anion cyclised into the Boc carbamate group, forming bicylic carbamate **313** in 66% yield (Scheme 78b). No evidence of di-allyl ether **310** was observed.



Scheme 78: Attempted alcohol allylation

2.3.5 Summary

Unfortunately, due to time constraints, it was not possible to continue the investigation of the project beyond this point. However, there are a number of positive elements that can be taken away from the work conducted so far. The enol triflate can be synthesised in good yield, and awareness of the acid sensitivity of the molecule has been noted for future work. Despite the unreliable results obtained during the investigations of the NHK couplings, it has been shown that good yields are possible with some aliphatic and aromatic aldehydes. With more time and further investigation, it is likely that improved conditions could be found for the consistent formation of the desired alcohols. Finally, knowledge of the potential cyclisation side reaction observed in the attempted di-allyl ether synthesis can be used to inform future work.

3 Conclusions

In summary, this research programme consisted of three distinct projects, which will be considered in turn below.

The synthesis of 2-pyrrolidones and 2-piperidones has, as discussed above, received a substantial amount of attention. The aim of the first project was to develop a flexible, efficient synthesis towards these classes of compounds, and this objective was achieved. There are several attractive facets of the developed methodology. The starting material L-phenylalanine is inexpensive and of high enantiopurity, and the stereocentre present in the starting material is utilised in a chelation-controlled reduction, affording the desired allylic alcohols with good selectivity and without the use of chiral reducing agents. The stereochemistry of the allylic alcohol is transferred to the key stereocentre of the target products by employing the highly efficient Overman rearrangement, and the substituent present on the target products can be varied by variation of the aldehyde utilised in the HWE reaction. It is possible to synthesise both 2-pyrrolidones and 2-piperidones from a common amine intermediate by employing the reported acylation and RCM reaction procedures. As noted above, chiral HPLC analysis of target products suggests that the methodology affords high enantiopurity products.

Whilst this project achieved its primary aims, there are a number of avenues that could be investigated to extend the methodology further. For example, a broader range of aldehydes could be employed, and the effect of the resulting substituents on the Overman rearrangement investigated. Amine acylation using homologues of those reagents currently utilised may allow for the synthesis of larger ring sizes. Finally, as mentioned previously, the carbon-carbon double bond present in the RCM reaction products could be further functionalised in a variety of ways.

The second project began as an optimisation of methodology previously developed in the group for the synthesis of 2,6-*trans*-4-oxopipecolic acid derivatives. The primary aim was to develop a cyclisation procedure that did not utilise hydride reducing reagents, therefore avoiding the issues of poor yields observed in the original methodology. Several dead ends were met whilst developing the ultimate synthetic route reported above, requiring reappraisals of strategy. However, thanks to the serendipitous discovery of a mild and efficient cyclisation procedure, an efficient and high yielding synthesis of 2,6-*cis*-4-

oxopipecolic acid derivatives can be reported. Whilst the selectivity of the cyclisation is poorer than the hydride based method, higher overall efficiency affords greater yields of the major cyclisation products. It has been demonstrated that the *cis*-diastereomer is the major product of the novel methodology, as opposed to the preference seen for the *trans*-diastereomer in the previous synthetic route, and in this respect, the syntheses can be considered as complementary.

An aspect of the novel methodology towards 4-oxopipecolic acid derivatives that may warrant further investigation is the diastereoselectivity of the cyclisation. Whilst yields of the major product are acceptable, diastereoselectivities between 2:1 and 3:1 *syn*:*anti* could benefit from further improvement. As mentioned above, one possible solution to this may be the investigation of a bulkier ester group, which could modulate the preference for either stereoisomer.

Finally, the aim of project three was to develop a synthesis of quaternary substituted heterocycles. The proposed methodology has the potential to efficiently access traditionally challenging quaternary stereocentres. Unfortunately, investigations in this project were dogged by temperamental compounds and unexpected reaction outcomes, compounded by a lack of time to fully investigate these issues. It was demonstrated that the chromium and nickel mediated addition of enol triflates to aldehydes can proceed in good yield, but reproducibility was poor. With time, it is hoped that conditions would be found that could afford consistent results. A second issue was found during the attempted alkylation; the cyclisation of the alkoxide anion into the Boc protecting group. This would appear to be a fundamental issue that would likely require reappraisal of at least the protecting group, and possibly strategy.

Despite these setbacks, the proposed methodology has great potential for the synthesis of valuable target molecules, and with further work, it is felt likely that a robust and efficient route could be developed.

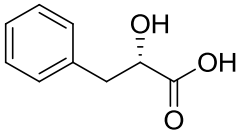
4 Experimental

4.1 General Experimental

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Brine refers to a saturated solution of sodium chloride. 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 potassium permanganate. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to tetramethylsilane as the standard. Assignment of ^{1}H and ^{13}C NMR signals are based on two-dimensional COSY and DEPT experiments, respectively. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410 spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. Melting points were determined on a Reichert platform melting point apparatus. 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}.

4.2 Experimental Procedures

(2*S*)-2-Hydroxy-3-phenylpropionic acid[96]

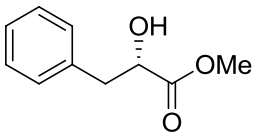


178

To a solution of L-phenylalanine (10.00 g, 60.6 mmol) stirring at 0 °C in 2.5 M sulfuric acid (50 mL, 125 mmol) was added a solution of sodium nitrite (8.36 g, 121 mmol) in water (50 mL) dropwise. The reaction was stirred at 0 °C for 3 h, then allowed to warm to room temperature and stirred for 48 h. The reaction mixture was extracted with diethyl ether (3 × 50 mL) and dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield an off-white solid. The solid was triturated with petroleum ether and dried

by vacuum filtration to afford the desired compound (7.11 g, 71%) as a white solid. Mp. 104–110 °C, lit.[95] 123–125 °C; ν_{max} /cm^{-1} 3443 (OH), 2929 (CH), 1727 (CO), 1394, 1240, 1191, 1089; $[\alpha]_D^{16}$ –19.3 (*c* 1.0, MeOH), lit.[95] $[\alpha]_D^{24}$ –20.0 (*c* 2.0, H_2O); δ_H (400 MHz, CD_3OD) 2.91 (1H, dd, *J* 13.8, 8.1 Hz, 3-*H*H), 3.13 (1H, dd, *J* 13.8, 4.2 Hz, 3-H*H*), 4.34 (1H, dd, *J* 8.1, 4.2 Hz, 2-H), 7.20–7.36 (5H, m, Ph); δ_C (101 MHz, CD_3OD) 41.7 (CH_2), 73.0 (CH), 127.5 (2 × CH), 129.2 (2 × CH), 130.6 (CH), 139.1 (C), 195.3 (C); *m/z* (CI) 167 (MH^+, 100%), 149 (14), 121 (21), 79 (27).

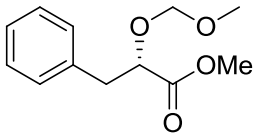
Methyl (2*S*)-2-hydroxy-3-phenylpropionate[97]



314

A solution of (2*S*)-2-hydroxy-3-phenyl-propionic acid (**178**) (6.89 g, 41.5 mmol) and concentrated hydrochloric acid (17 mL, 207 mmol) in methanol (200 mL) and toluene (80 mL) was heated to 80 °C for 18 h. The reaction was cooled to room temperature, then concentrated under reduced pressure to yield an aqueous residue. The residue was extracted with ethyl acetate (2 × 150 mL), and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography (petroleum ether/ethyl acetate 8:2) afforded the desired compound (6.75 g, 90%) as a pale yellow oil which solidified upon standing. Mp. 41–44 °C, lit.[96] 42–43 °C; ν_{max} /cm^{-1} 3434 (OH), 1734 (CO), 1642 (C=C), 1217, 1096, 746; $[\alpha]_D^{25}$ –5.8 (*c* 1.4, $CHCl_3$), lit.[96] $[\alpha]_D^{20}$ –7.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.71 (1H, d, *J* 6.4 Hz, OH), 2.97 (1H, dd, *J* 14.0, 6.8 Hz, 3-*H*H), 3.13 (1H, dd, *J* 14.0, 4.4 Hz, 3-H*H*), 3.78 (3H, s, CH_3), 4.44–4.49 (1H, m, 2-H), 7.20–7.32 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 40.3 (CH_2), 52.3 (CH_3), 71.0 (CH), 126.7 (2 × CH), 128.2 (2 × CH), 129.2 (CH), 136.0 (C), 174.4 (C); *m/z* (CI) 181 (MH^+, 100%), 162 (7), 121 (9), 81 (6).

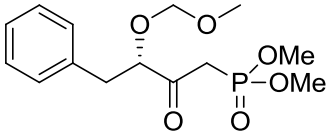
Methyl (2*S*)-2-methoxymethoxy-3-phenylpropionate[98]



179

To a solution of methyl (2*S*)-2-hydroxy-3-phenylpropionate (**314**) (4.69 g, 26 mmol) stirring at 0 °C in dichloromethane (250 mL) was added diisopropylethylamine (9.07 mL, 52 mmol) followed by bromomethyl methyl ether (4.24 mL, 52 mmol) dropwise. The reaction was heated to 40 °C for 18 h then cooled to room temperature. The mixture was washed with 1 M hydrochloric acid (100 mL) and water (100mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography (petroleum ether/diethyl ether 6:4) afforded the desired compound (5.19 g, 89%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2952 (CH), 1751 (CO), 1438, 1210, 1022, 700; $[\alpha]_D^{23}$ –56.9 (*c* 0.9, $CHCl_3$), lit.[97] –56.6 (*c* 1.0 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.98 (1H, dd, *J* 13.8, 9.0 Hz, 3-*H*H), 3.07 (3H, s, OCH_3), 3.11 (1H, dd, *J* 13.8, 4.0 Hz, 3-H*H*), 3.73 (3H, s, OCH_3), 4.34 (1H, dd, *J* 9.0, 4.0 Hz, 2-H), 4.51 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.64 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.21–7.36 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 38.8 (CH_2), 51.6 (CH_3), 55.3 (CH_3), 75.9 (CH), 95.6 (CH_2), 126.3 (CH), 127.9 (2 × CH), 129.0 (2 × CH), 136.6 (C), 172.2 (C); *m/z* (CI) 225.1124 (MH^+. $C_{12}H_{17}O_4$ requires 225.1127), 193 (100%), 162 (12), 133 (39), 85 (22).

(3*S*)-1-(Dimethoxyphosphoryl)-2-oxo-3-methoxymethoxy-4-phenylbutane

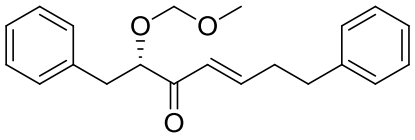


171

To a solution of dimethyl methylphosphonate (6.39 mL, 60 mmol) in tetrahydrofuran (100 mL) stirring at –78 °C was added 1.6 M *n*-butyllithium in hexane (45 mL, 72.4 mmol) dropwise and the reaction stirred for 1 h. The mixture was added dropwise to a solution of methyl (2*S*)-2-methoxymethoxy-3-phenylpropionate (**179**) (6.01 g, 26.8 mmol) in tetrahydrofuran (200 mL) stirring at –78 °C. The mixture was allowed to warm to room

temperature over 18 h, quenched with 2 M ammonium chloride solution (50 mL), then concentrated under reduced pressure. The residue was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography (100% ethyl acetate) afforded the desired compound (7.62 g, 90%) as a pale yellow oil. ν_{max}/cm^{-1} (neat) 2955 (CH), 1723 (CO), 1455, 1257, 1031, 810; $[\alpha]_D^{21}$ –29.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.92 (1H, dd, *J* 13.9, 8.6 Hz, 4-*H*H), 3.05 (1H, dd, *J* 13.9, 4.2 Hz, 4-H*H*), 3.10–3.28 (5H, m, 1-H_2 and OMe), 3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.37 (1H, dd, *J* 8.6, 4.2 Hz, 3-H), 4.49 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.59 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.21–7.43 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 37.1 (d, $J_{C\text{-}P}$ 132 Hz, CH_2), 38.0 (CH_2), 53.0 (CH_3), 53.1 (CH_3), 55.9 (CH_2), 83.1 (CH), 96.5 (CH_2), 126.8 (CH), 128.5 (2 × CH), 129.5 (2 × CH), 136.7 (C), 202.8 (C); *m/z* (FAB) 317.1158 (MH^+. $C_{14}H_{22}O_6P$ requires 317.1154), 285 (93%), 267 (51), 255 (39), 152 (54), 110 (12), 86 (6).

(3*E*,6*S*)-1,7-Diphenyl-6-methoxymethoxyhept-3-en-5-one

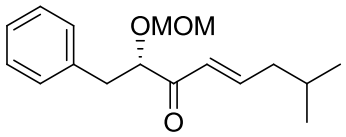


181

To a solution of dimethyl (3*S*)-1-(dimethoxyphosphoryl)-2-oxo-3-methoxymethoxy-4-phenylbutane (**171**) (100 mg, 0.32 mmol) in acetonitrile (10 mL) was added anhydrous potassium carbonate (52 mg, 0.38 mmol) followed by hydrocinnamaldehyde (85 mg, 0.63 mmol), and the reaction was heated to 75 °C for 24 h. The reaction was cooled to room temperature and concentrated under reduced pressure to yield a yellow oil. The oil was partitioned between water (25 mL) and ethyl acetate (25 mL). The organic layer was separated then washed with water (2 × 25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 8:2) afforded the desired compound (94 mg, 92%) as a pale yellow oil. ν_{max}/cm^{-1} (neat) 3028, 2929 (CH), 1693 (CO), 1496, 1454, 1148, 1051; $[\alpha]_D^{23}$ –36.3 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.55 (2H, q, *J* 7.4 Hz, 2-H_2), 2.78 (2H, t, *J* 7.4 Hz, 1-H_2), 2.85 (1H, dd, *J* 13.8, 9.1 Hz, 7-*H*H), 2.95 (1H, dd, *J* 13.8, 4.2 Hz, 7-H*H*), 3.03 (3H, s, OCH_3), 4.35 (1H, dd, *J* 9.1, 4.2 Hz, 6-H), 4.44 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.49 (1H, d, *J* 6.9 Hz, OCH*H*O), 6.49 (1H, d, *J* 15.8 Hz, 4-H), 7.01 (1H, dt, *J* 15.8, 7.4 Hz, 3-H), 7.14–7.32 (10H, m, 2 ×

Ph); δ_C (100 MHz, $CDCl_3$) 34.3 (CH_2), 34.4 (CH_2), 38.9 (CH_2), 55.7 (CH_3), 81.9 (CH), 96.0 (CH_2), 126.2 (CH), 126.3 (CH), 126.7 (CH), 128.4 (2 × CH), 128.4 (2 × CH), 128.5 (2 × CH), 129.5 (2 × CH), 137.2 (C), 140.7 (C), 148.1 (CH), 199.3 (CO); *m/z* (CI) 325.1806 (MH^+. $C_{21}H_{25}O_3$ requires 325.1804), 294 (100%), 266 (13), 220 (5), 159 (4), 137 (5), 85(9).

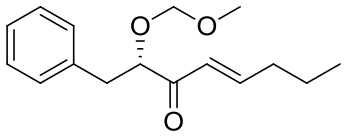
(4*E*,7*S*)-2-Methyl-7-methoxymethoxy-8-phenyloct-4-en-6-one



182

To a solution of (3*S*)-1-(dimethoxyphosphoryl)-2-oxo-3-methoxymethoxy-4-phenylbutane (4.52 g, 14.3 mmol) (**171**) in acetonitrile (150 mL) was added anhydrous potassium carbonate (2.37 g, 17.1 mmol) and 3-methylbutanal (3.08 mL, 28.6 mmol), and the reaction heated to 70 °C for 24 h. The reaction was cooled to room temperature then partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous layer was removed, and the organic layer was washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 95:5 to 15:85) afforded the desired product (3.63 g, 92%) as a pale yellow oil. ν_{max}/cm^{-1} (neat) 2955 (CH), 1693 (CO), 1625 (C=C), 1496, 1455, 1316, 1149, 920; $[\alpha]_D^{21}$ –37.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.92 (6H, d, *J* 6.8 Hz, 1-H_3 and 2-CH_3), 1.77 (1H, nonet, *J* 6.8 Hz, 2-H), 2.11 (2H, td, *J* 6.8, 1.3 Hz, 3-H_2), 2.89 (1H, dd, *J* 14.0, 9.0 Hz, 8-*H*H), 3.01 (1H, dd, *J* 14.0, 4.2 Hz, 8-H*H*), 3.06 (3H, s, OCH_3), 4.40 (1H, dd, *J* 9.0, 4.2 Hz, 7-H), 4.49 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.54 (1H, d, *J* 6.9 Hz, OCH*H*O), 6.40 (1H, dt, *J* 15.6, 1.3 Hz, 5-H), 7.00 (1H, dt, *J* 15.6, 6.8 Hz, 4-H), 7.20–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 22.4 (2 × CH_3), 27.9 (CH), 39.0 (CH_2), 42.0 (CH_2), 55.7 (CH_3), 81.8 (CH), 96.0 (CH_2), 126.6 (CH), 126.7 (CH), 128.4 (2 × CH), 129.5 (2 × CH), 137.2 (C), 148.5 (CH), 199.3 (C); *m/z* (CI) 277.1802 (MH^+. $C_{17}H_{25}O_3$ requires 277.1804), 245 (100%), 217 (13), 215 (10), 157 (4), 111 (6), 85 (7).

(4*E*,7*S*)-7-Methoxymethoxy-8-phenyloct-4-en-6-one



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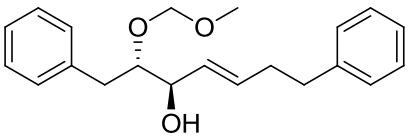
To a solution of dimethyl (3*S*)-1-(dimethoxyphosphoryl)-2-oxo-3-methoxymethoxy-4-phenylbutane (**171**) (5.28 g, 16.69 mmol) in acetonitrile (150 mL) was added butanal (3.01 mL, 33.39 mmol) and anhydrous potassium carbonate (3.46 g, 25.04 mmol) and the mixture heated to 70 °C for 18 h. The mixture was cooled to room temperature and partitioned between water (150 mL) and ethyl acetate (150 mL). The organic layer was separated and washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 9:1 to 8:2) afforded the desired product (2.71 g, 62%) as a yellow oil. ν_{max}/cm^{-1} (neat) 2959 (CH), 1693 (CO), 1625 (C=C), 1455, 1149, 1053, 700; $[\alpha]_D^{28}$ –51.7 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.4 Hz, 1-H_3), 1.49 (2H, sextet, *J* 7.4 Hz, 2-H_2), 2.20 (2H, qd, *J* 7.4, 1.6 Hz, 3-H_2), 2.89 (1H, dd, *J* 14.0, 9.2 Hz, 8-*H*H), 3.00 (1H, dd, *J* 14.0, 4.4 Hz, 8-H*H*), 3.06 (3H, s, OCH_3), 4.40 (1H, dd, *J* 9.2, 4.4 Hz, 7-H), 4.48 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.54 (1H, d, *J* 6.8 Hz, OCH*H*O), 6.40 (1H, d, *J* 15.7 Hz, 5-H), 7.01 (1H, dt, *J* 15.7, 7.4 Hz, 4-H), 7.20–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.7 (CH_3), 21.3 (CH_2), 34.7 (CH_2), 39.0 (CH_2), 55.7 (CH_3), 81.9 (CH), 96.0 (CH_2), 125.8 (CH), 126.6 (CH), 128.4 (2 × CH), 129.5 (2 × CH), 137.2 (C), 149.4 (CH), 199.4 (C); *m/z* (CI) 263.1651 (MH^+. $C_{16}H_{23}O_3$ requires 263.1647), 231 (100%), 201 (8), 143 (%), 121 (9), 85 (9).

(3*E*,5*R*,6*S*)- and (3*E*,5*S*,6*S*)-1,7-Diphenyl-6-methoxymethoxyhept-3-en-5-ol

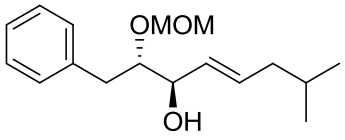


184

To a solution of anhydrous zinc chloride (1.48 g, 10.8 mmol) in tetrahydrofuran (200 mL) stirring at 0 °C was added sodium borohydride (0.82 g, 21.5 mmol) and the reaction mixture was stirred while warming to room temperature over 18 h. Stirring of the reaction

was stopped, the solids allowed to settle, and the solution was cooled to –78 °C. The supernatant solution was added dropwise *via* cannula to a solution of (3*E*,6*S*)-1,7-diphenyl-6-methoxymethoxyhept-3-en-5-one (**181**) (0.87 g, 2.69 mmol) in tetrahydrofuran (50 mL) at –78 °C. The reaction was stirred while warming to room temperature over 18 h, then cooled to 0 °C and quenched dropwise with water (20 mL). The mixture was partitioned between water (150 mL) and diethyl ether (150 mL). The organic phase was separated, washed with water (150 mL) then brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 9:1 to 7:3) afforded (3*E*,5*R*,6*S*)- and (3*E*,5*S*,6*S*)-1,7-diphenyl-6-methoxymethoxyhept-3-en-5-ol (0.76 g, 87%) in a 7:1 ratio, respectively as a colourless oil. ν_{max}/cm^{-1} (neat) 3435 (OH), 2927 (CH), 1638 (C=C), 1496, 1454, 1036, 699; NMR spectroscopic data for major diastereomer (3*E*,5*R*,6*S*): δ_H (400 MHz, $CDCl_3$) 2.44 (2H, q, *J* 7.0 Hz, 2-H_2), 2.59 (1H, dd, *J* 14.1, 5.1 Hz, 7-*H*H), 2.64–2.75 (3H, m, 1-H_2 and 7-H*H*), 2.99 (1H, d, *J* 6.8 Hz, OH), 3.23 (3H, s, OCH_3), 3.73 (1H, ddd, *J* 8.1, 5.1, 2.4 Hz, 6-H), 4.07 (1H, td, *J* 6.8, 2.4 Hz, 5-H), 4.38 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.60 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.61 (1H, ddt, *J* 15.5, 6.8, 1.3 Hz, 4-H), 5.78 (1H, dt, *J* 15.5, 7.0 Hz, 3-H), 7.15–7.30 (10H, m, 2 × Ph); δ_C (100 MHz, $CDCl_3$) 34.2 (CH_2), 35.5 (CH_2), 37.5 (CH_2), 55.7 (CH_3), 73.9 (CH), 84.7 (CH), 97.2 (CH_2), 125.9 (2 × CH), 126.3 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 128.5 (2 × CH), 129.4 (2 × CH), 133.5 (CH), 138.6 (C), 141.7 (C); *m/z* (CI) 309.1853 (MH^+–H_2O. $C_{21}H_{25}O_2$ requires 309.1855), 277 (100), 265 (24), 247 (18), 175 (6), 131 (16).

(4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-2-Methyl-7-methoxymethoxy-8-phenyloct-4-en-6-ol

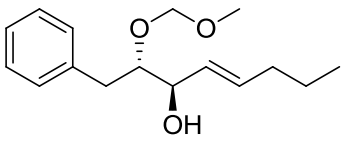


185

To a solution of anhydrous zinc chloride (6.50 g, 47.7 mmol) in tetrahydrofuran (200 mL) stirring at 0 °C was added sodium borohydride (3.61 g, 95.5 mmol) and the reaction mixture was stirred while warming to room temperature over 18 h. Stirring of the reaction was stopped, the solids allowed to settle, and the solution was cooled to –78 °C. The supernatant solution was added dropwise *via* cannula to a solution of (4*E*,7*S*)-2-methyl-7-methoxymethoxy-8-phenyloct-4-en-6-one (**182**) (3.30 g, 11.9 mmol) in tetrahydrofuran (50

mL) at –78 °C. The reaction was stirred while warming to room temperature over 18 h, then cooled to 0 °C and quenched dropwise with water (20 mL). The mixture was partitioned between water (150 mL) and diethyl ether (150 mL). The organic phase was separated, washed with water (150 mL) then brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 95:5 to 3:1) afforded (4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-2-methyl-7-methoxymethoxy-8-phenyloct-4-en-6-ol (2.17 g, 65%) in a 7:1 ratio, respectively as a colourless oil. ν_{max}/cm^{-1} (neat) 3451 (OH), 2955 (CH), 1667 (C=C), 1604, 1496, 1454, 1367, 1038, 918; NMR spectroscopic data for major diastereomer (4*E*,6*R*,7*S*): δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.8 Hz, 1-H_3), 0.93 (3H, d, *J* 6.8 Hz, 2-CH_3), 1.68 (1H, nonet, *J* 6.8 Hz, 2-H), 1.96–2.03 (2H, m, 3-H_2), 2.75 (1H, dd, *J* 14.0, 5.2 Hz, 8-*H*H), 2.81 (1H, dd, *J* 14.0, 8.2 Hz, 8-H*H*), 2.99 (1H, d, *J* 6.4 Hz, OH), 3.24 (3H, s, OCH_3), 3.84 (1H, ddd, *J* 8.2, 5.2, 2.4 Hz, 7-H), 4.09 (1H, td, *J* 6.4, 2.4 Hz, 6-H), 4.40 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.62 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.58 (1H, ddt, *J* 15.2, 6.4, 1.2 Hz, 5-H), 5.74 (1H, dt, *J* 15.2, 7.6 Hz, 4-H), 7.18–7.30 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_3), 22.4 (CH_3), 28.3 (CH), 37.5 (CH_2), 41.9 (CH_2), 55.7 (CH_3), 74.0 (CH), 84.6 (CH), 97.2 (CH_2), 126.2 (CH), 128.3 (2 × CH), 128.9 (CH), 129.4 (2 × CH), 133.3 (CH), 138.7 (C); *m/z* (CI) 261.1854 (MH^+–H_2O. $C_{17}H_{25}O_2$ requires 261.1855), 262 (23%), 229 (16), 217 (17), 113 (42).

(4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-7-Methoxymethoxy-8-phenyloct-4-en-6-ol

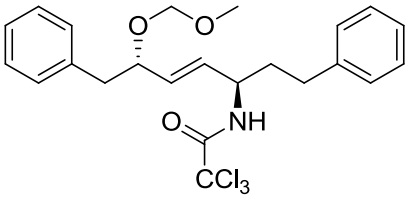


186

To a solution of anhydrous zinc chloride (4.63 g, 34.00 mmol) in tetrahydrofuran (200 mL) stirring at 0 °C was added sodium borohydride (2.57 g, 68.00 mmol) and the reaction mixture was stirred while warming to room temperature over 18 h. Stirring of the reaction was stopped, the solids allowed to settle, and the solution was cooled to –78 °C. The supernatant solution was added dropwise *via* cannula to a solution of (4*E*,7*S*)-7-methoxymethoxy-8-phenyloct-4-en-6-one (**183**) (2.23 g, 8.50 mmol) in tetrahydrofuran (50 mL) at –78 °C. The reaction was stirred while warming to room temperature over 18 h, then cooled to 0 °C and quenched dropwise with water (20 mL). The mixture was partitioned between water (150 mL) and diethyl ether (150 mL). The organic phase was

separated, washed with water (150 mL) then brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 85:15 to 4:1) afforded (4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-7-Methoxymethoxy-8-phenyloct-4-en-6-ol (2.25 g, 100%) in a 7:1 ratio, respectively as a colourless oil. ν_{max} (film)/cm^{-1} 3441 (OH), 2924 (CH), 1450, 1149, 1096, 1034, 702; NMR spectroscopic data for major diastereomer (4*E*,6*R*,7*S*): δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.4 Hz, 1-H_3), 1.46 (2H, sextet, *J* 7.4 Hz, 2-H_2), 2.09 (2H, q, *J* 7.4 Hz, 3-H_2), 2.75 (1H, dd, *J* 14.4, 5.2 Hz, 8-*H*H), 2.81 (1H, dd, *J* 14.4, 8.0 Hz, 8-H*H*), 2.91 (1H, d, *J* 6.8 Hz, OH), 3.24 (3H, s, OCH_3), 3.84 (1H, ddd, *J* 8.0, 5.2, 2.6 Hz, 7-H), 4.09 (1H, td, *J* 6.8, 2.6 Hz, 6-H), 4.56 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.61 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.58 (1H, dd, *J* 15.6, 6.8 Hz, 5-H), 5.75 (1H, dt, *J* 15.6, 7.4 Hz, 4-H), 7.18–7.30 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.7 (CH_3), 22.4 (CH_2), 34.6 (CH_2), 37.5 (CH_2), 55.7 (CH_3), 74.0 (CH), 84.6 (CH), 97.2 (CH_2), 126.2 (CH), 128.0 (CH), 128.3 (2 × CH), 129.4 (2 × CH), 134.4 (CH), 138.7 (C); *m/z* (CI) 247.1699 (MH^+–H_2O. $C_{16}H_{23}O_2$ requires 247.1698), 215 (100%), 203 (55), 185 (36), 171 (21), 113 (14), 99 (42).

(3*R*,4*E*,6*S*)- and (3*S*,4*E*,6*S*)-1,7-Diphenyl-3-(2',2',2'-trichlomethylcarbonylamino)-6-methoxymethoxyhept-4-ene

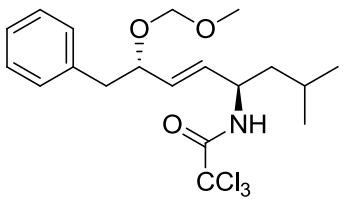


193

To a solution of (3*E*,5*R*,6*S*)- and (3*E*,5*S*,6*S*)-1,7-diphenyl-6-methoxymethoxyhept-3-en-5-ol (**184**) (1.54 g, 4.7 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.71 mL, 4.7 mmol) in dichloromethane (150 mL) was added trichloroacetonitrile (0.95 mL, 9.4 mmol) and the reaction stirred for 48 h at room temperature. The mixture was filtered under reduced pressure through silica gel and washed with diethyl ether (50 mL). Concentration under reduced pressure gave a yellow oil. The oil was dissolved in *p*-xylene (250 mL), and potassium carbonate (0.10 g, 0.7 mmol) was added to the mixture. The mixture was heated to 140 °C for 18 h, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate 95:5 to 7:3) gave (3*R*,4*E*,6*S*)- and (3*S*,4*E*,6*S*)-1,7-diphenyl-3-(2',2',2'-trichlomethylcarbonylamino)-6-methoxymethoxyhept-

4-ene (1.85 g, 84% over two steps) in a 7:1 ratio, respectively as a yellow oil. ν_{max}/cm^{-1} (neat) 3328 (NH), 2928 (CH), 1697 (CO), 1516, 1040, 822; NMR spectroscopic data for major diastereomer (3*R*,4*E*,6*S*): δ_H (400 MHz, $CDCl_3$) 1.91 (2H, q, *J* 7.5 Hz, 2-H_2), 2.60 (2H, t, *J* 7.5 Hz, 1-H_2), 2.80 (1H, dd, *J* 13.6, 6.4 Hz, 7-*H*H), 2.92 (1H, dd, *J* 13.6, 6.4 Hz, 7-H*H*), 3.12 (3H, s, OCH_3), 4.27 (1H, q, *J* 6.4 Hz, 6-H), 4.39–4.46 (1H, m, 3-H), 4.47 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.64 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.54 (1H, dd, *J* 15.8, 5.2 Hz, 4-H), 5.61 (1H, dd, *J* 15.8, 6.4 Hz, 5-H), 6.42 (1H, d, *J* 8.2 Hz, NH), 7.10–7.32 (10H, m, 2 × Ph); δ_C (100 MHz, $CDCl_3$) 31.9 (CH_2), 36.2 (CH_2), 42.2 (CH_2), 52.4 (CH), 55.3 (CH_3), 76.8 (CH), 92.7 (CCl_3), 93.9 (CH_2), 126.3 (CH), 126.4 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 128.7 (2 × CH), 129.7 (2 × CH), 131.0 (CH), 132.3 (CH), 137.8 (C), 140.7 (C), 161.0 (CO); *m/z* (CI) 470.1049 (MH^+. $C_{23}H_{27}{}^{35}Cl_3NO_3$ requires 470.1057), 408 (38%), 374 (100), 340 (43).

(4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-2-Methyl-4-(2',2',2'-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene

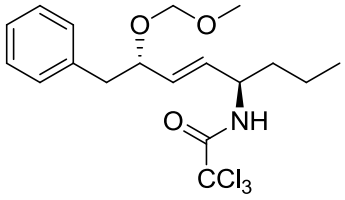


194

To a solution of (4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-2-methyl-7-methoxymethoxy-8-phenyloct-4-en-6-ol (**185**) (2.17 g, 7.79 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.17 mL, 7.79 mmol) in dichloromethane (150 mL) was added trichloroacetonitrile (1.56 mL, 15.6 mmol) and the reaction stirred for 48 h at room temperature. The mixture was filtered under reduced pressure through silica gel and washed with diethyl ether (50 mL). Concentration under reduced pressure gave a yellow oil. The oil was dissolved in *p*-xylene (250 mL), and potassium carbonate (0.10 g, 0.7 mmol) was added to the mixture. The mixture was heated to 140 °C for 18 h, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 8:2) gave (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-2-methyl-4-(2',2',2'-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (1.40 g, 42% over two steps) in a 7:1 ratio, respectively as a yellow oil. ν_{max}/cm^{-1} (neat) 3347 (NH), 2956 (CH), 2929, 1693 (CO), 1684 (C=C), 1519, 1037, 820; NMR spectroscopic data for major diastereomer (4*R*,5*E*,7*S*): δ_H (400 MHz, $CDCl_3$) 0.94

(3H, d, *J* 7.6 Hz, 1-H_3) 0.95 (3H, d, *J* 7.6 Hz, 2-CH_3), 1.37–1.53 (2H, m, 3-H_2), 1.60 (1H, nonet, *J* 7.6 Hz, 2-H), 2.82 (1H, dd, *J* 13.6, 6.4 Hz, 8-*H*H), 2.92 (1H, dd, *J* 13.6, 7.6 Hz, 8-H*H*), 3.13 (3H, s, OCH_3), 4.24–4.30 (1H, m, 7-H), 4.43–4.49 (2H, m, 4-H and OC*H*HO), 4.64 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.51 (1H, dd, *J* 16.0, 6.4 Hz, 5-H), 5.57–5.66 (1H, m, 6-H), 6.42 (1H, d, *J* 8.5 Hz, NH), 7.19–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_3), 22.5 (CH_3), 24.8 (CH), 42.2 (CH_2), 43.8 (CH_2), 51.1 (CH_3), 55.2 (CH), 76.8 (CH), 92.8 (C), 93.7 (CH_2), 126.3 (CH), 128.2 (2 × CH), 129.7 (2 × CH), 131.6 (CH), 131.7 (CH), 137.8 (C), 160.9 (C); *m/z* (FAB) 444.0886 (MNa^+. $C_{19}H_{26}{}^{35}Cl_3NNaO_3$ requires 444.0876), 360 (100%), 325 (14), 199 (36), 143 (44).

(4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-4-(2',2',2'-Trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene



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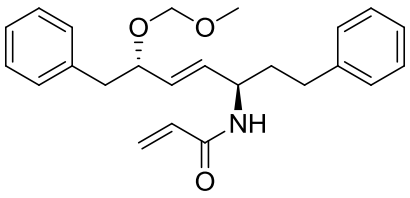
To a solution of (4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-7-methoxymethoxy-8-phenyloct-4-en-6-ol (**186**) (2.52 g, 9.53 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.43 mL, 9.53 mmol) in dichloromethane (150 mL) was added trichloroacetonitrile (1.91 mL, 19.06 mmol) and the reaction stirred for 48 h at room temperature. The mixture was filtered under reduced pressure through silica gel and washed with diethyl ether (50 mL). Concentration under reduced pressure gave a yellow oil. The oil was dissolved in *p*-xylene (250 mL), and potassium carbonate (0.10 g, 0.7 mmol) was added to the mixture. The mixture was heated to 140 °C for 18 h, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 7:3) gave (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-4-(2',2',2'-Trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (1.94 g, 48% over two steps) in a 7:1 ratio, respectively as a yellow oil. ν_{max}/cm^{-1} (neat) 3325 (NH), 2932 (CH), 1697 (CO), 1512, 1033, 817; NMR spectroscopic data for major diastereomer (4*R*,5*E*,7*S*): δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.4 Hz, 1-H_3), 1.26 (2H, sextet, *J* 7.4 Hz, 2-H_2), 1.47 (2H, q, *J* 7.4 Hz, 3-H_2), 2.72 (1H, dd, *J* 13.6, 7.0 Hz, 8-*H*H), 2.84 (1H, dd, *J* 13.6, 7.0 Hz, 8-H*H*), 3.05 (3H, s, OCH_3), 4.18 (1H, q, *J* 7.0 Hz, 7-H), 4.29–4.34 (1H, m, 4-H), 4.39 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.45 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.44 (1H, dd, *J* 15.6, 6.0 Hz, 5-H), 5.48–5.55 (1H, m, 6-H), 6.33 (1H, br d, *J* 8.2 Hz, NH),

7.10–7.21 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.7 (CH_3), 18.8 (CH_2), 36.8 (CH_2), 42.2 (CH_2), 52.5 (CH), 55.2 (CH_3), 76.9 (CH), 92.8 (C), 93.8 (CH_2), 126.3 (CH), 128.2 (2 × CH), 129.7 (2 × CH), 131.5 (CH), 131.8 (CH), 137.8 (C), 161.0 (C); *m/z* (FAB) 430.0717 (MNa^+. $C_{18}H_{24}{}^{35}Cl_3NNaO_3$ requires 430.0719), 348 (52%), 346 (50), 297 (14), 185 (59), 117 (18).

(3*R*,4*E*,6*S*)-1,7-Diphenyl-3-(prop-2'-enoylamino)-6-methoxymethoxyhept-4-ene



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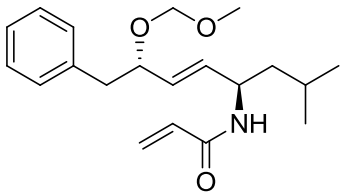
To a solution of (3*R*,4*E*,6*S*)- and (3*S*,4*E*,6*S*)-1,7-diphenyl-3-(2',2',2'-trichlomethylcarbonylamino)-6-methoxymethoxyhept-4-ene (**193**) (0.67 g, 1.42 mmol) in methanol (100 mL) was added 1 M aqueous sodium hydroxide (50 mL, 50 mmol) and the solution heated to 70 °C for 18 h. The reaction mixture was cooled, concentrated under reduced pressure and extracted with dichloromethane (2 × 25 mL) and ethyl acetate (2 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. A portion of the oil (0.35 g, 1.08 mmol) was dissolved in diethyl ether (15 mL), cooled to –78 °C, and triethylamine (0.20 mL, 1.40 mmol) was added. A solution of acryloyl chloride (0.11 mL, 1.40 mmol) in diethyl ether (15 mL) was added dropwise and the reaction was stirred while returning to room temperature over 18 h. The reaction mixture was partitioned between water (30 mL) and diethyl ether (15 mL) and the organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 8:2) gave (3*R*,4*E*,6*S*)-1,7-diphenyl-3-(prop-2'-enoylamino)-6-methoxymethoxyhept-4-ene (0.19 g, 48%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3273 (NH), 2941 (CH), 1655 (CO), 1542, 1039, 699; $[\alpha]_D{}^{27}$ –20.7 (c, 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.83 (2H, q, *J* 6.9 Hz, 2-H_2), 2.57–2.61 (2H, m, 1-H_2), 2.79 (1H, dd, *J* 13.6, 6.1 Hz, 7-*H*H), 2.90 (1H, dd, *J* 13.6, 7.5 Hz, 7-H*H*), 3.09 (3H, s, OCH_3), 4.21–4.26 (1H, m, 6-H), 4.45 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.57–4.64 (1H, m, 3-H), 4.63 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.34 (1H, d, *J* 8.6 Hz, NH), 5.53–5.54 (2H, m, 4-H and 5-H), 5.65 (1H, dd, *J* 10.2, 1.4 Hz, 3'-*H*H), 6.02 (1H, dd, *J* 17.0, 10.2 Hz, 2'-H), 6.26 (1H, dd, *J* 17.0, 1.4 Hz,

3'-H*H*), 7.00–7.47 (10H, m, 2 × Ph); δ_C (100 MHz, $CDCl_3$) 32.1 (CH_2), 36.6 (CH_2), 42.3 (CH_2), 50.3 (CH), 55.2 (CH_3), 77.1 (CH), 93.7 (CH_2), 126.1 (CH), 126.3 (CH), 126.7 (CH_2), 128.2 (2 × CH), 128.4 (2 × CH), 128.5 (2 × CH), 129.7 (2 × CH), 130.8 (CH), 131.1 (CH), 132.9 (CH) 138.1 (C), 141.4 (C), 164.6 (CO); *m/z* (CI) 380.2227 (MH^+. $C_{24}H_{28}NO_3$ requires 380.2226), 318 (100%), 288 (9), 249 (6), 97 (18).

(4*R*,5*E*,7*S*)-2-Methyl-4-(prop-2'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene

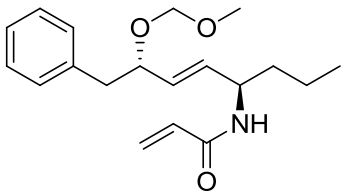


199

To a solution of (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-2-methyl-4-(2',2',2'-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyl-oct-5-ene (**194**) (1.40 g, 3.31 mmol) in methanol (100 mL) was added 1 M aqueous sodium hydroxide (50 mL, 50 mmol) and the solution heated to 70 °C for 18 h. The reaction mixture was cooled, concentrated under reduced pressure and extracted with dichloromethane (2 × 25 mL) and ethyl acetate (2 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. A portion of the oil (0.28 g, 0.87 mmol) was dissolved in diethyl ether (15 mL), cooled to –78 °C, and triethylamine (0.16 mL, 1.13 mmol) was added. A solution of acryloyl chloride (0.09 mL, 1.13 mmol) in diethyl ether (15 mL) was added dropwise and the reaction was stirred while returning to room temperature over 18 h. The reaction mixture was partitioned between water (30 mL) and diethyl ether (15 mL) and the organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 8:2 to 7:3) gave (4*R*,5*E*,7*S*)-2-methyl-4-(prop-2'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (0.14 g, 48%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3270 (NH), 2954 (CH), 1654 (CO), 1625 (C=C), 1542, 1148, 1040; $[\alpha]_D^{25}$ +12.7 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8 Hz, 1-H_3), 0.91 (3H, d, *J* 6.8 Hz, 2-CH_3), 1.28–1.41 (2H, m, 3-H_2), 1.56 (1H, nonet, *J* 6.8 Hz, 2-H), 2.78 (1H, dd, *J* 13.6, 6.4 Hz, 8-*H*H), 2.88 (1H, dd, *J* 13.6, 8.0 Hz, 8-H*H*), 3.07 (3H, s, OCH_3), 4.18–4.23 (1H, m, 7-H), 4.43 (1H, d, *J* 8.0 Hz, OC*H*HO), 4.57–4.64 (2H, m, OCH*H*O and 4-H), 5.31 (1H, br d, *J* 8.6 Hz, NH), 5.44 (1H, dd, *J* 15.6, 6.0 Hz, 5-H), 5.54 (1H, dd, *J* 15.6, 7.2 Hz, 6-H), 5.66 (1H, dd, *J* 10.2, 1.4 Hz, 3'-*H*H), 6.06 (1H, dd, *J* 16.9, 10.2 Hz, 2'-H), 6.29 (1H,

dd, *J* 16.9, 1.4 Hz, 3'-H*H*), 7.19–7.27 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 22.5 (CH_3), 22.6 (CH_3), 24.8 (CH), 42.3 (CH_2), 44.6 (CH_2), 48.7 (CH_3), 55.2 (CH), 77.1 (CH), 93.6 (CH_2), 126.2 (CH), 126.6 (CH_2), 128.1 (2 × CH), 129.8 (2 × CH), 130.5 (CH), 130.9 (CH), 133.6 (CH), 138.1 (C), 164.5 (C); *m/z* (CI) 332.2222 (MH^+. $C_{20}H_{30}NO_3$ requires 332.2226), 333 (8%), 307 (12), 271 (100), 240 (7).

(4*R*,5*E*,7*S*)-4-(Prop-2'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene

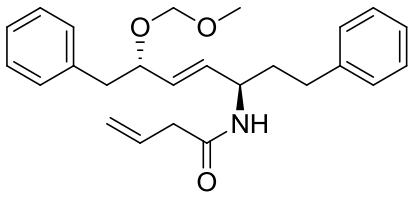


200

To a solution of (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-4-(2',2',2'-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**195**) (92 mg, 0.23 mmol) in methanol (10 mL) was added 1 M aqueous sodium hydroxide (5 mL, 5 mmol) and the solution heated to 70 °C for 18 h. The reaction mixture was cooled, concentrated under reduced pressure and extracted with dichloromethane (2 × 25 mL) and ethyl acetate (2 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The product was dissolved in diethyl ether (15 mL), cooled to –78 °C, and triethylamine (35 μL, 0.25 mmol) was added. A solution of acryloyl chloride (20 μL, 0.25 mmol) in diethyl ether (3 mL) was added dropwise and the reaction was stirred while returning to room temperature over 18 h. The reaction mixture was partitioned between water (30 mL) and diethyl ether (15 mL) and the organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 8:2 to 7:3) gave (4*R*,5*E*,7*S*)-4-(prop-2'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (31 mg, 44%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3278 (NH), 2931 (CH), 1656 (CO), 1626 (C=C), 1544, 1041, 700; $[\alpha]_D^{25}$ +3.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.3 Hz, 1-H_3), 1.24–1.36 (2H, m, 2-H_2), 1.45–1.52 (2H, m, 3-H_2), 2.80 (1H, dd, *J* 13.6, 6.0 Hz, 8-*H*H), 2.91 (1H, dd, *J* 13.6, 7.6 Hz, 8-H*H*), 3.10 (3H, s, OCH_3), 4.21–4.26 (1H, m, 7-H), 4.46 (1H, d, *J* 6.8 Hz, OCH*H*O), 4.52–4.60 (1H, m, 4-H), 4.65 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.31 (1H, d, *J* 8.9 Hz, NH), 5.46–5.58 (2H, m, 5-H and 6-H), 5.68 (1H, dd, *J* 10.2, 1.4 Hz, 3'-*H*H), 6.08 (1H, dd, *J* 16.9, 10.2 Hz, 2'-H), 6.31 (1H, dd, *J* 16.9, 1.4 Hz, 3'-H*H*), 7.18–7.30 (5H, m, Ph); δ_C

(100 MHz, $CDCl_3$) 13.8 (CH_3), 18.9 (CH_2), 37.2 (CH_2), 42.3 (CH_2), 50.2 (CH), 55.2 (CH_3), 77.1 (CH), 93.7 (CH_2), 126.2 (CH), 126.5 (CH_2), 128.1 (2 × CH), 129.7 (2 × CH), 130.6 (CH), 131.0 (CH), 133.3 (CH), 138.1 (C), 168.5 (C); *m/z* (CI) 318.2067 (MH^+. $C_{19}H_{28}NO_3$ requires 318.2069), 292 (45%), 256 (100), 226 (11), 85 (9).

(3*R*,4*E*,6*S*)-1,7-Diphenyl-3-(but-3'-enoylamino)-6-methoxymethoxyhept-4-ene

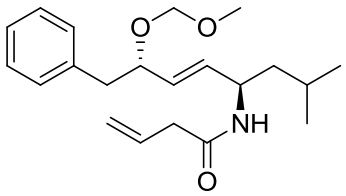


201

To a solution of (3*R*,4*E*,6*S*)- and (3*S*,4*E*,6*S*)-1,7-diphenyl-3-(2',2',2'-trichlomethylcarbonylamino)-6-methoxymethoxyhept-4-ene (**193**) (1.37 g, 2.91 mmol) in methanol (100 mL) was added 1 M aqueous sodium hydroxide (50 mL, 50 mmol) and the solution heated to 70 °C for 18 h. The reaction mixture was cooled, concentrated under reduced pressure and extracted with dichloromethane (2 × 100 mL) and ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. A portion of the oil (0.51 g, 1.57 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C, to which was added 3-butenoic acid (0.16 mL, 1.88 mmol), 4-dimethylaminopyridine (0.02 g, 0.16 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.36 g, 1.88 mmol). The reaction mixture was stirred while returning to room temperature over 18 h, then partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 9:1 to 6:4) gave (3*R*,4*E*,6*S*)-1,7-diphenyl-3-(but-3'-enoylamino)-6-methoxymethoxyhept-4-ene (0.24 g, 39%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3287 (NH), 2942 (CH), 1648 (CO), 1546 (C=C), 1147, 1040; $[\alpha]_D^{28}$ –60.8 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.72–1.85 (2H, m, 2-H_2) 2.56 (2H, t, *J* 7.8 Hz, 1-H_2), 2.79 (1H, dd, *J* 13.6, 6.0 Hz, 7-*H*H), 2.90 (1H, dd, *J* 13.6, 7.6 Hz, 7-H*H*), 2.95 (2H, dt, *J* 7.2, 1.1 Hz, 2'-H_2), 3.10 (3H, s, OCH_3), 4.21–4.27 (1H, m, 6-H), 4.45 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.48–4.55 (1H, m, 3-H), 4.63 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.17–5.25 (2H, m, 4'-H_2), 5.35 (1H, d, *J* 8.7 Hz, NH), 5.45–5.54 (2H, m, 4-H and 5-H), 5.86 (1H, ddt, *J* 17.2, 10.0, 7.2 Hz, 3'-H), 7.12–7.29 (10H, m, 2 × Ph); δ_C (100 MHz,

$CDCl_3$) 32.1 (CH_2), 36.6 (CH_2), 41.8 (CH_2), 42.3 (CH_2), 50.2 (CH), 55.2 (CH_3), 77.0 (CH) 93.7 (CH_2), 120.1 (CH_2), 126.1 (CH), 126.3 (CH), 128.2 (2 × CH), 128.3 (2 × CH), 128.5 (2 × CH), 129.7 (2 × CH), 130.7 (CH), 131.3 (CH), 133.1 (CH), 138.0 (C), 141.4 (C), 169.6 (C); *m/z* (CI) 394.2376 (MH^+. $C_{25}H_{32}NO_3$ requires 394.2382), 374 (35%), 333 (100), 302 (82), 264 (5), 185 (4), 91 (7).

(4*R*,5*E*,7*S*)-2-Methyl-4-(but-3'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene

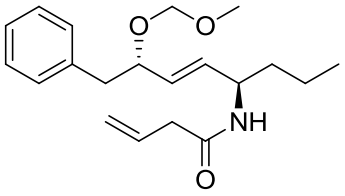


202

To a solution of (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-2-methyl-4-(2',2',2'-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**194**) (0.70 g, 1.66 mmol) in methanol (100 mL) was added 1 M aqueous sodium hydroxide (50 mL, 50 mmol) and the solution heated to 70 °C for 18 h. The reaction mixture was cooled, concentrated under reduced pressure and extracted with dichloromethane (2 × 100 mL) and ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. A portion of the oil (0.30 g, 1.08 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C, to which was added 3-butenoic acid (0.11 mL, 1.30 mmol), 4-dimethylaminopyridine (0.01 g, 0.11 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.25 g, 1.30 mmol). The reaction mixture was stirred while returning to room temperature over 18 h, then partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 9:1 to 6:4) gave (4*R*,5*E*,7*S*)-2-methyl-4-(but-3'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (0.24 g, 42%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3277 (NH), 2954 (CH), 1646 (CO), 1635 (C=C) 1544, 1040, 916; $[\alpha]_D^{23}$ –15.5 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.81 (6H, d, *J* 6.8 Hz, 1-H_3 and 2-CH_3), 1.18–1.25 (2H, m, 3-H_2), 1.46 (1H, nonet, *J* 6.8 Hz, 2-H), 2.71 (1H, dd, *J* 13.6, 6.0 Hz, 8-*H*H), 2.81 (1H, dd, *J* 13.6, 7.6 Hz, 8-H*H*), 2.91 (2H, dt, *J* 7.2, 1.2 Hz, 2'-H_2), 3.00 (3H, s, OCH_3), 4.11–4.16 (1H, m, 7-H), 4.35 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.40–4.47 (1H, m, 4-H), 4.54 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.11–5.18 (2H, m, 4'-H_2), 5.31

(1H, d, *J* 8.6 Hz, NH), 5.34–5.44 (2H, m, 5-H and 6-H), 5.82 (1H, ddt, *J* 17.6, 14.3, 7.2 Hz, 3'-H), 7.09–7.21 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 18.0 (CH), 22.5 (CH_3), 22.6 (CH_3), 41.8 (CH_2), 42.3 (CH_2), 44.3 (CH_2), 48.6 (CH), 55.1 (CH_3), 77.0 (CH), 93.6 (CH_2), 119.9 (CH_2), 126.2 (CH), 127.9 (CH), 128.1 (CH), 129.7 (2 × CH), 130.0 (CH), 131.5 (CH), 133.8 (CH), 138.1 (C), 169.4 (C); *m/z* (CI) 346.2378 (MH^+. $C_{21}H_{32}NO_3$ requires 346.2382), 284 (100%), 254 (5), 107 (9), 81 (24).

(4*R*,5*E*,7*S*)-4-(But-3'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene

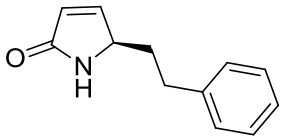


203

To a solution of (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-4-(2',2',2'-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**195**) (1.45 g, 3.55 mmol) in methanol (100 mL) was added 1 M aqueous sodium hydroxide (50 mL, 50 mmol) and the solution heated to 70 °C for 18 h. The reaction mixture was cooled, concentrated under reduced pressure and extracted with dichloromethane (2 × 100 mL) and ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. A portion of the oil (0.20 g, 0.76 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C, to which was added 3-butenoic acid (0.08 mL, 0.91 mmol), 4-dimethylaminopyridine (0.01 mg, 0.08 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.18 g, 0.91 mmol). The reaction mixture was stirred while returning to room temperature over 18 h, then partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 9:1 to 6:4) gave (4*R*,5*E*,7*S*)-4-(But-3'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (0.12 g, 49%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3284 (NH), 2931 (CH), 1646 (CO), 1635 (C=C), 1544, 1039, 916; $[\alpha]_D^{25}$ –34.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.3 Hz, 1-H_3), 1.20–1.30 (2H, m, 2-H_2), 1.39–1.45 (2H, m, 3-H_2), 2.78 (1H, dd, *J* 13.6, 6.0 Hz, 8-*H*H), 2.89 (1H, dd, *J* 13.6, 7.6 Hz, 8-H*H*), 2.99 (2H, dt, *J* 7.2, 1.1 Hz, 2'-H_2), 3.09 (3H, s, OCH_3), 4.19–4.24 (1H, m, 7-H), 4.43–4.48 (2H, m, OC*H*HO and 4-H), 4.62 (1H, d, *J* 6.8 Hz, OCH*H*O),

5.19–5.27 (2H, m, 4'-H_2), 5.34 (1H, d, *J* 8.5 Hz, NH), 5.44–5.47 (2H, m, 5-H and 6-H), 5.91 (1H, ddt, *J* 17.2, 14.4, 7.2 Hz, 3'-H), 7.17–7.28 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 18.9 (CH_2), 37.2 (CH_2), 41.8 (CH_2), 42.3 (CH_2), 50.0 (CH), 55.2 (CH_3), 77.0 (CH), 93.6 (CH_2), 119.9 (CH_2), 126.2 (CH), 128.1 (2 × CH), 129.7 (2 × CH), 130.2 (CH), 131.5 (CH), 133.6 (CH), 138.1 (C), 169.5 (C); *m/z* (FAB) 332.2224 (MH^+. $C_{20}H_{30}NO_3$ requires 332.2226), 270 (100%), 241 (68), 204 (96), 187 (16), 175 (15), 121 (14), 96 (22), 77 (24), 51 (98).

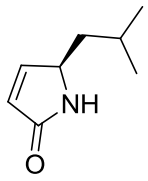
(5*R*)-5-Phenethyl-1*H*-pyrrol-2(5*H*)-one



204

A solution of (3*R*,4*E*,6*S*)-1,7-diphenyl-3-(prop-2'-enoylamino)-6-methoxymethoxyhept-4-ene (**198**) (185 mg, 0.49 mmol) stirring in dichloromethane (250 mL) was heated to 40 °C for 0.25 h. Grubbs 2nd generation catalyst (21 mg, 0.02 mmol) was added, and the mixture stirred at 40 °C for 18 h. The reaction was cooled and the mixture concentrated under reduced pressure. Flash column chromatography (dichloromethane/methanol 99:1) afforded (5*R*)-5-phenethyl-1*H*-pyrrol-2(5*H*)-one (72 mg, 83%) as a white solid. Mp 124–126 °C (decomposition); ν_{max}/cm^{-1} (neat) 3176 (CH), 1676 (CO), 1647 (C=C) 1647, 1456, 820; $[\alpha]_D^{23}$ –93.5 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.81–1.92 (1H, m, 1'-*H*H), 1.94–2.04 (1H, m, 1'-H*H*), 2.68 (2H, t, *J* 8.0 Hz, 2'-H_2), 4.18–4.26 (1H, m, 5-H), 6.11 (1H, dt, *J* 5.8, 1.6 Hz, 3-H), 7.05 (1H, dt, *J* 5.8, 1.2 Hz, 4-H), 7.11–7.24 (5H, m, Ph), 7.75 (1H, s, NH); δ_C (100 MHz, $CDCl_3$) 32.4 (CH_2), 34.8 (CH_2), 59.4 (CH), 126.4 (CH), 127.2 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 140.7 (C), 150.2 (CH), 174.3 (C); *m/z* (EI) 187.0999 (M^+. $C_{12}H_{13}NO$ requires 187.0997), 118 (40%), 87 (100), 85 (100), 47 (100).

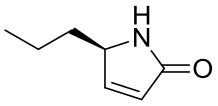
(5*R*)-5-Isobutyl-1*H*-pyrrol-2(5*H*)-one



205

A solution of (4*R*,5*E*,7*S*)-2-methyl-4-(prop-2'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**199**) (145 mg, 0.44 mmol) stirring in dichloromethane (250 mL) was heated to 40 °C for 0.25 h. Grubbs 2nd generation catalyst (19 mg, 0.02 mmol) was added, and the mixture stirred at 40 °C for 18 h. The reaction was cooled and the mixture concentrated under reduced pressure. Flash column chromatography (dichloromethane/methanol 99:1) afforded (5*R*)-5-isobutyl-1*H*-pyrrol-2(5*H*)-one (50 mg, 82%) as a white solid. Mp 76–81 °C; ν_{max}/cm^{-1} 3184 (NH), 2925 (CH), 1681 (CO), 1370, 1220, 810; $[\alpha]_D^{24}$ –203.0 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.6 Hz, 2'-CH_3), 0.99 (3H, d, *J* 6.6 Hz, 3'-H_3), 1.37–1.50 (2H, m, 1'-H_2), 1.76 (1H, nonet, *J* 6.6 Hz, 2'-H), 4.25–4.29 (1H, m, 5-H), 6.09 (1H, dt, *J* 5.8, 1.6 Hz, 3-H), 7.08 (1H, dt, *J* 5.8, 1.6 Hz, 4-H), 7.46 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_3), 23.2 (CH_3), 26.1 (CH), 42.3 (CH_2), 58.5 (CH), 126.7 (CH), 150.9 (CH), 174.4 (C); *m/z* (CI) 140.1072 (MH^+. $C_8H_{14}NO$ requires 140.1075), 133 (12%), 113 (16), 97 (20), 81 (66).

(5*R*)-5-Propyl-1*H*-pyrrol-2(5*H*)-one

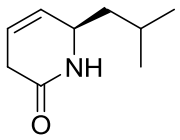


206

A solution of (4*R*,5*E*,7*S*)-4-(prop-2'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**200**) (27 mg, 0.09 mmol) stirring in dichloromethane (50 mL) was heated to 40 °C for 0.25 h. Grubbs 2nd generation catalyst (4 mg, 4.25 μmol) was added, and the mixture stirred at 40 °C for 18 h. The reaction was cooled and the mixture concentrated under reduced pressure. Flash column chromatography (100% ethyl acetate) afforded (5*R*)-5-propyl-1*H*-pyrrol-2(5*H*)-one (9 mg, 85%) as a white solid. Mp 98–101 °C; ν_{max}/cm^{-1} (neat) 3150 (NH), 1681 (CO), 1654 (C=C), 1379, 1218, 826; $[\alpha]_D^{26}$ –134.2 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.3 Hz, 3'-H_3), 1.33–1.60 (4H, m, 1'-H_2 and 2'-H_2),

4.13–4.16 (1H, m, 5-H), 6.02 (1H, dt, *J* 5.8, 1.6 Hz, 4-H), 7.00 (1H, dt, *J* 5.8, 1.6 Hz, 3-H), 7.06 (1H, s, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 19.5 (CH_2), 35.3 (CH_2), 59.9 (CH), 126.9 (CH), 150.4 (CH), 174.2 (C); *m/z* (EI) 125.0837 (M^+. $C_7H_{11}NO$ requires 125.0841), 110 (32%), 82 (100), 69 (39), 55 (29).

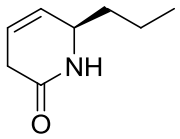
(6*R*)-6-Isobutyl-1,6-dihydropyridin-2-one



208

A solution of (4*R*,5*E*,7*S*)-2-methyl-4-(but-3'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**202**) (159 mg, 0.46 mmol) stirring in dichloromethane (230 mL) was heated to 40 °C for 0.25 h. Grubbs 2nd generation catalyst (20 mg, 0.02 mmol) was added, and the mixture stirred at 40 °C for 18 h. The reaction was cooled and the mixture concentrated under reduced pressure. Flash column chromatography (100% ethyl acetate) afforded (6*R*)-6-isobutyl-1,6-dihydropyridin-2-one (57 mg, 82%) as a white solid. Mp 69–71 °C; ν_{max}/cm^{-1} (neat) 3206 (NH), 2957 (CH), 1676 (CO), 1655 (C=C), 1406, 827; $[\alpha]_D^{22}$ –26.8 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.94 (6H, t, *J* 6.8 Hz, 2'-CH_3 and 3'-H_3), 1.37–1.47 (2H, m, 1'-H_2), 1.74 (1H, nonet, *J* 6.8 Hz, 2'-H), 2.91–2.94 (2H, m, 3-H_2), 4.04–4.15 (1H, m, 6-H), 5.68–5.77 (2H, m, 4-H and 5-H), 6.03 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 22.2 (CH_3), 23.1 (CH_3), 24.3 (CH), 31.3 (CH_2), 46.6 (CH_2), 52.1 (CH), 121.3 (CH), 125.8 (CH), 169.5 (C); *m/z* (CI) 154.1231 (MH^+. $C_9H_{16}NO$ requires 154.1232), 142 (4%), 113 (2), 96 (4), 69 (3).

(6*R*)-6-Propyl-3,6-dihydro-1*H*-pyridin-2-one[50]

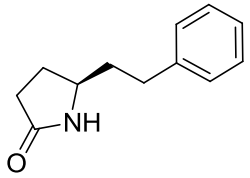


209

A solution of (4*R*,5*E*,7*S*)-4-(but-3'-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**203**) (304 mg, 0.92 mmol) stirring in dichloromethane (460 mL) was heated to 40 °C for

0.25 h. Grubbs 2nd generation catalyst (39 mg, 0.05 mmol) was added, and the mixture stirred at 40 °C for 18 h. The reaction was cooled and the mixture concentrated under reduced pressure. Flash column chromatography (100% ethyl acetate) afforded (6*R*)-6-propyl-3,6-dihydro-1*H*-pyridin-2-one (72 mg, 56%) as a white solid. Mp 134–136 °C (decomposition); ν_{max}/cm^{-1} (neat) 3185 (NH), 2959 (CH), 1679 (CO, 1656 (C=C 1341, 1153, 827; $[\alpha]_D^{26}$ –122.8 (*c* 1.0, $CHCl_3$), lit. opposite enantiomer[50] $[\alpha]_D^{22}$ +110.5 (c 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.3 Hz, 3'-H_3), 1.34–1.44 (2H, m, 2'-H_2), 1.51–1.61 (2H, m, 1'-H_2), 2.90–2.94 (2H, m, 3-H_2), 4.06–4.10 (1H, m, 6-H), 5.66–5.72 (1H, m, 5-H), 5.76 (1H, dtd, *J* 10.0, 3.2, 1.6 Hz, 4-H), 6.58 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 17.8 (CH_2), 31.2 (CH_2), 39.3 (CH_2), 53.8 (CH), 121.6 (CH), 125.5 (CH), 169.8 (C); *m/z* (CI) 140.1078 (MH^+. $C_8H_{14}NO$ requires 140.1075), 113 (4%), 97 (8), 85 (12), 71 (17).

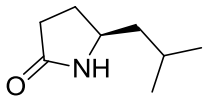
(5*R*)-5-Phenethylpyrrolidin-2-one[51]



211

To a solution of (5*R*)-5-phenethyl-1*H*-pyrrol-2(5*H*)-one (**204**) (52 mg, 0.27 mmol) in ethyl acetate (15 mL) was added 10% palladium on carbon (30 mg, 0.03 mmol wrt Pd). The solution was purged with hydrogen gas for 0.25 h then stirred under an atmosphere of hydrogen at room temperature for 24 h. The reaction mixture was filtered under reduced pressure through Celite® which was washed with ethyl acetate (15 mL). The filtrate was concentrated under reduced pressure to yield a brown solid. Flash column chromatography (100% ethyl acetate) afforded (5*R*)-5-phenethylpyrrolidin-2-one (38 mg, 72%) as a white solid. Mp. 69–71 °C; ν_{max} (film)/cm^{-1} 3412 (NH), 2927 (CH), 1688 (CO), 1454, 1147, 1040; $[\alpha]_D^{23}$ +24.5 (*c* 0.5, $CHCl_3$), lit. opposite enantiomer[51] $[\alpha]_D^{20}$ –23.5 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.73–1.90 (3H, m, 4-*H*H and 1'-H_2), 2.26–2.39 (3H, m, 4-H*H* and 3-H_2), 2.66 (2H, m, 2'-H_2), 3.62–3.68 (1H, m, 5-H), 5.58 (1H, br s, NH), 7.16–7.32 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 27.4 (CH_2), 29.9 (CH_2), 32.4 (CH_2), 38.4 (CH_2), 53.9 (CH), 126.3 (CH), 128.3 (2 × CH), 128.7 (2 × CH), 140.8 (C), 177.8 (C); *m/z* (CI) 190.1235 (MH^+. $C_{12}H_{16}NO$ requires 190.1232), 171 (45%), 137 (8), 121 (9), 85 (12).

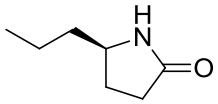
(5*R*)-5-Isobutylpyrrolidin-2-one[52]



212

To a solution of (5*R*)-5-isobutyl-1*H*-pyrrol-2(5*H*)-one (**205**) (50 mg, 0.36 mmol) in ethyl acetate (25 mL) was added 10% palladium on carbon (38 mg, 0.04 mmol wrt Pd). The solution was purged with hydrogen gas for 0.25 h then stirred under an atmosphere of hydrogen at room temperature for 24 h. The reaction mixture was filtered under reduced pressure through Celite® which was washed with ethyl acetate (25 mL). The filtrate was concentrated under reduced pressure to yield a brown solid. Flash column chromatography (dichloromethane/methanol 99:1) afforded (5*R*)-5-isobutylpyrrolidin-2-one (38 mg, 75%) as a white solid. Mp. 61–63 °C, lit.[52] 61–62 °C; ν_{max} (film)/cm^{-1} 3187 (NH), 2956 (CH), 1678 (CO), 1460, 1291, 781; $[\alpha]_D^{26}$ +7.5 (*c* 1.1, $CHCl_3$), lit.[52] $[\alpha]_D$ +9.6 (c 2.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.85 (3H, s, 3'-H_3), 0.87 (3H, s, 2'-CH_3), 1.23–1.29 (1H, m, 1'-*H*H), 1.35–1.42 (1H, m, 1'-H*H*), 1.53–1.62 (1H, m, 2'-H), 1.60–1.67 (1H, m, 4-*H*H), 2.15–2.25 (1H, m, 4-H*H*), 2.23–2.28 (2H, m, 3-H_2), 3.61–3.68 (1H, m, 5-H), 5.89 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_3), 22.9 (CH_3), 25.4 (CH), 27.9 (CH), 30.1 (CH), 46.0 (CH_2), 52.6 (CH), 178.1 (C); *m/z* (CI) 142.1230 (MH^+. $C_8H_{16}NO$ requires 142.1232) 141 (3%), 107 (1), 84 (6), 69 (4).

(5*R*)-5-Isobutylpyrrolidin-2-one[53]

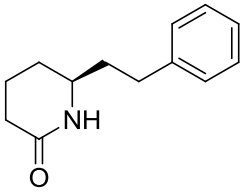


213

To a solution of (5*R*)-5-propyl-1*H*-pyrrol-2(5*H*)-one (**206**) (38 mg, 0.30 mmol) in ethyl acetate (25 mL) was added 10% palladium on carbon (32 mg, 0.03 mmol wrt Pd). The solution was purged with hydrogen gas for 0.25 h then stirred under an atmosphere of hydrogen at room temperature for 24 h. The reaction mixture was filtered under reduced pressure through Celite® which was washed with ethyl acetate (25 mL). The filtrate was concentrated under reduced pressure to yield a brown solid. Flash column chromatography

(dichloromethane/methanol 99:1 to 97:3) afforded (5*R*)-5-isobutylpyrrolidin-2-one (33 mg, 85%) as a white solid. Mp. 43–45 °C; ν_{max} (film)/cm^{-1} 3179 (NH), 2951 (CH), 1691 (CO), 1458, 1286, 753; $[\alpha]_D^{25}$ +7.4 (*c* 1.1, $CHCl_3$), lit. opposite enantiomer[53] $[\alpha]_D^{26}$ –9.2 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.2 Hz, 3'-H_3), 1.24–1.51 (4H, m, 1'-H_2 and 2'-H_2), 1.58–1.68 (1H, m, 4-*H*H), 2.12–2.33 (3H, m, 3-H_2 and 4-H*H*), 3.54–3.60 (1H, m, 5-H), 6.84 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 19.2 (CH_2), 27.3 (CH_2), 30.4 (CH_2), 39.0 (CH_2), 54.5 (CH), 178.5 (C); *m/z* (CI) 128.1078 (MH^+. $C_7H_{14}NO$ requires 128.1075) 112 (4%), 97 (6), 85 (14), 71 (16).

(6*S*)-6-Phenethylpiperidin-2-one

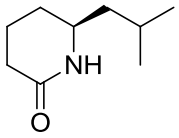


214

A solution of (3*R*,4*E*,6*S*)-1,7-diphenyl-3-(but-3'-enoylamino)-6-methoxymethoxyhept-4-ene (**201**) (240 mg, 0.60 mmol) in dichloromethane (250 mL) was heated to 45 °C for 0.25 h. Grubbs 2nd generation catalyst (60 mg, 70 μmol) was added, and the reaction stirred for 42 h. The reaction was cooled to room temperature and concentrated under reduced pressure to yield a brown oil. Flash column chromatography (dichloromethane/methanol 99:1) afforded a white solid. To a solution of the solid in ethyl acetate (35 mL) was added 10% palladium on carbon (40 mg, 0.04 mmol wrt Pd). The solution was purged with hydrogen gas for 0.25 h then stirred under an atmosphere of hydrogen at room temperature for 18 h. The reaction mixture was filtered through Celite®, which was washed with ethyl acetate (35 mL). The filtrate was concentrated under reduced pressure to yield a white solid. Flash column chromatography (dichloromethane/methanol 1:0 to 96:4) afforded (6*S*)-6-phenethylpiperidin-2-one (110 mg, 88% over two steps) as a white solid. Mp. 84–86 °C; ν_{max} (film)/cm^{-1} 3214 (NH), 2942 (CH), 1651 (CO), 1603 (C=C), 1402, 1343, 1090; $[\alpha]_D^{22}$ +5.0 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.37–1.47 (1H, m, 5-H*H*), 1.63–1.75 (1H, m, 5-*H*H), 1.78–1.84 (2H, m, 1'-H_2), 1.86–1.98 (2H, m, 4-H_2), 2.25–2.43 (2H, m, 3-H_2), 2.62–2.73 (2H, m, 2'-H_2), 3.36–3.42 (1H, m, 6-H), 6.03 (1H, br s, N*H*), 7.16–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 19.7 (CH_2), 28.4 (CH_2), 31.4 (CH_2), 31.6 (CH_2), 38.6

(CH_2), 52.6 (CH_2), 126.2 (CH), 128.3 (2 × CH), 128.6 (2 × CH), 140.9 (C), 172.4 (C); *m/z* (EI) 203.1313 (M^+. $C_{13}H_{17}NO$ requires 203.1310), 186 (5%), 125 (27), 112 (66), 98 (100).

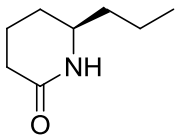
(6*S*)-6-Isobutylpiperidin-2-one



215

To a solution of (6*R*)-6-isobutyl-1,6-dihydropyridin-2-one (**208**) (57 mg, 0.37 mmol) in ethyl acetate (30 mL) was added 10% palladium on carbon (40 mg, 0.04 mmol wrt Pd). The solution was purged with hydrogen gas for 0.25 h then stirred under an atmosphere of hydrogen at room temperature for 24 h. The reaction mixture was filtered under reduced pressure through Celite® which was washed with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure to yield a yellow solid. Flash column chromatography (dichloromethane/methanol 99:1) afforded (6*S*)-6-isobutylpiperidin-2-one (58 mg, 100%) as a white solid. Mp. 89–91 °C; ν_{max} (film)/cm^{-1} 3194 (NH), 2951 (CH), 1651 (CO), 1404, 1169, 822; $[\alpha]_D^{30}$ −12.1 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.85 (6H, dd, *J* 6.6, 1.5 Hz, 3'-H_3 and 2'-CH_3), 1.21–1.33 (3H, m, 3-H_2 and 1'-*H*H), 1.56–1.68 (2H, m, 5-*H*H and 2'-H), 1.79–1.87 (2H, m, 5-H*H* and 1'-H*H*), 2.17–2.36 (2H, m, 4-H_2), 3.33–3.39 (1H, m, 6-H), 5.67 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 19.9 (CH_2), 22.3 (CH_3), 22.8 (CH_3), 24.3 (CH), 29.0 (CH_2), 31.4 (CH_2), 46.2 (CH_2), 51.0 (CH), 172.2 (C); *m/z* (EI) 155.1308 (M^+. $C_9H_{17}NO$ requires 155.1310) 120 (29%), 112 (96), 99 (100), 70 (100).

(6*R*)-6-Propylpiperidin-2-one[54]

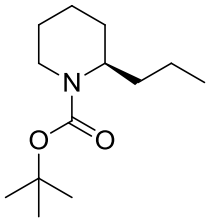


216

To a solution of (6*R*)-6-propyl-3,6-dihydro-1*H*-pyridin-2-one (**209**) (72 mg, 0.52 mmol) in ethyl acetate (50 mL) was added 10% palladium on carbon (55 mg, 0.05 mmol wrt Pd). The solution was purged with hydrogen gas for 0.25 h then stirred under an atmosphere of

hydrogen at room temperature for 24 h. The reaction mixture was filtered under reduced pressure through Celite® which was washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure to yield (6*S*)-6-propylpiperidin-2-one (69 mg, 94%) a white solid, with no further purification required. Mp. 73–76 °C; ν_{max} (film)/cm^{-1} 2960 (CH), 2360, 1653 (CO), 1410, 1215, 747; $[\alpha]_D^{25}$ −18.1 (*c* 1.3, $CHCl_3$), lit. opposite enantiomer[54] $[\alpha]_D^{20}$ +17.9 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.2 Hz, 3'-H_3), 1.21–1.41 (5H, m, 3-H_2, 1'-*H*H, 2'-H_2), 1.56–1.66 (1H, m, 5-*H*H), 1.79–1.87 (2H, m, 1'-H*H*, 5-H*H*), 2.17–2.36 (2H, m, 4-H_2), 3.26–3.32 (1H, m, 6-H), 5.76 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 18.5 (CH_2), 19.8 (CH_2), 28.5 (CH_2), 31.4 (CH_2), 39.1 (CH_2), 53.0 (CH), 172.3 (C); *m/z* (CI) 142.1236 (MH^+. $C_8H_{16}NO$ requires 142.1232) 113 (26%), 97 (42), 85 (78), 71 (100).

(6*R*)-6-Propyl-*N*-Boc-piperidine[59]

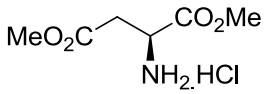


217

To a solution of (6*S*)-6-Propylpiperidin-2-one (**216**) (44 mg, 0.31 mmol) in diethyl ether (50 mL) was added lithium aluminium hydride 1 M in diethyl ether (1.87 mL, 1.87 mmol) and the reaction was heated to 30 °C for 18 h. The reaction was quenched with 2 M potassium hydroxide solution (10 mL) then partitioned between diethyl ether (20 mL) and water (20 mL). The organic layer was separated, washed with water (3 × 20 mL), dried over magnesium sulphate, filtered and concentrated at atmospheric pressure and 40 °C. The residue was dissolved in diethyl ether (20 mL) to which was added di-*tert*-butyl dicarbonate (272 mg, 1.25 mmol), 4-dimethylamino pyridine (15 mg, 0.13 mmol) and distilled triethylamine (181 μL, 1.31 mmol). The reaction was stirred at room temperature for 18 h, then washed with 1 M hydrochloric acid solution (10 mL), saturated sodium hydrogencarbonate solution (10 mL), and brine. The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield a clear oil. Flash column chromatography (Petroleum ether/diethyl ether 85:15) afforded the desired product (34 mg, 48%) as a colourless oil. Spectroscopic data consistent with literature.

$[\alpha]_D^{24}$ –25.6 (*c* 0.6, $CHCl_3$), lit.[59] $[\alpha]_D^{23}$ –31.6 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.2 Hz, 3'-H_3), 1.14–1.32 (4H, m, 1'-H_2 and 2'-H_2), 1.38 (9H, s, O*t*Bu), 1.41-1.63 (6H, m, 3-H_2, 4-H_2 and 5-H_2), 2.67 (1H, td, *J* 13.6, 2.6 Hz, 6-*H*H), 3.89 (1H, d, *J* 2.6 Hz, 6-H*H*), 4.14 (1H, br. s, 2-H); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 19.1 (2 × CH_2), 19.5 (2 × CH_2), 25.7 (CH_2), 28.5 (3 × CH_3), 31.9 (CH_2), 50.1 (CH), 17.9 (C), 155.2 (C); *m/z* (EI) 227 (M^+, 4%), 184 (M^+–C_3H_7, 18), 149 (17), 128 (100).

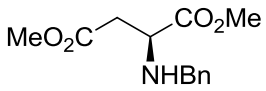
Dimethyl (2*S*)-2-aminobutanedioate hydrochloride[74]



224

To a suspension of L-aspartic acid (5.00 g, 37.56 mmol) in methanol (50 mL) at 0 °C was added thionyl chloride (3.84 mL, 52.59 mmol) dropwise. The mixture was warmed to room temperature, heated to 60 °C for 3 h, then cooled to room temperature and concentrated under reduced pressure. The residue was azeotroped with toluene followed by dichloromethane, then dried under reduced pressure to afford dimethyl (2*S*)-2-aminobutanedioate hydrochloride (7.36 g, 99%) as a white solid. Mp. 63–65 °C; $[\alpha]_D^{26}$ +14.0 (*c* 1.1, MeOH), lit.[74] $[\alpha]_D^{24}$ +22.0 (*c* 1.0, MeOH); δ_H (400 MHz, D_2O) 3.05–3.18 (2H, m, 3-H_2), 3.69 (3H, s, OMe), 3.79 (3H, s, OMe), 4.44 (1H, dd, *J* 6.0, 4.9 Hz, 2-H); δ_C (101 MHz, D_2O) 33.9 (CH_2), 48.3 (CH), 52.0 (CH_3), 52.9 (CH_3), 168.6 (C), 169.5 (C); *m/z* (CI) 162.0769 (MH^+. $C_6H_{12}NO_4$ requires 162.0766), 148 (22%), 128.2 (4) 102.2 (9).

Dimethyl (2*S*)-2-(benzylamino)butanedioate[99]

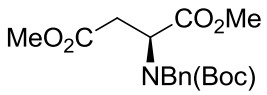


230

To a solution of dimethyl (2*S*)-2-aminobutanedioate hydrochloride (**224**) (5.76 g, 29.2 mmol) in anhydrous methanol (125 mL) at 0 °C was added triethylamine (4.84 mL, 35.0 mmol) and benzaldehyde (3.55 mL, 35.0 mmol). The mixture was warmed to room temperature and stirred for 3 h, then cooled to 0 °C and sodium borohydride (2.21 g, 58.3 mmol) was added portionwise over 0.5 h. The mixture was concentrated under reduced

pressure and the residue partitioned between diethyl ether (50 mL) and 4 M hydrochloric acid solution (50 mL). The aqueous layer was separated and the organic phase extracted with 4 M hydrochloric acid solution (50 mL). The aqueous extractions were combined, neutralised to pH 8 with solid sodium hydrogen carbonate then extracted with diethyl ether (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford an orange oil. Flash column chromatography (petroleum ether/ethyl acetate 3:1 with 1% triethylamine) afforded dimethyl (2*S*)-2-(benzylamino)butanedioate (6.35 g, 87%) as a pale yellow oil. $[\alpha]_D^{26}$ –39.9 (*c* 1.1, $CHCl_3$), lit.[98] $[\alpha]_D^{20}$ –33.0 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.14 (1H, s, NH), 2.68–2.80 (2H, m, 3-H_2), 3.69 (1H, dd, *J* 6.9, 6.2 Hz, 2-H), 3.70 (3H, s, OMe), 3.75 (1H, d, *J* 13.1 Hz, 1'-*H*H), 3.77 (3H, s, OMe), 3.90 (1H, d, *J* 13.1 Hz, 1'-H*H*), 7.25–7.34 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 38.0 (CH_2), 51.9 (CH_3), 52.0 (CH_2), 52.2 (CH_3), 56.9 (CH), 127.2 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 139.5 (C), 171.3 (C), 174.1 (C); *m/z* (CI) 252 (MH^+, 100%), 229 (5), 215 (8), 192 (6).

Dimethyl (2*S*)-2-[benzyl(*tert*-butoxycarbonyl)amino]butanedioate

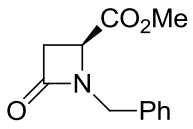


231

To a solution of dimethyl (2*S*)-2-(benzylamino)butanedioate (**230**) (121 mg, 0.48 mmol) in dichloromethane at room temperature was added di-*tert*-butyl dicarbonate (210 mg, 0.96 mmol), triethylamine (140 μL, 1.01 mmol) and 4-dimethylaminopyridine (12 mg, 0.10 mmol). The mixture was stirred for 18 h then washed with 1 M hydrochloric acid solution (10 mL). The aqueous washings were extracted with dichloromethane (10 mL). The organic layers were combined, washed with saturated sodium hydrogen carbonate solution (20 mL) then brine, then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Flash column chromatography (petroleum ether/ethyl acetate 4:1) afforded the desired product (127 mg, 75%) as a pale yellow oil. ν_{max} (neat)/cm^{-1} 2954 (CH), 1795, 1734 (CO), 1699, 1436, 1156; $[\alpha]_D^{26}$ –81.6 (*c* 1.2, $CHCl_3$); ^1H NMR showed a 4:3 mixture of rotomers, only signals for the major rotomer are recorded: δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, O*t*Bu), 2.74 (1H, dd, *J* 17.1, 6.8, 3-*H*H), 3.23 (1H, dd, *J* 17.1, 6.8 Hz, 3-H*H*), 3.63 (3H, s, OMe), 3.64 (3H, s, OMe), 4.51–4.56 (1H, m, 2-H), 4.63–4.72 (2H, m, 1'-H_2), 7.29–7.38 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 27.4 (3 × CH_3), 34.4 (CH_2), 52.0

(CH_3), 52.7 (CH_2), 53.1 (CH_3), 57.2 (CH), 85.4 (C), 128.1 (2 × CH), 128.6 (2 × CH), 135.6 (CH), 146.9 (C), 149.8 (C), 169.5 (C), 171.3 (C); *m/z* (CI) 352.1766 (MH^+. $C_{18}H_{26}NO_6$ requires 352.1760), 296 (22%), 264 (13), 252 (100), 192 (6).

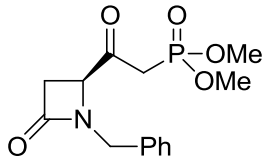
Methyl (4*S*)-1-benzyl-2-oxoazetidine-4-carboxylate[100]



235

To a solution of dimethyl (2*S*)-2-(benzylamino)butanedioate (**230**) (300 mg, 1.19 mmol) in diethyl ether (25 mL) at 0 °C was added *tert*-butyl magnesium chloride (1.10 mL, 1.43 mmol). The mixture was warmed to room temperature and stirred for 18 h, then quenched with saturated ammonium chloride solution (5 mL). The organic layer was separated, washed with water (30 mL) and brine (30 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford an orange oil. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded methyl (4*S*)-1-benzyl-2-oxoazetidine-4-carboxylate (102 mg, 39%) as a pale yellow oil. ν_{max} (neat)/cm^{-1} 2955 (CH), 1743 (CO), 1389, 1211, 1018, 709; $[\alpha]_D^{16}$ –29.5 (*c* 1.1, $CHCl_3$), lit. opposite enantiomer[99] $[\alpha]_D^{25}$ +28.0 (c 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.06 (1H, ddd, *J* 14.5, 2.7, 0.7 Hz, 3-*H*H), 3.23 (1H, dd, *J* 14.5, 5.6, 3-H*H*), 3.72 (3H, s, CH_3), 3.96 (1H, dd, *J* 5.6, 2.7 Hz, 4-H), 4.21 (1H, d, *J* 14.9 Hz, 1'-*H*H), 4.77 (1H, d, *J* 14.9 Hz, 1'-H*H*), 7.25–7.39 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 42.0 (CH_2), 45.7 (CH_2), 49.9 (CH_3), 52.4 (CH), 128.0 (CH), 128.6 (2 × CH), 128.9 (2 × CH), 134.9 (C), 165.7 (C), 170.8 (C); *m/z* (EI) 219.0892 (M^+. $C_{12}H_{13}NO_3$ requires 219.0895), 191 (100%), 132 (93), 91 (100).

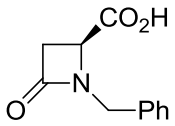
Dimethyl 2-[(4*S*)-1-benzyl-2-oxoazetidin-4-yl]-2-oxoethylphosphonate



236

To a solution of dimethyl methylphosphonate (63 μL, 0.58 mmol) in tetrahydrofuran (10 mL) at –78 °C was added 2.5 M *n*-butyl lithium in hexanes (234 μL, 0.58 mmol), and the mixture was stirred for 1.5 h. A solution of methyl (4*S*)-1-benzyl-2-oxoazetidine-4-carboxylate (**235**) (64 mg, 0.29 mmol) in tetrahydrofuran (10 mL) was added to the mixture dropwise then stirred for 0.75 h. The mixture was warmed to room temperature, quenched with saturated ammonium chloride solution then diluted with dichloromethane (25 mL). The aqueous phase was removed, and the organic layer washed with water (2 × 20 mL) then brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Flash column chromatography (dichloromethane/methanol 19:1 with 1% triethylamine) afforded dimethyl 2-[(4*S*)-1-benzyl-2-oxoazetidin-4-yl]-2-oxoethylphosphonate (35 mg, 39%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3009 (CH), 2955, 1751 (CO), 1258, 1026; $[\alpha]_D^{19}$ –19.9 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.83 (1H, dd, *J* 22.7, 13.9 Hz, C*H*HP(O)$(OMe)_2$), 2.89 (1H, ddd, *J* 14.4, 2.8, 0.7 Hz, 3-*H*H), 2.98 (1H, dd, *J* 22.7, 13.9 Hz, CH*H*P(O)$(OMe)_2$), 3.15 (1H, dd, *J* 14.4, 6.0 Hz, 3-H*H*), 3.62 (3H, d, *J* 11.3 Hz, OMe), 3.68 (3H, d, *J* 11.3 Hz, OMe), 4.10 (1H, d, *J* 14.8 Hz, 1'-*H*H), 4.12 (1H, dd, *J* 6.0, 2.8 Hz, 4-H), 4.73 (1H, d, *J* 14.8 Hz, 1'-H*H*), 7.14–7.30 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 38.2 (d, *J* 129.0 Hz, CH_2), 41.5 (CH_2), 45.9 (CH_2), 53.1 (d, *J* 3.7 Hz, CH_3), 53.2 (d, *J* 3.7 Hz, CH_3), 56.1 (CH), 128.0 (CH), 128.7 (2 × CH), 128.9 (2 × CH), 134.9 (C), 164.9 (C), 199.0 (C); *m/z* (EI) 311.0920 (M^+. $C_{14}H_{18}NO_5P$ requires 311.0923), 179 (93%), 160 (100), 151 (54), 106 (63), 91 (100).

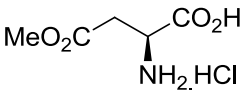
(4*S*)-1-Benzyl-2-oxoazetidine-4-carboxylic acid



237

To a solution of methyl (4*S*)-1-benzyl-2-oxoazetidine-4-carboxylate (**235**) (33 mg, 0.15 mmol) in methanol was added 2 M sodium hydroxide solution (113 μL, 0.23 mmol). The mixture was stirred for 16 h then concentrated under reduced pressure. The residue was acidified to pH 3 with 1 M hydrochloric acid solution then extracted with ethyl acetate (3 × 10 mL). The organic extractions were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a brown oil. Flash column chromatography (dichloromethane/methanol 49:1) afforded (4*S*)-1-benzyl-2-oxoazetidine-4-carboxylic acid (15 mg, 49%) as a pale yellow oil. ν_{max} (neat)/cm^{-1} 3033 (OH), 1740 (CO), 1707 (CO), 1399, 1199; $[\alpha]_D^{23}$ –22.0 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.03 (1H, ddd, *J* 14.7, 2.5, 0.8 Hz, 3-*H*H), 3.21 (1H, dd, *J* 14.7, 5.7 Hz, 3-H*H*), 3.91 (1H, dd, *J* 5.7, 2.5 Hz, 4-H), 4.08 (1H, d, *J* 14.9 Hz, 1'-*H*H), 4.78 (1H, d, *J* 14.9 Hz, 1'-H*H*), 7.18–7.31 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 41.9 (CH_2), 45.7 (CH_2), 49.6 (CH), 128.1 (CH), 128.6 (2 × CH), 129.0 (2 × CH), 134.5 (C), 166.1 (C), 174.7 (C); *m/z* (CI) 206.0816 (MH^+. $C_{11}H_{12}NO_3$ requires 206.0817), 180 (7%), 162 (9), 134 (4).

L-Aspartic acid β-methyl ester hydrochloride[78]

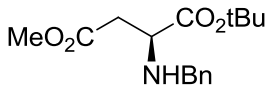


239

To a solution of L-aspartic acid (5.00 g, 37.6 mmol) in methanol (25 mL) at –10 °C was added thionyl chloride (3.84 mL, 52.6 mmol). The mixture was warmed to room temperature over 0.5 h then diluted with diethyl ether (50 mL). Scratching of the reaction vessel with a glass rod caused precipitation of a white solid, which was vacuum filtered and washed with diethyl ether, then dried under reduced pressure to afford the desired product (2.53 g, 37%) as a white solid. Mp. 169–173 °C, lit.[78] 191–193 °C; ν_{max} (neat)/cm^{-1} 2847 (OH), 1736 (CO), 1497, 1196, 1103, 849; $[\alpha]_D^{29}$ +17.2 (*c* 1.0, MeOH); δ_H (400

MHz, D_2O) 3.01–3.04 (2H, m, 3-H_2), 3.69 (3H, s, OMe), 4.17–4.23 (1H, m, 2-H); δ_C (101 MHz, D_2O) 34.0 (CH_2), 49.8 (CH), 52.8 (CH_3), 171.5 (C), 172.1 (C); *m/z* (CI) 148.0612 (MH^+. $C_5H_{10}NO_4$ requires 148.0610), 116 (2%), 102 (6), 81 (2).

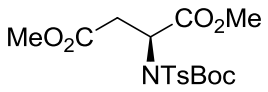
_N_-Benzyl L-aspartic acid α-_tert_-butyl ester, β-methyl ester



241

To a solution of L-aspartic acid β-methyl ester hydrochloride (**239**) (250 mg, 1.36 mmol) in *tert*-butyl acetate (10 mL) at room temperature was added 70% wt. perchloric acid solution (117 μL, 1.36 mmol) and the mixture stirred for 72 h. The mixture was extracted with 0.5 M hydrochloric acid solution (3 × 10 mL), the aqueous layer was neutralised immediately with solid sodium hydrogen carbonate then extracted with diethyl ether (3 × 10 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow oil. The oil was dissolved in methanol (20 mL), to which was added triethylamine (82 μL, 0.59 mmol) and benzaldehyde (60 μL, 0.59 mmol), and the reaction stirred for 18 h. The mixture was cooled to 0 °C and sodium borohydride (30 mg, 0.79 mmol) was added portionwise over 0.5 h. The mixture was concentrated under reduced pressure and the residue partitioned between diethyl ether (25 mL) and 1 M sodium hydrogen carbonate solution (25 mL). The organic layer was washed with 1 M sodium hydrogen carbonate solution (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography (petroleum ether/ethyl acetate 9:1) afforded the desired compound (18 mg, 5% over two steps) as a yellow oil. ν_{max} (neat)/cm^{-1} 2980 (CH), 1729 (CO), 1368, 1151; $[\alpha]_D^{25}$ –27.7 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, O*t*Bu), 2.63 (1H, dd, *J* 15.5, 6.8 Hz, 3-*H*H), 2.69 (1H, dd, *J* 15.5, 6.2 Hz, 3-H*H*), 3.55 (1H, dd, *J* 6.8, 6.2 Hz, 2-H), 3.68 (3H, s, OMe), 3.72 (1H, d, *J* 13.0 Hz, 1'-*H*H), 3.88 (1H, d, *J* 13.0 Hz, 1'-H*H*), 7.22–7.33 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 28.0 (3 × CH_3), 38.3 (CH_2), 51.7 (CH_2), 52.0 (CH_3), 57.7 (CH), 81.6 (C), 127.1 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 139.8 (C), 171.4 (C), 172.8 (C); *m/z* (CI) 294.1703 (MH^+. $C_{16}H_{24}NO_4$ requires 294.1705), 279 (14%), 263 (8), 238 (27), 192 (13).

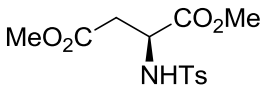
Dimethyl-*N*-(*tert*-butoxycarbonyl)-*N*-(*p*-toluenesulfonyl)-2-aminobutanedioate[101]



243

To a solution of dimethyl (2*S*)-2-aminobutanedioate hydrochloride (**224**) (1.00 g, 5.06 mmol) in methanol (50 mL) at 0 °C was added triethylamine (2.10 mL, 15.2 mmol) and *p*-toluenesulfonylchloride (1.45 g, 7.59 mmol). The mixture was warmed to room temperature then stirred for 20 h. The mixture was concentrated under reduced pressure, and the residue partitioned between ethyl acetate (25 mL) and 0.5 M hydrochloric acid solution (25 mL). The aqueous phase was discarded, and the organic phase was washed with saturated sodium hydrogen carbonate solution (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow oil. The oil was dissolved in dichloromethane (50 mL), to which was added di-*tert*-butyl dicarbonate (2.08 g, 9.51 mmol), triethylamine (1.38 mL, 9.99 mmol) and 4-dimethylaminopyridine (0.12 g, 0.95 mmol). The mixture was warmed to room temperature and stirred for 24 h. The mixture was washed with 1 M hydrochloric acid solution (30 mL) then saturated sodium hydrogen carbonate solution (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a brown oil. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 7:3) afforded *N*-(*tert*-butoxycarbonyl)-*N*-(*p*-toluenesulfonyl)-2-aminobutanedioate (0.91 g, 43% over two steps) as a pale yellow solid. Mp. 90–91 °C, lit.[101] 91–92 °C; ν_{max} (neat)/cm^{-1} 2955 (CH), 1728 (CO), 1358, 1150, 1049, 972; $[\alpha]_D^{25}$ –80.4 (*c* 0.5, $CHCl_3$), lit.[101] $[\alpha]_D^{25}$ –56.1 (*c* 3.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, O*t*Bu), 2.45 (3H, s, C*H*$_3$C$_6$H$_4$), 2.84 (1H, dd, *J* 16.4, 5.8 Hz, 3-*H*H), 3.38 (1H, dd, *J* 16.4, 7.8 Hz, 3-H*H*), 3.73 (3H, s, OMe), 3.75 (3H, s, OMe), 5.67 (1H, dd, *J* 7.8, 5.8 Hz, 2-H), 7.32 (2H, dd, *J* 8.5, 0.7 Hz, ArH), 7.92 (2H, d, *J* 8.5 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 21.7 (CH_3), 27.8 (3 × CH_3), 36.5 (CH_2), 52.2 (CH_3), 52.8 (CH_3), 55.5 (CH), 85.5 (C), 128.7 (2 × CH), 129.1 (2 × CH), 136.5 (C), 146.3 (C), 154.9 (C), 169.6 (C), 170.7 (C); *m/z* (FAB) 416.1378 (MH^+. $C_{18}H_{26}NO_8S$ requires 416.1379), 360 (100%), 316 (96), 256 (58), 188 (62), 160 (57).

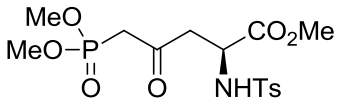
Dimethyl (2*S*)-2-(*p*-toluenesulfonyl)aminobutanedioate



242

To a solution of dimethyl (2*S*)-2-aminobutanedioate hydrochloride (**224**) (5.00 g, 25.3 mmol) in dichloromethane (100 mL) at room temperature was added triethylamine (9.46 mL, 68.3 mmol) followed by *p*-toluenesulfonyl chloride (7.23 g, 38.0 mmol), and the mixture was stirred for 24 h. The mixture was washed with 0.5 M hydrochloric acid solution (100 mL) then saturated sodium hydrogen carbonate solution (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow solid. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:2) afforded dimethyl (2*S*)-2-(*p*-toluenesulfonyl)aminobutanedioate (5.40 g, 68%) as a white solid. Mp. 75–77 °C; ν_{max} (neat)/cm^{-1} 3295 (NH), 1745 (CO), 1732 (CO), 1339, 1223, 1161, 1092; $[\alpha]_D^{28}$ +39.1 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s, C*H*$_3$C$_6$H$_4$), 2.85 (1H, dd, *J* 17.0, 4.5 Hz, 3-*H*H), 2.96 (1H, dd, *J* 17.0, 4.5 Hz, 3-H*H*), 3.60 (3H, s, OMe), 3.67 (3H, s, OMe), 4.15 (1H, dt, *J* 8.0, 4.5 Hz, 2-H), 5.59 (1H, d, *J* 8.0 Hz, NH), 7.30 (2H, d, *J* 8.2 Hz, ArH), 7.74 (2H, d, *J* 8.2 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 21.6 (CH_3), 37.7 (CH_2), 52.1 (CH_3), 52.1 (CH_3), 53.0 (CH), 127.2 (2 × CH), 129.7 (2 × CH), 136.7 (C), 143.8 (C), 170.4 (C), 170.7 (C); *m/z* (CI) 316.0854 (MH^+. $C_{13}H_{18}NO_6S$ requires 316.0855), 296 (2%), 256 (8), 242 (2), 160 (7).

Methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(*p*-toluenesulfonyl)aminopentanoate

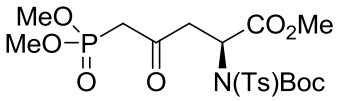


247

To a solution of dimethyl methylphosphonate (0.52 mL, 4.82 mmol) in tetrahydrofuran (25 mL) at –78 °C was added 2.5 M *n*-butyl lithium in hexanes (1.80 mL, 4.50 mmol) and the mixture stirred for 0.75 h. The mixture was added *via* cannula to a solution of dimethyl (2*S*)-2-(*p*-toluenesulfonyl)aminobutanedioate (**242**) (0.51 g, 1.61 mmol) in tetrahydrofuran (25 mL) at –78 °C. The mixture was stirred at –78 °C for 1 h, then warmed to room temperature over 1.5 h. The mixture was quenched with saturated ammonium chloride

solution (10 mL), concentrated under reduced pressure, and the residue extracted with ethyl acetate (3 × 25 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography (ethyl acetate) afforded methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(*p*-toluenesulfonyl)aminopentanoate (0.37 g, 57%) as a white solid. Mp. 93–96 °C; ν_{max} (neat)/cm^{-1} 3133 (NH), 2963 (CH), 1721 (CO), 1327, 1235, 1026, 810; $[\alpha]_D^{22}$ –11.2 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, C*H*$_3$C$_6$H$_4$), 2.59 (1H, dd, *J* 17.0, 5.0 Hz, 3-*H*H), 2.75 (1H, dd, *J* 17.0, 5.0 Hz, 3-H*H*), 3.26 (1H, dd, *J* 22.5, 14.0 Hz, 5-*H*H), 3.39 (1H, dd, *J* 22.5, 14.0 Hz, 5-H*H*), 3.59 (3H, s, OMe), 3.73 (3H, d, *J* 11.2 Hz, OMe), 3.78 (3H, d, *J* 11.2 Hz, OMe), 4.28 (1H, dt, *J* 8.7, 5.0 Hz, 2-H), 6.54 (1H, d, *J* 8.7 Hz, NH), 7.32 (2H, d, *J* 8.4 Hz, ArH), 7.77 (2H, d, *J* 8.4 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 21.6 (CH_3), 29.7 (CH_2), 37.4 (d, *J* 129.1 Hz, CH_2), 52.1 (CH_3), 53.3 (d, *J* 2.9 Hz, CH_3), 53.4 (d, *J* 2.9 Hz, CH_3), 59.0 (CH), 127.3 (2 × CH), 129.9 (2 × CH), 137.2 (C), 143.9 (C), 171.1 (C), 198.8 (C); *m/z* (CI) 408.0877 (MH^+. $C_{15}H_{23}NO_8PS$ requires 408.0882), 252 (44%), 237 (19), 220 (9), 157 (22).

Dimethyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-*N*-(*tert*-butoxycarbonyl)-*N*-(*p*-toluenesulfonyl)-2-aminopentandioate

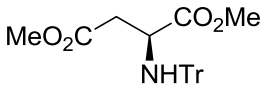


244

To a solution of methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(*p*-toluenesulfonyl)aminopentanoate (**247**) (0.21 g, 0.51 mmol) in acetonitrile (15 mL) at room temperature was added di-*tert*-butyl dicarbonate (0.12 g, 0.56 mmol) and 4-dimethylaminopyridine (0.01 g, 0.05 mmol). The mixture was stirred for 18 h, concentrated under reduced pressure, and the residue dissolved in ethyl acetate (25 mL). The organic layer was washed with 0.2 M citric acid solution (2 × 15 mL), saturated sodium hydrogen carbonate solution (30 mL) and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography (ethyl acetate/petroleum ether 1:1 to 1:0) afforded dimethyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-*N*-(*tert*-butoxycarbonyl)-*N*-(*p*-toluenesulfonyl)-2-aminopentandioate (0.17 g, 65%) as a colourless oil. NMR data for major rotomer: δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, O*t*Bu), 2.46 (3H, s, CH_3), 2.55 (1H, dd, *J* 16.3, 5.2 Hz, 3-*H*H),

3.28 (1H, dd, *J* 16.3, 7.8 Hz, 3-H*H*), 3.36–3.58 (2H, m, 5-H_2), 3.68 (3H, s, OMe), 3.82 (3H, d, *J* 14.5 Hz, OMe), 3.85 (3H, d, *J* 14.5 Hz, OMe), 5.56 (1H, dd, *J* 7.8, 5.2 Hz, 2-H), 7.36 (2H, d, *J* 8.1 Hz, ArH), 7.92 (2H, d, *J* 8.1 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 21.7 (CH_3), 27.8 (3 × CH_3), 34.6 (CH_2), 35.6 (d, *J* 134 Hz, CH_2), 52.0 (CH_3), 52.1 (CH_3), 62.0 (CH_3), 62.1 (CH), 86.5 (C), 128.6 (CH), 128.8 (CH), 129.4 (CH), 129.5 (CH), 135.9 (C), 145.2 (C), 150.0 (C), 170.6 (C), 195.9 (C).

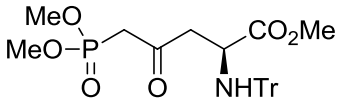
Dimethyl (2*S*)-2-(tritylamino)butanedioate[73]



225

To a solution of dimethyl (2*S*)-2-aminobutanedioate hydrochloride (**224**) (7.36 g, 37.24 mmol) in dichloromethane (100 mL) at 0 °C was added triethylamine (10.32 mL, 74.99 mmol) and triphenylmethyl chloride (12.46 g, 44.69 mmol). The mixture was warmed to room temperature then stirred for 20 h. The mixture was washed with 2 M citric acid solution (50 mL) then water (50 mL) and brine (50 mL), then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a brown oil. Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired product (11.80 g, 79%) as a white solid. Mp. 70–71 °C, lit.[73] 71–72 °C; ν_{max} (neat)/cm^{-1} 2338, 1736 (CO), 1443, 1173, 902; $[\alpha]_D^{29}$ +15.9 (*c* 1.0, $CHCl_3$), lit.[73] $[\alpha]_D^{24}$ +36.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.50 (1H, dd, *J* 14.7, 7.1 Hz, 3-*H*H), 2.65 (1H, dd, *J* 14.7, 5.4 Hz, 3-H*H*), 2.93 (1H, d, *J* 10.1 Hz, NH), 3.26 (3H, s, OMe), 3.67 (3H, s, OMe), 3.68–3.72 (1H, m, 2-H), 7.08–7.19 (9H, m, ArH), 7.39–7.41 (6H, m, ArH); δ_C (101 MHz, $CDCl_3$) 40.3 (CH_2), 51.8 (CH_3), 52.0 (CH_3), 53.7 (CH), 71.2 (C), 126.5 (3 × CH), 127.9 (6 × CH), 128.8 (6 × CH), 145.7 (3 × C), 171.0 (C), 173.9 (C); *m/z* (CI) 404.1858 (MH^+. $C_{25}H_{26}NO_4$ requires 404.1862), 326 (23%), 285 (31), 244 (100), 243 (100), 162 (73).

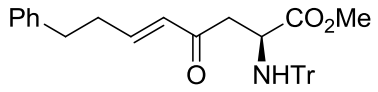
Methyl (2*S*)-2-(tritylamino)-5-(dimethoxyphosphoryl)-4-oxopentanoate[73]



226

To a solution of dimethyl methylphosphonate (0.26 mL, 2.38 mmol) in tetrahydrofuran (15 mL) at –78 °C was added 1.6 M *n*-butyl lithium in hexanes (1.39 mL, 2.23 mmol). The mixture was stirred for 0.75 h, then added *via* cannula to a solution of dimethyl (2*S*)-2-(tritylamino)butanedioate (**225**) (0.30 g, 0.74 mmol) in tetrahydrofuran (10 mL) at –78 °C. The mixture was stirred for 3 h, then warmed to room temperature over 0.5 h and quenched with saturated ammonium chloride solution (10 mL). The mixture was concentrated under reduced pressure, the residue was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a brown oil. Flash column chromatography (petroleum ether/ethyl acetate 1:4) afforded methyl (2*S*)-2-(tritylamino)-5-(dimethoxyphosphoryl)-4-oxopentanoate (0.32 g, 88%) as a yellow solid. Mp. 112–114 °C, lit.[73] 117–118 °C; ν_{max} (neat)/cm^{-1} 3321 (NH), 2924 (CH), 1720 (CO), 1443, 1266, 1026; $[\alpha]_D^{25}$ +18.4 (*c* 0.6, $CHCl_3$), lit.[73] $[\alpha]_D^{24}$ +31.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.70 (1H, dd, *J* 16.8, 7.0 Hz, 3-*H*H), 2.81 (1H, dd, *J* 16.8, 4.6 Hz, 3-H*H*), 2.86 (1H, d, *J* 9.4 Hz, NH), 2.97 (2H, dd, *J* 22.7, 1.7 Hz, 5-H_2), 3.21 (3H, s, OMe), 3.59–3.65 (1H, m, 2-H), 3.67 (3H, s, OMe), 3.70 (3H, s, OMe), 7.08–7.19 (9H, m, ArH), 7.39–7.41 (6H, m, ArH); δ_C (101 MHz, $CDCl_3$) 41.9 (d, *J* 128 Hz, CH_2), 48.8 (CH_2), 52.0 (CH_3), 52.9 (CH), 53.1 (d, *J* 6.1 Hz, CH_3), 53.2 (d, *J* 6.1 Hz, CH_3), 71.3 (C), 126.6 (3 × CH), 127.9 (6 × CH), 128.8 (6 × CH), 145.7 (3 × C), 174.1 (C), 199.3 (C); *m/z* (FAB) 496 (MH^+. 8%), 417 (10), 251 (14), 242 (100), 153 (37).

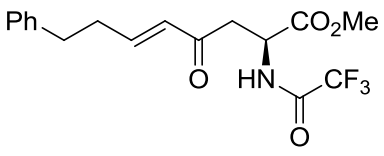
Methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-8-phenyloct-5-enoate[73]



250

To a solution of methyl (2*S*)-2-(tritylamino)-5-(dimethoxyphosphoryl)-4-oxopentanoate (**226**) (0.53 g, 1.06 mmol) in acetonitrile (30 mL) was added hydrocinnamaldehyde (0.28 mL, 2.12 mmol) and anhydrous potassium carbonate (0.16 g, 1.17 mmol) and the mixture heated to 50 °C for 48 h. The reaction mixture was cooled and concentrated under reduced pressure, and the residue dissolved in ethyl acetate (25 mL) and washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL) and the organic layers were combined then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 9:1 to 7:3) afforded methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-8-phenyloct-5-enoate (0.40 g, 75%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3012 (CH), 2338, 1736 (CO), 1674 (CO), 1645 (C=C), 1204, 1026; $[\alpha]_D^{25}$ +19.3 (*c* 1.0, $CHCl_3$), lit.[73] $[\alpha]_D^{27}$ +26.6 (*c* 1.0, $CHCl_3$); δ_H (40 0 MHz, $CDCl_3$) 2.49–2.86 (7H, m, 3-H_2, 7-H_2, 8-H_2 and NH), 3.27 (3H, s, OMe), 3.70 (1H, m, 2-H), 6.05 (1H, dt, *J* 16.0, 1.5 Hz, 5-H), 6.76 (1H, dt, *J* 16.0, 6.7 Hz, 6-H), 7.08–7.19 (9H, m, ArH), 7.39–7.41 (6H, m, ArH); δ_C (101 MHz, $CDCl_3$) 34.2 (CH_2), 34.4 (CH_2), 45.0 (CH_2), 51.9 (CH_3), 53.7 (CH), 71.3 (C), 126.3 (CH), 126.6 (3 × CH), 127.9 (6 × CH), 128.4 (2 × CH), 128.6 (2 × CH), 128.9 (6 × CH), 131.0 (CH), 140.7 (C), 145.9 (CH), 147.1 (3 × C), 174.5 (C), 197.6 (C); *m/z* (FAB) 504.2534 (MH^+. $C_{34}H_{34}NO_3$ requires 504.2539), 426 (69%), 378 (2), 266 (6), 252 (78), 243 (100).

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

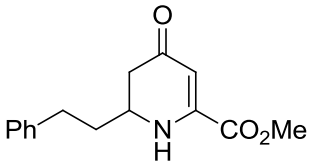


253

To a solution of methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-8-phenyloct-5-enoate (**250**) (70 mg, 0.14 mmol) in dichloromethane (10 mL) at room temperature was added trifluoroacetic acid (103 μL, 1.39 mmol), and the mixture was stirred for 3 h. The mixture was

concentrated under reduced pressure, the residue dissolved in water and washed with diethyl ether (2 × 10 mL). The aqueous phase was concentrated under reduced pressure then azeotroped with ethyl acetate and chloroform to afford a yellow oil. The oil was dissolved in dichloromethane (10 mL), to which was added triethylamine (46 μL, 0.34 mmol) and *p*-toluenesulfonyl chloride (36 mg, 0.19 mmol). The mixture was stirred for 18 h, washed with 0.5 M hydrochloric acid solution (10 mL) then saturated sodium hydrogen carbonate solution (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Flash column chromatography (petroleum ether/diethyl ether 1:1) afforded methyl (2*S*,5*E*)-4-oxo-8-phenyl-2-(trifluoroacetylamino)oct-5-enoate (18 mg, 36%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3022 (CH), 1751, 1727 (CO), 1628, 1215; $[\alpha]_D^{29}$ +65.9 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.55–2.60 (2H m, 7-H_2), 2.80 (2H, t, *J* 7.5 Hz, 8-H_2), 3.11 (1H, dd, *J* 18.3, 4.0 Hz, 3-*H*H), 3.42 (1H, dd, *J* 18.3, 4.0 Hz, 3-H*H*), 3.77 (3H, s, CH_3), 4.81 (1H, dt, *J* 8.0, 4.0 Hz, 2-H), 6.11 (1H, dt, *J* 16.0, 1.5 Hz, 5-H), 6.92 (1H, dt, *J* 16.0, 6.8 Hz, 6-H), 7.16–7.32 (5H, m, Ph), 7.43 (1H, d, *J* 8.0 Hz, NH); δ_C (101 MHz, $CDCl_3$) 34.2 (CH_2), 34.3 (CH_2), 40.4 (CH_2), 48.5 (CH), 53.2 (CH_3), 115.6 (q, *J* 228 Hz, C) 126.4 (CH), 128.3 (2 × CH), 128.6 (2 × CH), 129.8 (CH), 140.3 (C), 149.1 (CH), 156.5–157.4 (m, C), 169.8 (C), 197.2 (C); *m/z* (CI) 358.1267 (MH^+. $C_{17}H_{19}F_3NO_4$ requires 358.1266), 302 (2%), 245 (5), 198 (3), 157 (8).

Methyl 4-oxo-6-(2-phenylethyl)-1,4,5,6-tetrahydropyridine-2-carboxylate

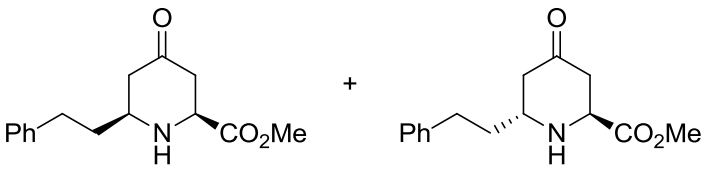


257

To a solution of methyl (2*S*,5*E*)-2-tritylamino-4-oxo-8-phenyloct-5-enoate (**250**) (0.30 g, 5.96 mmol) in methanol (15 mL) was added 2 M hydrochloric acid solution (15 mL). The mixture was stirred for 1 h, filtered and concentrated under reduced pressure. The residue was azeotroped with toluene (3 × 20 mL), ethyl acetate (3 × 20 mL) and chloroform (3 × 20 mL) and dried under reduced pressure. The residue was dissolved in dichloromethane (15 mL) to which was added triethylamine (0.17 mL, 1.24 mmol) and *p*-toluenesulfonyl chloride (0.13 g, 6.90 mmol). The mixture was stirred for 24 h, washed with 0.5 M hydrochloric acid solution (10 mL) then saturated sodium hydrogencarbonate solution (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow

oil. Flash column chromatography (petroleum ether/diethyl ether 1:1) afforded a white solid, methyl (2*S*,5*E*)-2-(*p*-toluenesulfonylamino)-4-oxo-8-phenyloct-5-enoate. δ_H (400MHz, $CDCl_3$) 2.34 (3H, s, C*H*$_3$C$_6$H$_4$), 2.43-2.49 (2H, m, 7-H$_2$), 2.70 (2H, t, *J* 7.4 Hz, 8-H$_2$), 3.06 (1H, dd, *J* 17.9, 4.5 Hz, 3-*H*H), 3.14 (1H, dd, *J* 17.9, 4.0 Hz, 3-H*H*), 3.46 (3H, s, OMe), 4.04–4.08 (1H, m, 2-H), 5.60 (1H, d, *J* 8.2 Hz, NH), 5.97 (1H, dt, *J* 16.0, 1.4 Hz, 5-H), 6.76 (1H, dt, *J* 16.0, 6.8 Hz, 6-H), 7.08–7.24 (7H, m, Ph and ArH), 7.65–7.68 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 34.2 (CH_2), 34.2 (CH_2), 42.9 (CH_2), 51.7 (CH_3), 52.8 (CH), 126.3 (CH), 127.2 (2 × CH), 128.3 (2 × CH), 128.6 (2 × CH), 129.6 (CH), 130.0 (2 × CH), 137.0 (C), 140.5 (C), 143.6 (C), 148.3 (CH), 170.9 (C), 196.9 (C). The solid was dissolved in dimethylsulfoxide (10 mL) to which was added anhydrous potassium carbonate (2 mg, 16 μmol). The mixture was stirred for 24 h then diluted with ethyl acetate (30 mL) and washed with water (2 × 15 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography (petroleum ether/diethyl ether 7:3 to 1:4 with 1% triethylamine) afforded methyl 4-oxo-6-(2-phenylethyl)-1,4,5,6-tetrahydropyridine-2-carboxylate (14 mg, 9% over three steps) as a pale yellow oil. ν_{max} (neat)/cm^{-1} 3356 (NH), 2931 (CH), 1732 (CO), 1632 (C=C), 1589, 1269, 1161; δ_H (400 MHz, $CDCl_3$) 1.85–2.02 (2H, m, 1'-H$_2$), 2.32 (1H, dd, *J* 16.3, 12.7 Hz, 5-*H*H), 2.47 (1H, dd, *J* 16.3, 4.9 Hz, 5-H*H*), 2.60–2.72 (2H, m, 2'-H$_2$), 3.59–3.65 (1H, m, 6-H), 3.80 (3H, s, OMe), 5.43 (1H, br s, NH), 5.63–5.64 (1H, m, 3-H), 7.11–7.26 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 31.7 (CH_2), 35.2 (CH_2), 41.7 (CH_2), 52.7 (CH), 53.4 (CH_3), 101.3 (CH), 126.4 (CH), 128.3 (2 × CH), 128.8 (2 × CH), 140.3 (C), 147.7 (C), 163.9 (C), 194.5 (C); *m/z* (EI) 259.1208 (M$^+$. $C_{15}H_{17}NO_3$ requires 259.1208), 155 (100%), 127 (24), 122 (21), 91 (70).

Methyl (2*S*,6*S*)-4-oxo-6-(2-phenylethyl)piperidine-2-carboxylate and methyl (2*S*,6*R*)-4-oxo-6-(2-phenylethyl)piperidine-2-carboxylate

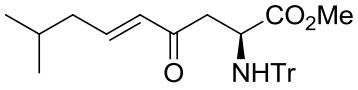


262a **262b**

To a solution of methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-8-phenyloct-5-enoate (**250**) (150 mg, 0.30 mmol) in methanol (10 mL) was added 2 M hydrochloric acid solution (2.5 mL).

The mixture was stirred for 1 h, then diluted with water (10 mL) and basified to pH 8 with *N*-ethyldiisopropylamine (1.5 mL). The mixture was stirred for 18 h then partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous layer was separated and re-extracted with ethyl acetate (20 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*S*)-4-oxo-6-(2-phenylethyl)piperidine-2-carboxylate (41 mg, 54%) as a white solid followed by (2*S*,6*R*)-4-oxo-6-(2-phenylethyl)piperidine-2-carboxylate (18 mg, 23%) as a colourless oil. Data for methyl (2*S*,6*S*)-4-oxo-6-(2-phenylethyl)piperidine-2-carboxylate: Mp. 76–78 °C; ν_{max} (neat)/cm^{-1} 3212 (NH), 2924 (CH), 1736 (CO), 1713 (CO), 1435, 1265; $[\alpha]_D^{26}$ –15.1 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.82–1.97 (2H, m, 1'-H_2), 2.16 (1H, ddd, *J* 14.4, 11.7, 0.9 Hz, 5-*H*H), 2.44 (1H, ddd, *J* 14.4, 12.2, 0.9 Hz, 3-H_{ax}), 2.48 (1H, ddd, *J* 14.4, 2.9, 2.0 Hz, 5-H*H*), 2.70 (1H, ddd, *J* 14.4, 3.4, 2.0 Hz, 3-H_{eq}), 2.73–2.77 (2H, m, 2'-H_2), 2.86–2.91 (1H, m, 6-H), 3.63 (1H, dd, *J* 12.2, 3.4 Hz, 2-H), 3.79 (3H, s, OMe), 7.19–7.33 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 30.3 (CH_2), 38.3 (CH_2), 44.5 (CH_2), 48.4 (CH_2), 52.5 (CH_3), 55.2 (CH), 57.9 (CH), 126.2 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 141.1 (C), 171.8 (C), 206.8 (C); *m/z* (CI) 262.1444 (MH^+. $C_{15}H_{20}NO_3$ requires 262.1443), 202 (9%), 156 (4), 135 (5), 113 (4). Data for (2*S*,6*R*)-4-oxo-6-(2-phenylethyl)piperidine-2-carboxylate: ν_{max} (neat)/cm^{-1} 3333 (NH), 2924 (CH), 1728 (CO), 1435, 1196, 1173; $[\alpha]_D^{27}$ –22.4 (*c* 1.1, $CHCl_3$); δ_H (400MHz, $CDCl_3$) 1.71–1.87 (2H, m, 1'-H_2), 2.21 (1H, ddd, *J* 14.6, 9.6, 1.0 Hz, 5-H_{eq}), 2.46 (1H, ddd, *J* 14.6, 3.9, 1.7 Hz, 5-H_{ax}), 2.60–2.72 (4H, m, 2'-H_2 and 3-H_2), 3.10–3.16 (1H, m, 6-H), 3.71 (3H, s, OMe), 4.04 (1H, dd, *J* 6.5, 4.2 Hz, 2-H), 7.17–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 31.9 (CH_2), 37.6 (CH_2), 42.3 (CH_2), 47.6 (CH_2), 52.1 (CH_3), 52.3 (CH), 55.7 (CH), 126.1 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 141.1 (C), 173.0 (C), 206.7 (C); *m/z* (CI) 262.1447 (MH^+. $C_{15}H_{20}NO_3$ requires 262.1443), 247 (5%), 202 (9), 156 (5), 113 (13).

Methyl (2*S*,5*E*)-2-(tritylamino)-8-methyl-4-oxonon-5-enoate[73]

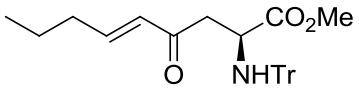


263

To a solution of methyl (2*S*)-2-(tritylamino)-5-(dimethoxyphosphoryl)-4-oxopentanoate (**226**) (0.30 g, 0.61 mmol) in acetonitrile (20 mL) was added isovaleraldehyde (0.13 mL,

1.21 mmol) and anhydrous potassium carbonate (0.09 g, 0.67 mmol), and the mixture heated to 50 °C for 96 h. The reaction mixture was cooled and concentrated under reduced pressure, and the residue dissolved in ethyl acetate (25 mL) and washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL) and the organic layers were combined then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 3:2) afforded methyl (2*S*,5*E*)-2-(tritylamino)-8-methyl-4-oxonon-5-enoate (0.16 g, 58%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3327 (NH), 2955 (CH), 1736 (CO), 1667 (CO), 1628 (C=C), 1204; $[\alpha]_D^{30}$ +18.9 (*c* 0.9, $CHCl_3$), lit.[73] $[\alpha]_D^{18}$ +18.1 (*c* 1.0 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.91 (6H, d, *J* 6.7 Hz, 2 × CH_3), 1.70–1.80 (1H, m, 8-H), 2.08 (2H, td, *J* 7.3, 1.4 Hz, 7-H_2), 2.64 (1H, dd, *J* 15.4, 7.1 Hz, 3-*H*H), 2.79 (1H, dd, *J* 15.4, 5.2 Hz, 3-H*H*), 2.86 (1H, d, *J* 9.8 Hz, NH), 3.27 (3H, s, OMe), 3.62–3.78 (1H, m, 2-H), 6.02 (1H, dt, *J* 15.9, 1.4 Hz, 5-H), 6.72 (1H, dt, *J* 15.9, 7.4 Hz, 6-H), 7.08–7.19 (9H, m, ArH), 7.39–7.41 (6H, m, ArH); δ_C (101 MHz, $CDCl_3$) 22.4 (CH_3), 22.4 (CH_3), 27.9 (CH), 41.8 (CH_2), 44.9 (CH_2), 51.9 (CH), 53.7 (CH_3), 71.2 (C), 126.5 (3 × CH), 127.9 (6 × CH), 128.8 (6 × CH), 131.7 (CH), 145.8 (3 × CH), 147.3 (CH), 174.6 (C), 197.7 (C); *m/z* (FAB) 478.2359 (MNa^+. $C_{30}H_{33}NO_3$ requires 478.2358), 378 (12%), 243 (100), 166 (17), 113 (4), 75 (11).

Methyl (2*S*,5*E*)-2-(tritylamino)-4-oxonon-5-enoate

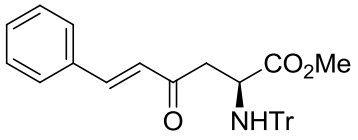


264

To a solution of methyl (2*S*)-2-(tritylamino)-5-(dimethoxyphosphoryl)-4-oxopentanoate (**226**) (0.39 g, 0.78 mmol) in acetonitrile (25 mL) was added butyraldehyde (0.14 mL, 1.56 mmol) and anhydrous potassium carbonate (0.12 g, 0.86 mmol), and the mixture heated to 50 °C for 96 h. The reaction mixture was cooled and concentrated under reduced pressure, and the residue dissolved in ethyl acetate (25 mL) and washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL) and the organic phases were combined then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 2:3) afforded methyl (2*S*,5*E*)-2-(tritylamino)-4-oxonon-5-enoate (0.20 g, 59%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3316 (NH), 2955 (CH), 1736 (CO), 1667 (CO), 1443, 1204, 1173; $[\alpha]_D^{27}$ +28.6 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.3 Hz, 9-H_3), 1.44–1.53 (2H, m, 8-H_2), 2.18

(2H, dtd, *J* 7.4, 7.0, 1.5 Hz, 7-H_2), 2.65 (1H, dd, *J* 15.3, 7.1 Hz, 3-*H*H), 2.79 (1H, dd, *J* 15.3, 5.2 Hz, 3-H*H*), 2.85 (1H, d, *J* 9.8 Hz, NH), 3.27 (3H, s, OMe), 3.67–3.74 (1H, m, 2-H), 6.04 (1H, dt, *J* 16.0, 1.5 Hz, 5-H), 6.74 (1H, dt, *J* 16.0, 7.0 Hz, 6-H), 7.08–7.19 (9H, m, ArH), 7.39–7.41 (6H, m, ArH); δ_C (101 MHz, $CDCl_3$) 13.7 (CH_3), 21.3 (CH_2), 34.5 (CH_2), 44.9 (CH_2), 51.9 (CH), 53.6 (CH_3), 71.2 (C), 126.5 (3 × CH), 127.9 (6 × CH), 129.1 (6 × CH), 130.7 (CH), 145.8 (C), 148.3 (CH), 174.6 (C), 198.0 (C); *m/z* (FAB) 442.2378 (MH^+. $C_{29}H_{32}NO_3$ requires 442.2382), 364 (60%), 243 (100), 198 (64), 165 (43).

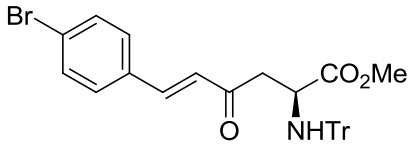
Methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-phenylhex-5-enoate[73]



265

To a solution of methyl (2*S*)-2-(tritylamino)-5-(dimethoxyphosphoryl)-4-oxopentanoate (**226**) (0.30 g, 0.61 mmol) in acetonitrile (25 mL) was added benzaldehyde (0.12 mL, 1.21 mmol) and anhydrous potassium carbonate (92 mg, 0.67 mmol), and the mixture heated to 50 °C for 96 h. The reaction mixture was cooled and concentrated under reduced pressure, and the residue dissolved in ethyl acetate (25 mL) and washed with water (25 mL). The aqueous layer was extracted with ethyl acetate (25 mL) and the organic layers were combined then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 2:3) afforded methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-phenylhex-5-enoate (0.20 g, 70%) as a yellow oil. NMR data consistent with literature.[73] ν_{max} (neat)/cm^{-1} 3297 (NH), 1736 (CO), 1688 (CO), 1657 (C=C), 1204, 1173, 1030; $[\alpha]_D^{27}$ +48.6 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.83 (1H, dd, *J* 15.2, 6.9 Hz, 3-*H*H), 2.93–2.98 (2H, m, 3-H*H* and NH), 3.32 (3H, s, OMe), 3.84 (1H, m, 2-H), 6.73 (1H, d, *J* 16.3 Hz, 5-H), 7.10–7.31 (9H, m ArH), 7.35–7.61 (12H, m, ArH and 6-H); δ_C (101 MHz, $CDCl_3$) 45.7 (CH_2), 51.9 (CH), 53.8 (CH_3), 71.3 (C), 126.4 (CH), 126.5 (3 × CH), 127.9 (6 × CH), 128.4 (2 × CH), 128.8 (6 × CH), 129.0 (2 × CH), 130.6 (CH), 134.4 (C), 143.3 (CH), 145.8 (3 × C), 174.5 (C), 197.5 (C); *m/z* (FAB) 476.2238 (MH^+. $C_{32}H_{30}NO_3$ requires 476.2226), 398 (35%), 307 (16), 243 (100), 131 (36).

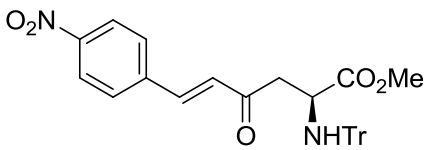
Methyl (2*S*,5*E*)-2-(tritylamino)-6-(4-bromophenyl)-4-oxohex-5-enoate[73]



266

To a solution of methyl (2*S*)-2-(tritylamino)-5-(dimethoxyphosphoryl)-4-oxopentanoate (**226**) (0.30 g, 0.61 mmol) in acetonitrile (20 mL) was added *p*-bromobenzaldehyde (0.22 g, 1.21 mmol) and anhydrous potassium carbonate (0.09 g, 0.67 mmol), and the mixture heated to 50 °C for 96 h. The reaction mixture was cooled and concentrated under reduced pressure, and the residue dissolved in ethyl acetate (25 mL) and washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL) and the organic phases were combined then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 2:3) afforded methyl (2*S*,5*E*)-2-(tritylamino)-6-(4-bromophenyl)-4-oxohex-5-enoate (0.29 g, 85%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3312 (NH), 2949 (CH), 1733 (CO), 1688 (CO), 1658 (C=C), 1487, 1071; $[\alpha]_D^{27}$ +46.2 (*c* 1.0, $CHCl_3$), lit.[73] $[\alpha]_D^{27}$ +64.6 (*c* 1.0 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.77 (1H, dd, *J* 15.2, 7.1 Hz, 3-*H*H), 2.89 (1H, dd, *J* 15.2, 5.1 Hz, 3-H*H*), 2.91 (1H, d, *J* 9.4 Hz, NH), 3.28 (3H, s, OMe), 3.76–3.81 (1H, m, 2-H), 6.66 (1H, d, *J* 16.1 Hz, 5-H), 7.15–7.25 (10H, m, ArH and 6-H), 7.40–7.62 (10H, m, ArH); δ_C (101 MHz, $CDCl_3$) 45.9 (CH_2), 52.0 (CH), 53.8 (CH_3), 71.3 (C), 125.0 (C), 126.6 (2 × CH), 126.8 (3 × CH), 128.0 (6 × CH), 128.6 (6 × CH), 129.7 (2 × CH), 132.3 (CH), 133.3 (3 × C), 141.8 (C), 145.8 (CH), 174.4 (C), 197.3 (C); *m/z* (EI) 554 (M^+, 1%), 478 (28%), 309 (30), 242 (100).

Methyl (2*S*,5*E*)-2-(tritylamino)-6-(4-nitrophenyl)-4-oxohex-5-enoate

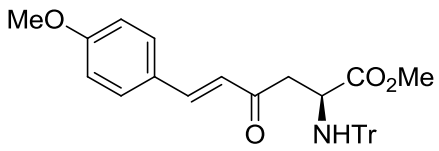


267

To a solution of methyl (2*S*)-2-(tritylamino)-5-(dimethoxyphosphoryl)-4-oxopentanoate (**226**) (0.30 g, 0.61 mmol) in acetonitrile (25 mL) was added *p*-nitrobenzaldehyde (0.18 g, 1.21 mmol) and anhydrous potassium carbonate (0.09 g, 0.67 mmol), and the mixture

heated to 50 °C for 24 h. The reaction mixture was cooled and concentrated under reduced pressure, and the residue dissolved in ethyl acetate (25 mL) and washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL) and the organic phases were combined then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 3:7) afforded methyl (2*S*,5*E*)-2-(tritylamino)-6-(4-nitrophenyl)-4-oxohex-5-enoate (0.22 g, 69%) as an off-white solid. Mp. 139–141 °C; ν_{max} (neat)/cm^{-1} 2951 (CH), 1742 (CO), 1712 (CO), 1490, 1509 (NO), 1341 (NO); $[\alpha]_D^{25}$ +43.3 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.80 (1H, dd, *J* 15.5, 6.9 Hz, 3-*H*H), 2.91 (1H, dd, J 15.5, 5.1 Hz, 3-H*H*), 2.95 (1H, br s, NH), 3.31 (3H, s, OMe), 3.81 (1H, m, 2-H), 6.77 (1H, d, *J* 16.2 Hz, 5-H), 7.17–7.51 (16H, m, 6-H and 3 × Ph), 7.66 (2H, d, *J* 8.8 Hz, ArH), 8.26 (2H, d, *J* 8.8 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 46.2 (CH_2), 52.1 (CH_3), 53.7 (CH), 71.3 (C), 124.3 (CH), 126.6 (3 × CH), 128.0 (6 × CH), 128.8 (6 × CH), 128.9 (2 × CH). 129.6 (2 × CH), 139.9 (CH), 140.6 (C), 145.7 (3 × C), 148.6 (C), 174.3 (C), 197.0 (C); *m/z* (FAB + NaI) 543.1903 (MNa^+. $C_{32}H_{28}NO_5Na$ requires 543.1896), 443 (9%), 413 (9), 351 (19), 243 (100), 176 (78).

Methyl (2*S*,5*E*)-2-(tritylamino)-6-(4-methoxyphenyl)-4-oxohex-5-enoate[73]

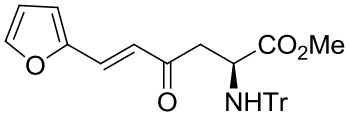


268

To a solution of methyl (2*S*)-2-(tritylamino)-5-(dimethoxyphosphoryl)-4-oxopentanoate (**226**) (0.30 g, 0.61 mmol) in acetonitrile (25 mL) was added *p*-methoxybenzaldehyde (0.15 mL, 1.21 mmol) and anhydrous potassium carbonate (0.09 g, 0.67 mmol), and the mixture heated to 50 °C for 144 h. The reaction mixture was cooled and concentrated under reduced pressure, and the residue dissolved in ethyl acetate (25 mL) and washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL) and the organic phases were combined then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 2:3) afforded methyl (2*S*,5*E*)-2-(tritylamino)-6-(4-methoxyphenyl)-4-oxohex-5-enoate (0.14 g, 46%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3299 (NH), 3016 (CH), 1736 (CO), 1651 (CO), 1597 (C=C), 1257, 1173; $[\alpha]_D^{25}$ +47.8 (*c* 1.1, $CHCl_3$), lit.[73] $[\alpha]_D^{23}$ +54.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.81 (1H, dd, *J* 15.0, 6.9 Hz, 3-*H*H), 2.92–2.97 (2H, m, 3-H*H* and NH), 3.30

(3H, s, OMe), 3.81–3.84 (1H, m, 2-H), 3.88 (3H, s, OMe), 6.61 (1H, d, *J* 16.1 Hz, 5-H), 6.95 (2H, d, J 8.7 Hz, ArH), 7.18–7.30 (9H, m, 6-H and ArH) 7.51–7.55 (9H, m, ArH); δ_C (100 MHz, $CDCl_3$) 45.7 (CH_2), 51.9 (CH_3), 53.9 (CH), 55.4 (CH_3), 71.3 (C), 114.5 (2 × CH), 124.3 (CH), 126.5 (3 × CH), 127.1 (C), 127.9 (6 × CH), 128.8 (6 × CH), 130.1 (2 × CH), 143.1 (CH), 145.8 (3 × C), 161.8 (C), 174.5 (C), 197.4 (C); *m/z* (FAB) 506.2332 (MH^+. $C_{33}H_{32}NO_4$ requires 506.2331), 428 (7%), 243 (100), 161 (22).

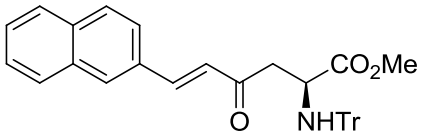
Methyl (2*S*,5*E*)-2-(tritylamino)-6-(furan-2-yl)-4-oxohex-5-enoate[73]



269

To a solution of methyl (2*S*)-2-(tritylamino)-5-(dimethoxyphosphoryl)-4-oxopentanoate (**226**) (0.33 g, 0.66 mmol) in acetonitrile (25 mL) was added 2-furfuraldehyde (0.11 mL, 1.31 mmol) and anhydrous potassium carbonate (0.10 g, 0.72 mmol), and the mixture heated to 50 °C for 72 h. The reaction mixture was cooled and concentrated under reduced pressure, and the residue dissolved in ethyl acetate (25 mL) and washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL) and the organic phases were combined then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 1:1) afforded methyl (2*S*,5*E*)-2-(tritylamino)-6-(furan-2-yl)-4-oxohex-5-enoate (0.26 g, 84%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3017 (CH), 1734 (CO), 1653 (CO), 1604 (C=C), 1215, 1017; $[\alpha]_D^{25}$ +47.0 (*c* 1.2, $CHCl_3$), lit.[73] $[\alpha]_D^{23}$ +42.9 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.73 (1H, dd, *J* 15.1, 7.0 Hz, 3-*H*H), 2.85 (1H, dd, *J* 15.1, 5.3 Hz, 3-H*H*), 2.90 (1H, d, *J* 8.6 Hz, NH), 3.27 (3H, s, OMe), 3.68–3.84 (1H, m, 2-H), 6.48 (1H, dd, *J* 3.4, 1.8 Hz, ArH), 6.60 (1H, d, *J* 15.9 Hz, 5-H), 6.66 (1H, d, *J* 3.4 Hz, ArH), 7.15–7.51 (17H, m, 6-H and ArH); δ_C (101 MHz, $CDCl_3$) 46.2 (CH_2), 51.9 (CH_3), 53.9 (CH), 71.3 (C), 112.6 (CH), 116.0 (CH), 123.7 (CH), 126.5 (3 × CH), 127.9 (6 × CH), 128.8 (6 × CH), 129.2 (CH), 145.1 (CH), 145.8 (3 × C), 151.0 (C), 174.4 (C), 197.0 (C); *m/z* (FAB) 466.2016 (MH^+. $C_{30}H_{28}NO_4$ requires 466.2018), 388 (7%), 243 (100), 222 (7), 165 (6).

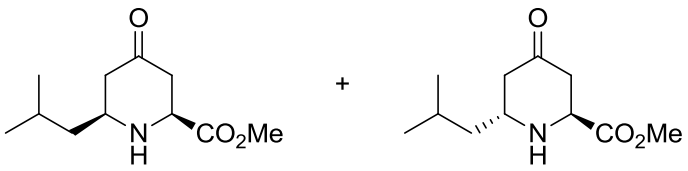
Methyl (2*S*,5*E*)-2-(tritylamino)-6-(naphthalen-2-yl)-4-oxohex-5-enoate[73]



270

To a solution of methyl (2*S*)-2-(tritylamino)-5-(dimethoxyphosphoryl)-4-oxopentanoate (**226**) (0.20 g, 0.41 mmol) in acetonitrile (20 mL) was added naphthaldehyde (0.13 g, 0.81 mmol) and anhydrous potassium carbonate (0.06 g, 0.45 mmol), and the mixture heated to 50 °C for 48 h. The reaction mixture was cooled and concentrated under reduced pressure, and the residue dissolved in ethyl acetate (25 mL) and washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL) and the organic phases were combined then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 2:3) afforded methyl (2*S*,5*E*)-2-(tritylamino)-6-(naphthalen-2-yl)-4-oxohex-5-enoate (0.15 g, 73%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3019 (CH), 1734 (CO), 1654 (C=C), 1604, 1215, 1175; $[\alpha]_D^{25}$ +51.6 (*c* 1.1, $CHCl_3$), lit.[73] $[\alpha]_D^{24}$ +64.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.88 (1H, dd, *J* 15.1, 7.1 Hz, 3-*H*H), 2.97–3.04 (2H, m, 3-H*H* and NH), 3.33 (3H, s, OMe), 3.84–3.90 (1H, m, 2-H), 6.84 (1H, d, *J* 16.2 Hz, 5-H), 7.19–7.31 (9H, m, ArH), 7.54–7.58 (8H, m, ArH), 7.67–7.71 (2H, m, 6-H and ArH), 7.87–7.97 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 45.9 (CH_2), 52.0 (CH), 53.6 (CH_3), 71.3 (C), 123.6 (CH), 126.5 (3 × CH), 126.8 (CH), 127.5 (CH), 127.8 (CH), 127.9 (6 × CH), 128.2 (CH), 128.6 (CH), 128.8 (CH), 128.9 (6 × CH), 130.6 (CH), 131.9 (C), 133.3 (C), 134.4 (C), 143.4 (CH), 145.8 (3 × C), 174.5 (C), 197.5 (C); *m/z* (FAB) 526.2388 (MH^+. $C_{36}H_{32}NO_3$ requires 526.2382), 448 (7%), 289 (7), 273 (11), 243 (100), 181 (19), 152 (17).

Methyl (2*S*,6*S*)-6-(2-methylpropyl)-4-oxopiperidine-2-carboxylate and methyl (2*S*,6*R*)-6-(2-methylpropyl)-4-oxopiperidine-2-carboxylate

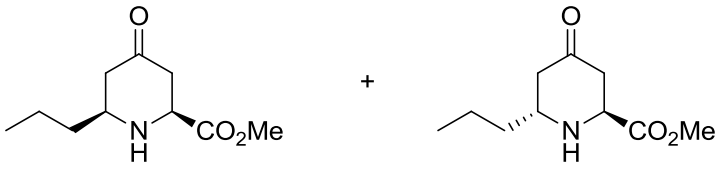


271a **271b**

To a solution of methyl (2*S*,5*E*)-2-(tritylamino)-8-methyl-4-oxonon-5-enoate (**263**) (65 mg, 0.14 mmol) in methanol (10 mL) was added 2 M hydrochloric acid solution (2.5 mL). The mixture was stirred for 1 h, then diluted with water (10 mL) and basified to pH 8 with *N*-ethyldiisopropylamine (1.5 mL). The mixture was stirred for 18 h then partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous layers were separated and re-extracted with ethyl acetate (20 mL). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*S*)-6-(2-methylpropyl)-4-oxopiperidine-2-carboxylate (19 mg, 62%) as a colourless oil followed by (2*S*,6*R*)-6-(2-methylpropyl)-4-oxopiperidine-2-carboxylate (4 mg, 13%) as a colourless oil. Data for methyl (2*S*,6*S*)-6-(2-methylpropyl)-4-oxopiperidine-2-carboxylate: ν_{max} (neat)/cm^{-1} 3332 (NH), 2957 (CH), 1740 (CO), 1716 (CO), 1437, 1216; $[\alpha]_D^{26}$ –11.2 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 5.2 Hz, 3'-H_3), 0.93 (3H, d, *J* 5.2 Hz, 2'-CH_3), 1.31–1.39 (1H, m, 1'-*H*H), 1.46–1.53 (1H, m, 1'-H*H*), 1.69–1.80 (1H, m, 2'-H), 2.07 (2H, ddd, *J* 14.1, 11.6, 0.9 Hz, 5-H_2), 2.38–2.45 (2H, m, NH and 3-H_{eq}), 2.69 (1H, ddd, *J* 14.3, 3.4, 2.0 Hz, 3-H_{ax}), 2.92 (1H, m, 6-H), 3.65 (1H, dd, *J* 12.1, 3.4 Hz, 2-H), 3.78 (3H, s, OMe); δ_C (101 MHz, $CDCl_3$) 22.5 (CH_3), 22.8 (CH_3), 24.4 (CH), 44.6 (CH_2), 46.1 (CH_2), 48.8 (CH_2), 52.5 (CH_3), 53.7 (CH), 58.0 (CH), 171.9 (C), 207.2 (C); *m/z* (CI) 214.1446 (MH^+. $C_{11}H_{20}NO_3$ requires 214.1443), 187 (3%), 154 (6), 130 (2), 112 (2). Data for (2*S*,6*R*)-6-(2-methylpropyl)-4-oxopiperidine-2-carboxylate: ν_{max} (neat)/cm^{-1} 3329 (NH), 1729 (CO), 1717 (CO), 1436, 1216, 1166; $[\alpha]_D^{27}$ –15.0 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 5.2 Hz, 3'-H_3), 0.93 (3H, d, *J* 5.2 Hz, 2'-CH_3), 1.20–1.29 (1H, m, NH), 1.39–1.45 (2H, m, 1'-H_2), 1.69 (1H, m, 2'-H), 2.14 (1H, dd, *J* 14.3, 9.9 Hz, 5-H_{ax}), 2.40 (1H, d, *J* 14.3 Hz, 5-H_{eq}), 2.63 (1H, dd, *J* 15.0, 6.8 Hz, 3-H_{eq}), 2.73 (1H, dd, *J* 15.0, 3.8 Hz, 3-H_{ax}), 3.12–3.18 (1H, m, 6-H), 3.74 (3H, s, CH_3), 4.04 (1H, dd, *J* 6.7, 3.8 Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 21.9 (CH_3), 23.2 (CH_3), 24.4 (CH), 42.2 (CH_2), 45.2 (CH_2), 48.2 (CH_2), 50.4 (CH_3), 52.3 (CH), 55.9 (CH), 173.1

(C), 207.0 (C); *m/z* (CI) 214.1441 (MH^+. $C_{11}H_{20}NO_3$ requires 214.1443), 195 (2%), 154(18), 128 (2), 112 (5).

Methyl (2*S*,6*S*)-4-oxo-6-propylpiperidine-2-carboxylate and methyl (2*S*,6*R*)-4-oxo-6-propylpiperidine-2-carboxylate

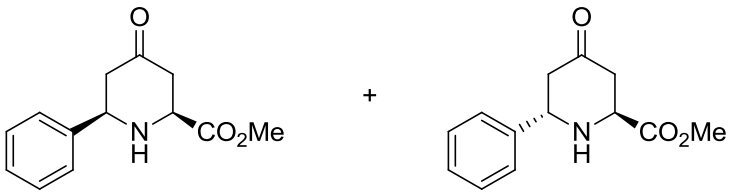


272a **272b**

To a solution of methyl (2*S*,5*E*)-2-(tritylamino)-4-oxonon-5-enoate (**264**) (103 mg, 0.23 mmol) in methanol (10 mL) was added 2 M hydrochloric acid solution (2.5 mL). The mixture was stirred for 1 h, then diluted with water (10 mL) and basified to pH 8 with *N*-ethyldiisopropylamine (1.5 mL). The mixture was stirred for 18 h then partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous layer was separated and re-extracted with ethyl acetate (20 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*S*)-4-oxo-6-propylpiperidine-2-carboxylate (26 mg, 56%) as a colourless oil followed by methyl (2*S*,6*R*)-4-oxo-6-propylpiperidine-2-carboxylate (11 mg, 24%) as a colourless oil. Data for methyl (2*S*,6*S*)-4-oxo-6-propylpiperidine-2-carboxylate: ν_{max} (neat)/cm^{-1} 3330 (NH), 2959 (CH), 2359, 1740 (CO), 1715 (CO), 1437, 1217, 1009; $[\alpha]_D^{25}$ –20.9 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.0 Hz, 3'-H_3), 1.36–1.63 (4H, m, 1'-H_2 and 2'-H_2), 2.09 (2H, dd, *J* 14.1, 11.7 Hz, 5-H_2), 2.39–2.46 (2H, m, 3-H_{ax}), 2.69 (1H, dddd, *J* 14.4, 3.4, 2.1, 0.6 Hz, 3-H_{eq}), 2.83–2.90 (1H, m, 6-H), 3.64 (1H, dd, *J* 12.2, 3.4 Hz, 2-H), 3.78 (3H, s, OMe); δ_C (101 MHz, $CDCl_3$) 14.0 (CH_3), 18.8 (CH_2), 38.9 (CH_2), 44.5 (CH_2), 48.4 (CH_2), 52.5 (CH_3), 55.6 (CH), 57.9 (CH), 171.9 (C), 207.3 (C); *m/z* (EI) 199.1212 (M^+. $C_{10}H_{17}NO_3$ requires 199.1208), 156 (95%), 140 (97), 114 (70), 98 (96). Data for by methyl (2*S*,6*R*)-4-oxo-6-propylpiperidine-2-carboxylate: ν_{max} (neat)/cm^{-1} 3325 (NH), 2957 (CH), 1732 (CO), 1717 (CO), 1435, 1120, 1163; $[\alpha]_D^{24}$ –7.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.3 Hz, 3'-H_3), 1.22–1.51 (4H, m, 1'-H_2 and 2'-H_2), 2.16 (1H, ddd, *J* 14.5, 9.9, 0.9 Hz, 5-H_{ax}), 2.43 (1H, ddd, *J* 14.5, 3.7, 1.7 Hz, 5-H_{eq}), 2.64 (1H, ddd, *J* 15.0, 6.6, 0.9 Hz, 3-H_{ax}), 2.72 (1H, ddd, *J* 15.0, 3.9, 1.7 Hz, 3-H_{eq}), 3.06–3.10 (1H, m, 6-H), 3.74

(3H, s, OMe), 4.04 (1H, dd, *J* 6.6, 3.9 Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 13.9 (CH_3), 18.7 (CH_2), 38.2 (CH_2), 42.1 (CH_2), 47.7 (CH_2), 52.3 (CH), 52.4 (CH_3), 55.8 (CH), 173.1 (C), 207.1 (C); *m/z* (CI) 200.1292 (MH^+. $C_{10}H_{18}NO_3$ requires 200.1287), 181 (9%), 164 (7), 156 (4), 140 (5).

Methyl (2*S*,6*R*)-4-oxo-6-phenylpiperidine-2-carboxylate and methyl (2*S*,6*S*)-4-oxo-6-phenylpiperidine-2-carboxylate

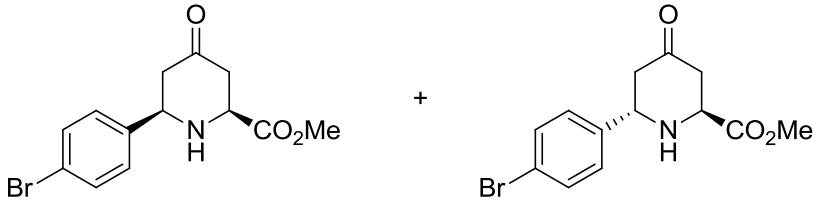


273a **273b**

To a solution of methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-phenylhex-5-enoate (**265**) (62 mg, 0.13 mmol) in methanol (10 mL) was added 2 M hydrochloric acid solution (2.5 mL). The mixture was stirred for 1 h, then diluted with water (10 mL) and basified to pH 8 with *N*-ethyldiisopropylamine (1.5 mL). The mixture was stirred for 18 h then partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous layer was separated and re-extracted with ethyl acetate (20 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-4-oxo-6-phenylpiperidine-2-carboxylate (17 mg, 56%) as a colourless oil followed by methyl (2*S*,6*S*)-4-oxo-6-phenylpiperidine-2-carboxylate (9 mg, 29%) as a colourless oil. Data for methyl (2*S*,6*R*)-4-oxo-6-phenylpiperidine-2-carboxylate: ν_{max} (neat)/cm^{-1} 3325 (NH), 3024 (CH), 1728 (CO), 1705 (CO), 1435, 1211; $[\alpha]_D^{25}$ +43.9 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.54–2.64 (4H, m, 5-H_2, 3-H_{ax} and NH), 2.79 (1H, ddd, *J* 14.5, 3.5, 1.5 Hz, 3-H_{eq}), 3.74–3.78 (4H, m, 2-H and OMe), 3.95 (1H, dd, *J* 10.0, 4.7 Hz, 6-H), 7.30–7.43 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 43.9 (CH_2), 50.1 (CH_2), 52.5 (CH_3), 57.9 (CH), 60.2 (CH), 126.5 (2 × CH), 128.2 (CH), 128.9 (2 × CH), 141.7 (C), 171.4 (C), 206.5 (C); *m/z* (CI) 234.1134 (MH^+. $C_{13}H_{16}NO_3$ requires 234.1130), 217 (2%), 190 (4), 174 (12), 131 (4). Data for methyl (2*S*,6*S*)-4-oxo-6-phenylpiperidine-2-carboxylate: ν_{max} (neat)/cm^{-1} 3322 (NH), 3024 (CH), 1728 (CO), 1443, 1211, 1034; $[\alpha]_D^{25}$ –34.3 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.55–2.59 (3H, m, 5-H_2 and NH), 2.74–2.84 (2H, m, 3-H_2), 3.77 (3H, s, OMe), 4.13 (1H, dd, *J* 6.3, 3.8 Hz, 2-H), 4.21 (1H, dd, *J* 7.6, 6.6 Hz, 6-H), 7.29–7.41 (5H, m, Ph);

δ_C (101 MHz, $CDCl_3$) 41.8 (CH_2), 49.2 (CH_2), 52.3 (CH_3), 56.0 (CH), 56.7 (CH), 126.6 (2 × CH), 128.0 (CH), 128.8 (2 × CH), 142.1 (C), 173.0 (C), 206.2 (C); *m/z* (CI) 234.1129 (MH^+. $C_{13}H_{16}NO_3$ requires 234.1130), 200 (1%), 174 (2), 146 (1), 131 (1).

Methyl (2*S*,6*R*)-6-(4-bromophenyl)-4-oxopiperidine-2-carboxylate and methyl (2*S*,6*S*)-6-(4-bromophenyl)-4-oxopiperidine-2-carboxylate

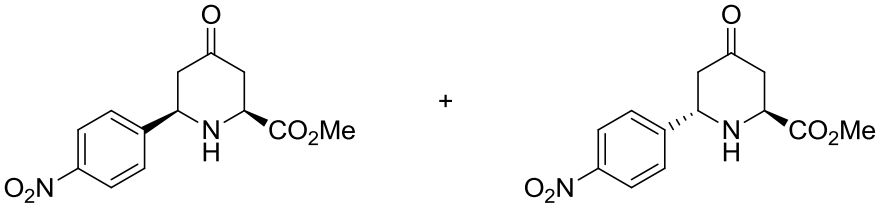


274a **274b**

To a solution of methyl (2*S*,5*E*)-2-(tritylamino)-6-(4-bromophenyl)-4-oxohex-5-enoate (**266**) (176 mg, 0.32 mmol) in methanol (10 mL) was added 2 M hydrochloric acid solution (2.5 mL). The mixture was stirred for 1 h, then diluted with water (10 mL) and basified to pH 8 with *N*-ethyldiisopropylamine (1.5 mL). The mixture was stirred for 18 h then partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous layers were separated and re-extracted with ethyl acetate (20 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-6-(4-bromophenyl)-4-oxopiperidine-2-carboxylate (39 mg, 39%) as a white solid followed by methyl (2*S*,6*S*)-6-(4-bromophenyl)-4-oxopiperidine-2-carboxylate (12 mg, 12%) as a white solid. Data for (2*S*,6*R*)-6-(4-bromophenyl)-4-oxopiperidine-2-carboxylate: Mp. 166–168 °C (decomposition); ν_{max} (neat)/cm^{-1} 3327 (NH), 2954 (CH), 1721 (CO), 1435, 1250, 1227; $[\alpha]_D^{27}$ +29.9 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.46 (1H, ddd, *J* 14.5, 11.4, 0.8 Hz, 5-H_{eq}), 2.51–2.55 (2H, m, NH and 5-H_{ax}), 2.59 (1H, ddd, *J* 14.5, 12.2, 0.8 Hz, 3-H_{eq}), 2.76–2.82 (1H, m, 3-H_{ax}), 3.75 (1H, dt, *J* 11.9, 3.0 Hz, 2-H), 3.79 (3H, s, OMe), 3.92 (1H, dt, *J* 11.4, 3.0 Hz, 6-H), 7.30 (2H, d, *J* 6.8 Hz, ArH), 7.50 (2H, d, J 6.8 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 43.8 (CH_2), 50.0 (CH_2), 52.6 (CH), 57.8 (CH_3), 59.6 (CH), 122.0 (C), 128.3 (2 × CH), 132.0 (2 × CH), 140.8 (C), 171.3 (C), 206.0 (C); *m/z* (CI) 314.0219 (MH^+. $C_{13}H_{15}{}^{81}BrNO_3$ requires 314.0216), 252 (3%), 234 (8), 167 (2). Data for methyl (2*S*,6*S*)-6-(4-bromophenyl)-4-oxopiperidine-2-carboxylate: Mp. 151–153 °C (decomposition); ν_{max} (neat)/cm^{-1} 3321 (NH), 2924 (CH), 1721 (CO), 1358, 1196, 1003; $[\alpha]_D^{25}$ –30.9 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.48–2.55 (3H, m, 5-H_2 and NH),

2.74–2.83 (2H, m, 3-H_2), 3.76 (3H, s, OMe), 4.12 (1H, dd, *J* 6.5, 3.6 Hz, 2-H), 4.20 (1H, dd, *J* 9.3, 4.8 Hz, 6-H), 7.28 (2H, d, *J* 6.8 Hz, ArH), 7.49 (2H, d, *J* 6.8 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 41.7 (CH_2), 49.2 (CH_2), 52.4 (CH_3), 56.0 (CH), 56.2 (CH), 121.8 (C), 128.4 (2 × CH), 131.9 (2 × CH), 141.2 (C), 173.0 (C), 205.8 (C); *m/z* (CI) 314.0217 (MH^+. $C_{13}H_{15}{}^{81}BrNO_3$ requires 314.0216), 252 (6%), 234 (3), 211 (3), 156 (2).

Methyl (2*S*,6*R*)-6-(4-nitrophenyl)-4-oxopiperidine-2-carboxylate and Methyl (2*S*,6*S*)-6-(4-nitrophenyl)-4-oxopiperidine-2-carboxylate

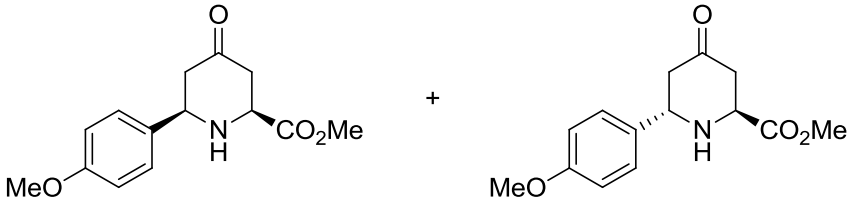


275a **275b**

To a solution of methyl (2*S*,5*E*)-2-(tritylamino)-6-(4-nitrophenyl)-4-oxohex-5-enoate (**267**) (152 mg, 0.29 mmol) in methanol (10 mL) was added 2 M hydrochloric acid solution (2.5 mL). The mixture was stirred for 1 h, then diluted with water (10 mL) and basified to pH 8 with *N*-ethyldiisopropylamine (1.5 mL). The mixture was stirred for 18 h then partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous layer was separated and re-extracted with ethyl acetate (20 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-6-(4-nitrophenyl)-4-oxopiperidine-2-carboxylate (30 mg, 37%) as a white solid followed by methyl (2*S*,6*S*)-6-(4-nitrophenyl)-4-oxopiperidine-2-carboxylate (16 mg, 20%) as a white solid. Data for methyl (2*S*,6*R*)-6-(4-nitrophenyl)-4-oxopiperidine-2-carboxylate: Mp. 121–123 °C; ν_{max} (neat)/cm^{-1} 3347 (NH), 2955 (CH), 1720, 1605, 1520 (NO), 1350 (NO), 1219; $[\alpha]_D{}^{26}$ +62.9 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.39 (1H, dd, *J* 14.6, 11.8 Hz, 3-H_{ax}), 2.49–2.58 (3H, m, 5-H_2 and NH), 2.76 (1H, ddd, *J* 14.6, 3.2, 1.9 Hz, 3-H_{eq}), 3.70–3.74 (4H, m, 2-H and OMe), 4.03 (1H, dd, *J* 11.8, 3.0 Hz, 6-H), 7.56 (2H, d, *J* 8.7 Hz, ArH), 8.17 (2H, *J* 8.7 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 43.7 (CH_2), 49.8 (CH_2), 52.7 (CH_3), 57.7 (CH), 59.4 (CH), 124.2 (2 × CH), 127.5 (2 × CH), 147.8 (C), 148.8 (C), 171.1 (C), 205.0 (C); *m/z* (CI) 279.0975 (MH^+. $C_{13}H_{15}N_2O_5$ requires 279.0981), 249 (7%), 219 (10), 203 (2), 177 (2). Data for methyl (2*S*,6*S*)-6-(4-nitrophenyl)-4-oxopiperidine-2-carboxylate: Mp. 133–135 °C; ν_{max} (neat)/cm^{-1} 3347 (NH), 2955 (CH), 1728 (CO), 1604

(C=C), 1520 (NO), 1350 (NO), 1204; $[\alpha]_D^{26}$ –40.0 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.42 (1H, dd, *J* 14.5, 10.5 Hz, 5-H_{ax}), 2.50 (1H, ddd, *J* 14.5, 4.0, 1.2 Hz, 5-H_{eq}), 2.51 (1H, br s, NH), 2.70–2.80 (2H, m, 3-H_2), 3.71 (3H, s, OMe), 4.11 (1H, dd, *J* 6.3, 3.6 Hz, 2-H), 4.31 (1H, dd, *J* 10.5, 4.0 Hz, 6-H), 7.53 (2H, d, *J* 8.8 Hz, ArH), 8.16 (2H, d, *J* 8.8 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 41.7 (CH_2), 49.0 (CH_2), 52.5 (CH_3), 56.0 (CH), 56.2 (CH), 124.1 (2 × CH), 127.5 (2 × CH), 147.7 (C), 149.4 (C), 172.8 (C), 204.8 (C); *m/z* (CI) 279.0987 (MH^+. $C_{13}H_{15}N_2O_5$ requires 279.0981), 249 (5%), 243 (6), 207 (4), 167 (3).

Methyl (2*S*,6*R*)-6-(4-methoxyphenyl)-4-oxopiperidine-2-carboxylate and methyl (2*S*,6*S*)-6-(4-methoxyphenyl)-4-oxopiperidine-2-carboxylate



276a **276b**

To a solution of methyl (2*S*,5*E*)-2-(tritylamino)-6-(4-methoxyphenyl)-4-oxohex-5-enoate (**268**) (51 mg, 0.10 μmol) in methanol (10 mL) was added 2 M hydrochloric acid solution (2.5 mL). The mixture was stirred for 1 h, then diluted with water (10 mL) and basified to pH 8 with *N*-ethyldiisopropylamine (1.5 mL). The mixture was stirred for 18 h then partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous layer was separated and re-extracted with ethyl acetate (20 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-6-(4-methoxyphenyl)-4-oxopiperidine-2-carboxylate (15 mg, 56%) as a colourless oil followed by methyl (2*S*,6*S*)-6-(4-methoxyphenyl)-4-oxopiperidine-2-carboxylate (8 mg, 30%) as a colourless oil. Data for methyl (2*S*,6*R*)-6-(4-methoxyphenyl)-4-oxopiperidine-2-carboxylate: ν_{max} (neat)/cm^{-1} 3317 (NH), 2955 (CH), 1743 (CO), 1713 (CO), 1512, 1250, 1219; $[\alpha]_D^{25}$ +38.4 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.52–2.54 (3H, m, 5-H_2 and NH), 2.59 (1H, dd, *J* 14.4, 12.2 Hz, 3-H_{ax}), 2.78 (1H, dd, *J* 14.4, 3.3 Hz, 3-H_{eq}), 3.75 (1H, dd, *J* 12.2, 3.3 Hz, 2-H), 3.78 (3H, s, OMe), 3.81 (3H, s, OMe), 3.90 (1H, dd, *J* 8.2, 6.7 Hz, 6-H), 6.90 (2H, d, *J* 7.0 Hz, ArH), 7.33 (2H, d, *J* 7.0 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 43.9 (CH_2), 50.2 (CH_2), 52.5 (CH_3), 55.3 (CH_3), 57.9 (CH), 59.7 (CH), 114.2 (2 × CH), 127.7 (2 × CH), 133.9 (C), 159.4 (C), 171.4 (C), 206.6

(C); *m/z* (EI) 263.1161 (M^+. $C_{14}H_{17}NO_4$ requires 263.1158), 204 (25%), 161 (100), 84 (32), 50 (33). Data for (2*S*,6*S*)-6-(4-methoxyphenyl)-4-oxopiperidine-2-carboxylate: ν_{max} (neat)/cm^{-1} 3319 (NH), 2932 (CH), 1728 (CO), 1612 (C=C), 1512, 1250, 1219; $[\alpha]_D^{25}$ –16.5 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.52–2.61 (2H, m, 3-H_2), 2.73–2.82 (2H, m, 5-H_2), 3.76 (3H, s, OMe), 3.81 (3H, s, OMe), 4.11 (1H, dd, *J* 6.2, 3.9 Hz, 2-H), 4.16 (1H, dd, *J* 9.0, 5.1 Hz, 6-H), 6.89 (2H, d, J 8.7 Hz, ArH), 7.30 (2H, d, J 8.7 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 41.8 (CH_2), 49.3 (CH_2), 52.3 (CH_3), 55.3 (CH_3), 55.9 (CH), 56.2 (CH), 114.1 (2 × CH), 127.8 (2 × CH), 134.3 (C), 159.3 (C), 173.0 (C), 206.4 (C); *m/z* (EI) 263.1164 (M^+. $C_{14}H_{17}NO_4$ requires 263.1158), 220 (8%), 204 (12), 161 (66), 134 (16).

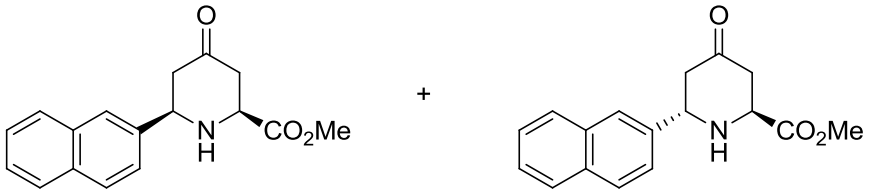
Methyl (2*S*,6*R*)-6-(furan-2-yl)-4-oxopiperidine-2-carboxylate and methyl (2*S*,6*S*)-6-(furan-2-yl)-4-oxopiperidine-2-carboxylate

277a **277b**

To a solution of methyl (2*S*,5*E*)-2-(tritylamino)-6-(furan-2-yl)-4-oxohex-5-enoate (**269**) (134 mg, 0.29 mmol) in methanol (10 mL) was added 2 M hydrochloric acid solution (2.5 mL). The mixture was stirred for 1 h, then diluted with water (10 mL) and basified to pH 8 with *N*-ethyldiisopropylamine (1.5 mL). The mixture was stirred for 18 h then partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous layer was separated and re-extracted with ethyl acetate (20 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-6-(furan-2-yl)-4-oxopiperidine-2-carboxylate (21 mg, 33%) as a colourless oil followed by methyl (2*S*,6*S*)-6-(furan-2-yl)-4-oxopiperidine-2-carboxylate (7 mg, 11%) as a colourless oil. Data for methyl (2*S*,6*R*)-6-(furan-2-yl)-4-oxopiperidine-2-carboxylate: ν_{max} (neat)/cm^{-1} 3356 (NH), 2924 (CH), 1743 (CO), 1636 (C=C), 1589, 1219, 1173; $[\alpha]_D^{24}$ +11.3 (*c* 0.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.55 (1H, dd, *J* 14.6, 12.0 Hz, 3-H_{ax}), 2.61–2.68 (3H, m, 5-H_2 and NH), 2.78 (1H, dd, *J* 14.6, 3.4 Hz, 3-H_{eq}), 3.74–3.79 (4H, m, 2-H and OMe), 4.11 (1H, dd, *J* 7.9, 7.0 Hz, 6-H), 6.25 (1H, d, *J* 3.3 Hz, ArH), 6.35 (1H, dd, *J* 3.3, 1.8 Hz, ArH), 7.40 (1H, dd, *J* 1.8, 0.8 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 44.2 (CH_2), 46.2 (CH_2), 52.6

(CH), 53.1 (CH_3), 57.5 (CH), 106.2 (CH), 110.3 (CH), 142.4 (CH), 153.8 (C), 171.3 (C), 205.7 (C); *m/z* (CI) 224.0927 (MH^+. $C_{11}H_{14}NO_4$ requires 224.0923), 196 (5%), 156 (100), 121 (2), 96 (3). Data for methyl (2*S*,6*S*)-6-(furan-2-yl)-4-oxopiperidine-2-carboxylate: ν_{max} (neat)/cm^{-1} 3342 (NH), 2955 (CH), 1743 (CO), 1636 (C=C), 1589, 1219, 1173; $[\alpha]_D^{24}$ +14.3 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.55 (1H, dd, *J* 15.2, 8.6 Hz, 3-H_{ax}), 2.59–2.72 (4H, m, 3-H_{eq}, 5-H_2 and NH), 3.66–3.71 (4H, m, 2-H and OMe), 4.50 (1H, t, *J* 5.5 Hz, 6-H), 6.11 (1H, d, *J* 3.3 Hz, ArH), 6.24 (1H, dd, *J* 3.3, 1.8 Hz, ArH), 7.31 (1H, dd, *J* 1.8, 0.7 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 43.2 (CH_2), 44.3 (CH_2), 50.3 (CH), 52.5 (CH_3), 54.1 (CH), 107.9 (CH), 110.2 (CH), 142.6 (CH), 153.7 (C), 172.3 (C), 205.7 (C); *m/z* (CI) 224.0921 (MH^+. $C_{11}H_{14}NO_4$ requires 224.0923), 196 (5%), 156 (100), 155 (13), 69 (2).

Methyl (2*S*,6*R*)-6-(naphthalen-2-yl)-4-oxopiperidine-2-carboxylate and methyl (2*S*,6*S*)-6-(naphthalen-2-yl)-4-oxopiperidine-2-carboxylate

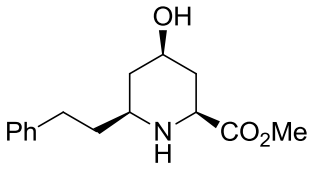


278a **278b**

To a solution of methyl (2*S*,5*E*)-2-(tritylamino)-6-(naphthalen-2-yl)-4-oxohex-5-enoate (**270**) (150 mg, 0.29 mmol) in methanol (10 mL) was added 2 M hydrochloric acid solution (2.5 mL). The mixture was stirred for 1 h, then diluted with water (10 mL) and basified to pH 8 with *N*-ethyldiisopropylamine (1.5 mL). The mixture was stirred for 18 h then partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous was separated and re-extracted with ethyl acetate (20 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-6-(naphthalen-2-yl)-4-oxopiperidine-2-carboxylate (53 mg, 66%) as a white solid followed by methyl (2*S*,6*S*)-6-(naphthalen-2-yl)-4-oxopiperidine-2-carboxylate (28 mg, 34%) as a white solid. Data for methyl (2*S*,6*R*)-6-(naphthalen-2-yl)-4-oxopiperidine-2-carboxylate: Mp. 115–117 °C; ν_{max} (neat)/cm^{-1} 3325 (NH), 2953 (CH), 1735 (CO), 1712 (CO), 1435, 1248, 1211; $[\alpha]_D^{25}$ +36.9 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.64–2.72 (4H, m, 5-H_2, 3-H_{ax} and NH), 2.86 (1H, ddd, *J* 14.5, 3.4, 1.3 Hz, 3-H_{eq}), 3.82 (3H, s, OMe), 3.85 (1H, dd, *J* 12.1, 3.5 Hz, 2-H), 4.15 (1H, dd, *J* 9.3, 5.4 Hz, 6-H), 7.49–7.57 (3H, m, ArH), 7.86–7.90

(4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 43.9 (CH_2), 50.1 (CH_2), 52.6 (CH_3), 58.0 (CH), 60.3 (CH), 124.5 (CH), 125.3 (CH), 126.2 (CH), 126.4 (CH), 127.7 (CH), 127.9 (CH), 128.7 (CH), 133.2 (C), 133.4 (C), 139.1 (C), 171.4 (C), 206.4 (C); *m/z* (CI) 284.1287 (MH^+. $C_{17}H_{18}NO_3$ requires 284.1287), 243 (7%), 224 (2), 182 (2), 156 (2). Data for methyl (2*S*,6*S*)-6-(naphthalen-2-yl)-4-oxopiperidine-2-carboxylate: Mp. 87–90 °C; ν_{max} (neat)/cm^{-1} 3327 (NH), 2953 (CH), 1732 (CO), 1437, 1198, 1161; $[\alpha]_D^{25}$ –39.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.62–2.73 (3H, m, 5-H_2 and NH), 2.82–2.84 (2H, m, 3-H_2), 3.78 (3H, s, OMe), 4.16 (1H, dd, *J* 5.7, 4.5 Hz, 2-H), 4.40 (1H, dd, *J* 9.5, 4.6 Hz, 6-H), 7.47–7.53 (3H, m, ArH), 7.82–7.87 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 41.9 (CH_2), 49.0 (CH_2), 52.4 (CH_3), 56.0 (CH), 56.8 (CH), 124.6 (CH), 125.4 (CH), 126.2 (CH), 126.4 (CH), 127.7 (CH), 127.9 (CH), 128.7 (CH), 133.1 (C), 133.3 (C), 139.5 (C), 173.0 (C), 206.2 (C); *m/z* (CI) 284.1291 (MH^+. $C_{17}H_{18}NO_3$ requires 284.1287), 224 (4%), 181 (2), 156 (2).

Methyl (2*S*,4*R*,6*S*)-4-hydroxy-6-(2-phenylethyl)piperidine-2-carboxylate

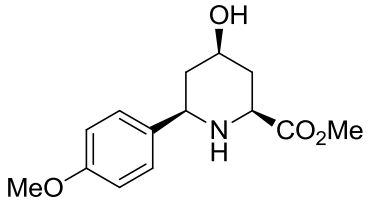


283a

To a solution of a methyl (2*S*,6*S*)-4-oxo-6-(2-phenylethyl)piperidine-2-carboxylate (**262a**) (49 mg, 0.19 mmol) in tetrahydrofuran (10 mL) at room temperature was added sodium triacetoxyborohydride (48 mg, 0.23 mmol), and the reaction stirred for 120 h. The mixture was quenched with 2 M hydrochloric acid solution then partitioned between saturated sodium hydrogen carbonate solution (15 mL) and ethyl acetate (15 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography afforded the desired product (43 mg, 87%) as a colourless oil and a 13:1 *syn*:*anti* mixture of diastereomers. ν_{max} (neat)/cm^{-1} 3330 (NH/OH), 2946 (CH), 1739 (CO), 1436, 1262, 1213; $[\alpha]_D^{29}$ –2.2 (*c* 0.7, $CHCl_3$); NMR data for major diastereomer: δ_H (400 MHz, $CDCl_3$) 0.99 (1H, q, *J* 11.2 Hz, 5-*H*H), 1.26 (1H, q, *J* 11.8 Hz, 3-*H*H), 1.65–1.81 (2H, m, 1'-H_2), 1.94–1.99 (1H, m, 5-H*H*), 2.22–2.28 (1H, m, 3-H*H*), 2.49–2.56 (1H, m, 6-H), 2.58–2.70 (2H, m, 2'-H_2), 3.30 (1H, dd, *J* 11.8, 2.7 Hz, 2-H), 3.60–3.69 (4H, m, 4-H and OMe), 7.10–7.23 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 32.2 (CH_2), 38.2 (CH_2), 38.5 (CH_2), 41.5 (CH_2), 52.2 (CH_3), 53.6 (CH), 57.2 (CH), 68.9 (CH),

125.9 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 141.7 (C), 172.9 (C); *m/z* (EI) 263.1519 (M^+. $C_{15}H_{21}NO_3$ requires 263.1521), 204 (100%), 187 (12), 158 (49), 140 (28), 91 (57).

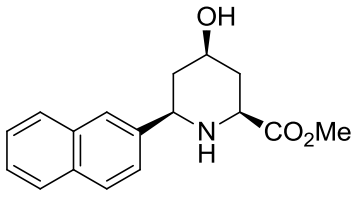
Methyl (2*S*,4*R*,6*R*)-4-hydroxy-6-(4-methoxyphenyl)piperidine-2-carboxylate



284a

To a solution of a methyl (2*S*,6*R*)-6-(4-methoxyphenyl)-4-oxopiperidine-2-carboxylate (**276a**) (33 mg, 0.13 mmol) in tetrahydrofuran (10 mL) at room temperature was added sodium triacetoxyborohydride (32 mg, 0.15 mmol), and the reaction stirred for 144 h. The mixture was quenched with 2 M hydrochloric acid solution then partitioned between saturated sodium hydrogen carbonate solution (15 mL) and ethyl acetate (15 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography afforded the desired product (31 mg, 96%) as a colourless oil and a 23:1 *syn*:*anti* mixture of diastereomers. ν_{max} (neat)/cm^{-1} 3333 (NH/OH), 2926 (CH), 1738 (CO), 1612 (C=C), 1514, 1245; $[\alpha]_D^{25}$ +16.4 (*c* 0.9, $CHCl_3$); NMR data for major diastereomer: δ_H (400 MHz, $CDCl_3$) 1.45–1.53 (2H, m, 3-*H*H and 5-*H*H), 2.08–2.12 (1H, m, 3-H*H*), 2.38–2.42 (1H, m, 5-H*H*), 3.52 (1H, dd, *J* 11.8, 2.6 Hz, 6-H), 3.64 (1H, dd, *J* 11.5, 2.5 Hz, 2-H), 3.74 (3H, s, OMe), 3.80 (3H, s, OMe), 3.79–3.88 (1H, m, 4-H), 6.85–6.88 (2H, m, ArH), 7.29–7.32 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) 37.6 (CH_2), 43.1 (CH_2), 52.2 (CH), 55.3 (CH), 57.5 (CH_3), 58.5 (CH_3), 69.3 (CH), 113.9 (2 × CH), 128.0 (2 × CH), 135.2 (C), 159.0 (C), 172.5 (C); *m/z* (CI) 266.1396 (MH^+. $C_{14}H_{20}NO_4$ requires 266.1392), 248 (30%), 234 (6), 206 (4), 178 (3).

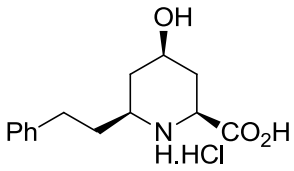
Methyl (2*S*,4*R*,6*R*)-4-hydroxy-6-(naphthalen-2-yl)piperidine-2-carboxylate



285a

To a solution of a methyl (2*S*,6*R*)-6-(naphthalen-2-yl)-4-oxopiperidine-2-carboxylate (**278a**) (67 mg, 0.24 mmol) in tetrahydrofuran (10 mL) at room temperature was added sodium triacetoxyborohydride (60 mg, 0.28 mmol), and the reaction stirred for 72 h. Further sodium triacetoxyborohydride (50 mg, 0.24 mmol) was added and the the mixture stirred for a further 72 h. The mixture was quenched with 2 M hydrochloric acid solution then partitioned between saturated sodium hydrogen carbonate solution (15 mL) and ethyl acetate (15 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography afforded the desired product (67 mg, 100%) as a white solid and a 17:1 *syn*:*anti* mixture of diastereomers. Mp. 109–111 °C; ν_{max} (neat)/cm^{-1} 3275 (NH/OH), 1728 (CO), 1431, 1223, 1123, 1049; $[\alpha]_D^{25}$ +25.3 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.50–1.61 (2H, m, 3-*H*H and 5-*H*H), 2.17–2.22 (1H, m, 3-H*H*), 2.41–2.47 (1H, m, 5-H*H*), 3.57 (1H, dd, *J* 11.9, 2.6 Hz, 2-H), 3.75 (3H, s, OMe), 3.84 (1H, dd, *J* 11.5, 2.3 Hz, 6-H), 3.85–3.93 (1H, m, 4-H), 7.43–7.51 (3H, m, ArH), 7.80–7.84 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 37.6 (CH_2), 43.2 (CH_2), 52.3 (CH_3), 57.5 (CH), 59.2 (CH), 69.3 (CH), 125.1 (CH), 125.2 (CH), 125.8 (CH), 126.1 (CH), 127.6 (CH), 127.9 (CH), 128.3 (CH), 133.0 (C), 133.4 (C), 140.5 (C), 172.6 (C); *m/z* (CI) 286.1444 (MH^+. $C_{17}H_{20}NO_3$ requires 286.1443), 266 (17%), 226 (4), 209 (2), 95 (3).

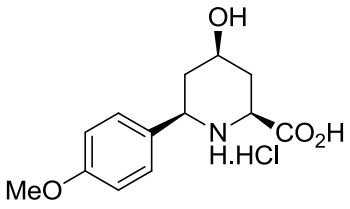
(2*S*,4*R*,6*S*)-4-Hydroxy-6-(2-phenylethyl)piperidine-2-carboxylic acid hydrochloride



288

Methyl (2*S*,4*R*,6*S*)-4-hydroxy-6-(2-phenylethyl)piperidine-2-carboxylate (**283a**) (58 mg, 0.22 mmol) was dissolved in 6 M hydrochloric acid (5 mL) and heated to 100 °C for 48 h. The mixture was cooled and concentrated under reduced pressure to afford a white solid, which was azetroped with acetone then dried under reduced pressure to afford the desired product (39 mg, 62%) as a white solid and a 13:1 *syn*:*anti* mixture of diastereomers. Mp. 219–221 °C; ν_{max} (neat)/cm^{-1} 3408 (NH/OH), 2921 (CH), 1757 (CO), 1453, 1184, 1066; $[\alpha]_D^{26}$ +50.3 (*c* 0.1, MeOH); δ_H (400 MHz, CD_3OD) 1.35–1.43 (1H, m, 5-*H*H), 1.56–1.63 (1H, m, 3-*H*H), 1.90–1.98 (1H, m, 1'-*H*H), 2.10–2.16 (1H, m, 1'-H*H*), 2.33–2.36 (1H, m, 5-H*H*), 2.52–2.55 (1H, m, 3-H*H*), 2.67–2.73 (1H, m, 2'-*H*H), 2.78–2.84 (1H, m, 2'-H*H*), 3.23–3.27 (1H, m, 6-H), 3.88–3.94 (1H, m, 4-H), 4.04–4.07 (1H, m, 2-H), 7.18–7.31 (5H, m, ArH); δ_C (101 MHz, CD_3OD) 32.3 (CH_2), 35.8 (2 × CH_2), 37.6 (CH_2), 56.0 (CH), 57.1 (CH), 66.3 (CH), 127.5 (CH), 129.4 (2 × CH), 129.8 (2 × CH), 141.6 (C), 170.6 (C); *m/z* (EI) 249.1368 (M^+. $C_{14}H_{19}NO_3$ requires 249.1365), 204 (100%), 160 (28), 144 (93), 126 (36), 117 (25), 91 (82).

(2*S*,4*R*,6*R*)-4-Hydroxy-6-(4-methoxyphenyl)piperidine-2-carboxylic acid hydrochloride

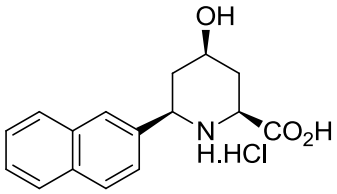


289

Methyl (2*S*,4*R*,6*R*)-4-hydroxy-6-(4-methoxyphenyl)piperidine-2-carboxylate (**284a**) (29 mg, 0.11 mmol) was dissolved in 6 M hydrochloric acid (5 mL) and heated to 100 °C for 48 h. The mixture was cooled and concentrated under reduced pressure to afford a white

solid, which was azetroped with acetone then dried under reduced pressure to afford the desired product (21 mg, 67%) as a white solid and a 23:1 *syn*:*anti* mixture of diastereomers. Mp. 173–175 °C; ν_{max} (neat)/cm^{-1} 3323 (NH/OH), 2926 (CH), 1732 (CO), 1612 (C=C), 1518, 1254; $[\alpha]_D^{29}$ –2.1 (*c* 1.0, MeOH); δ_H (400 MHz, CD_3OD) 1.71–1.78 (1H, m, 3-*H*H), 1.91–1.98 (1H, m, 5-*H*H), 2.24–2.27 (1H, m, 5-H*H*), 2.60–2.63 (1H, m, 3-H*H*), 3.82 (3H, s, OMe), 4.07–4.11 (1H, m, 4-H), 4.22–4.24 (1H, m, 2-H), 4.34–4.36 (1H, m, 6-H), 7.01 (2H, d, *J* 6.8 Hz, ArH), 7.46 (2H, d, *J* 6.8 Hz, ArH); δ_C (101 MHz, CD_3OD) 35.4 (CH_2), 39.3 (CH_2), 55.9 (CH_3), 57.8 (CH), 59.5 (CH), 66.9 (CH), 115.6 (2 × CH), 128.6 (C), 130.2 (2 × CH), 162.2 (C), 170.4 (C); *m/z* (EI) 251.1156 (M^+. $C_{13}H_{17}NO_4$ requires 251.1158), 234 (19%), 206 (100), 179 (28), 163 (74), 135 (62).

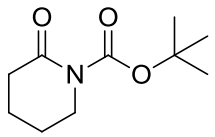
(2*S*,4*R*,6*R*)-4-Hydroxy-6-(naphthalen-2-yl)piperidine-2-carboxylic acid hydrochloride



290

Methyl (2*S*,4*R*,6*R*)-4-hydroxy-6-(naphthalen-2-yl)piperidine-2-carboxylate (**285a**) (61 mg, 0.21 mmol) was dissolved in 6 M hydrochloric acid (5 mL) and heated to 100 °C for 48 h. The mixture was cooled and concentrated under reduced pressure to afford a white solid, which was azetroped with acetone then dried under reduced pressure to afford the desired product (46 mg, 70%) as a white solid and a 17:1 *syn*:*anti* mixture of diastereomers. Mp. 203–205 °C; ν_{max} (neat)/cm^{-1} 3327 (NH/OH), 2951 (CH), 1744 (CO), 1622, 1410, 1213; $[\alpha]_D^{27}$ +10.1 (*c* 1.1, MeOH); δ_H (400 MHz, CD_3OD) 1.82–1.90 (1H, m, 3-*H*H), 2.04–2.12 (1H, m, 5-*H*H), 2.39–2.41 (1H, m, 5-H*H*), 2.67–2.70 (1H, m, 3-H*H*), 4.17–4.23 (1H, m, 4-H), 4.37 (1H, dd, *J* 13.1, 2.6 Hz, 2-H), 4.64 (1H, dd, *J* 12.7, 1.9 Hz, 6-H), 7.54–7.58 (2H, m, ArH), 7.66 (1H, dd, *J* 8.5, 1.4 Hz, ArH), 7.91 (1H, dd, *J* 6.1, 3.4 Hz, ArH), 7.95 (1H, dd, *J* 6.1, 3.4 Hz, ArH), 7.99 (1H, d, *J* 8.5 Hz, ArH), 8.07 (1H, s, ArH); δ_C (101 MHz, CD_3OD) 35.5 (CH_2), 39.6 (CH_2), 58.0 (CH), 60.1 (CH), 66.9 (CH), 125.6 (CH), 128.0 (CH), 128.3 (CH), 128.3 (CH), 128.9 (CH), 129.3 (CH), 130.3 (CH), 134.2 (C), 134.7 (C), 135.1 (C), 170.4 (C); *m/z* (EI) 271.1205 (M^+. $C_{16}H_{17}NO_3$ requires 271.1208), 226 (100%), 205 (41), 183 (46), 155 (54), 128 (23).

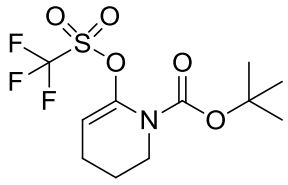
***N*-*tert*-Butoxycarbonyl-2-oxopiperidine**[102]



301

To a solution of piperidin-2-one (1.00 g, 10.1 mmol) in dichloromethane (100 mL) was added triethylamine (2.92 mL, 21.2 mmol), 4-dimethylaminopyridine (0.25 g, 2.00 mmol) and di-*tert*-butyl dicarbonate (4.40 g, 20.2 mmol). The mixture was stirred for 48 h then washed with 1 M hydrochloric acid solution (20 mL). The aqueous layer was extracted with dichloromethane (20 mL), the organic layers were combined then washed with saturated sodium hydrogencarbonate solution (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford an orange oil. Flash column chromatography (petroleum ether/ethyl acetate 4:1) afforded *N*-*tert*-butoxycarbonyl-2-oxopiperidine (1.51 g, 75%) as a colourless oil. NMR data consitent with literature.[102] ν_{max} (neat)/cm^{-1} 2977 (CH), 1769 (CO), 1708 (CO), 1287, 1246, 1136; δ_H (400 MHz, $CDCl_3$) 1.55 (9H, s, O*t*Bu), 1.81–1.87 (4H, m, 4-H_2 and 5-H_2), 2.51–2.54 (2H, m, 3-H_2), 3.65–3.69 (2H, m, 6-H_2); δ_C (101 MHz, $CDCl_3$) 20.5 (CH_2), 22.8 (CH_2), 28.0 (3 × CH_3), 34.9 (CH_2), 46.3 (CH_2), 82.9 (C), 152.8 (C), 171.3 (C); *m/z* (CI) 100 (MH^+–$C_5H_9O_2$), 71 (31%).

***N*-*tert*-Butoxycarbonyl-*Z*-[(trifluoromethyl)sulfonyloxy]-1,4,5,6-tetrahydropyridine**[89]

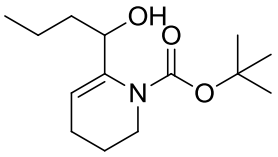


302

To a solution of 1 M lithium hexamethyldisilazide (750 μL, 0.75 mol) in tetrahydrofuran (30 mL) at –78 °C was added a solution of *N*-*tert*-butoxycarbonyl-2-oxopiperidine (**301**) (100 mg, 0.50 mmol) in tetrahydrofuran (10 mL). The mixture was stirred for 1 h, then a solution of *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (493 mg, 1.25 mmol) in tetrahydrofuran (10 mL) was added and the mixture was stirred for 2 h. The mixture was

warmed to room temperature and 10% wt. sodium hydroxide solution (20 mL) was added. The aqueous phase was separated and extracted with diethyl ether (2 × 20 mL). The organic phases were combined, washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield an orange solid. Flash column chromatography (petroleum ether/ethyl acetate 9:1 with 1% triethylamine) afforded *N*-*tert*-butoxycarbonyl-*Z*-[(trifluoromethyl)sulfonyloxy]-1,4,5,6-tetrahydropyridine (134 mg, 80%) as a colourless oil. NMR data consistent with literature.[89] ν_{max} (neat)/cm^{-1} 2982 (CH), 1721 (CO), 1682 (C=C), 1420, 1331, 1204, 1138; δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, O*t*Bu), 1.75–1.81 (2H, m, 5-H_2), 2.29 (2H, td, *J* 6.8, 4.0 Hz, 4-H_2), 3.61–3.64 (2H, m, 6-H_2), 5.31 (1H, t, *J* 4.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 22.2 (CH_2), 22.4 (CH_2), 28.0 (3 × CH_3), 45.5 (CH_2), 82.8 (C), 107.1 (CH), 118.4 (q, *J* 318 Hz, C), 140.2 (C), 152.7 (C); *m/z* (EI) 231 (M^+–$C_5H_9O_2$+H), 158 (82%), 149 (63), 101 (42).

tert-Butyl-6-(1-hydroxybutyl)-3,4-dihydropyridine-1(2H)-carboxylate

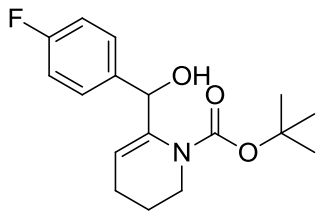


307

A solution of nickel chloride (0.8 mg, 6 μmol) and chromium chloride (223 mg, 1.81 mmol) in degassed dimethylformamide (15 mL) was stirred for 0.25 h, to which was added butyraldehyde (163 μL, 1.81 mmol) and a solution of *N*-*tert*-butoxycarbonyl-*Z*-[(trifluoromethyl)sulfonyloxy]-1,4,5,6-tetrahydropyridine (**302**) (100 mg, 0.30 mmol) in degassed dimethylformamide (10 mL). The mixture was stirred for 18 h then cooled to 0 °C, diluted with diethyl ether (20 mL) and quenched with 1% triethylamine in water (10 mL). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with water (2 × 15 mL) and brine (15 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a colourless oil. Flash column chromatography (petroleum ether/ethyl acetate 19:1 to 4:1) afforded *tert*-butyl-6-(1-hydroxybutyl)-3,4-dihydropyridine-1(2H)-carboxylate (51 mg, 66%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3417 (OH), 2932 (CH), 1682 (C=C), 1366, 1250, 1157; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.3 Hz, 4'-H_3), 1.24–1.67 (4H, m, 2'-H_2 and 3'-H_2), 1.52 (9H, s, O*t*Bu), 1.73–1.86 (2H, m, 5-H_2), 2.13–2.18 (2H, m, 4-H_2), 3.17–3.22 (1H,

m, 6-*H*H), 3.78–3.83 (1H, m, 6-H*H*), 4.10–4.15 (1H, m, 1'-H), 5.44 (1H, t, *J* 3.8 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.1 (CH_3), 19.5 (CH_2), 22.9 (CH_2), 23.3 (CH_2), 28.3 (3 × CH_3), 37.1 (CH_2), 45.6 (CH_2), 74.2 (CH), 81.2 (C), 116.5 (CH), 142.0 (C), 154.7 (C); *m/z* (CI) 182 (M^+–C_4H_9O), 165 (19%), 113 (24).

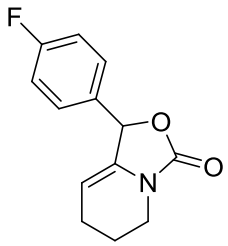
tert-Butyl-6-[(4-fluorophenyl)(hydroxy)methyl]-3,4-dihydropyridine-1(2H)-carboxylate



309

A solution of nickel chloride (0.8 mg, 6 μmol) and chromium chloride (223 mg, 1.81 mmol) in degassed dimethylformamide (15 mL) was stirred for 0.25 h, to which was added 4-fluorobenzaldehyde (194 μL, 1.81 mmol) and a solution of *N*-*tert*-butoxycarbonyl-*Z*-[(trifluoromethyl)sulfonyloxy]-1,4,5,6-tetrahydropyridine (**302**) (100 mg, 0.30 mmol) in degassed dimethylformamide (10 mL). The mixture was stirred for 18 h then cooled to 0 °C, diluted with diethyl ether (20 mL) and quenched with 1% triethylamine in water (10 mL). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with water (2 × 15 mL) and brine (15 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a colourless oil. Flash column chromatography (petroleum ether/ethyl acetate 19:1 to 4:1) afforded *tert*-butyl-6-[(4-fluorophenyl)(hydroxy)methyl]-3,4-dihydropyridine-1(2H)-carboxylate (66 mg, 71%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3381 (OH), 2932 (CH), 1680 (CO), 1507, 1393, 1367; δ_H (400 MHz, $CDCl_3$) 1.33 (9H, s, O*t*Bu), 1.73–1.88 (2H, m, 5-H_2), 2.18–2.22 (2H, m, 4-H_2), 2.98–3.03 (1H, m, 6-*H*H), 3.82 (1H, dt, *J* 12.7, 4.0 Hz, 6-H*H*), 5.33 (1H, d, *J* 9.4 Hz, 1'-H), 5.51 (1H, t, *J* 3.7 Hz, 3-H), 6.12 (1H, br s, OH), 6.96–7.01 (2H, m, ArH), 7.29–7.33 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) 23.0 (CH_2), 23.0 (CH_2), 28.0 (3 × CH_3), 45.6 (CH_2), 75.6 (CH), 81.4 (C), 114.4 (CH), 114.6 (CH), 118.6 (CH), 128.6 (CH), 128.7 (CH), 138.0 (C), 141.2 (C), 154.2 (C), 161.7 (d, *J* 244.2 Hz, C); *m/z* (CI) 308.1664 (MH^+. $C_{17}H_{23}FNO_3$ requires 308.1662), 290 (100%), 276 (33), 235 (100), 207 (66), 190 (32).

1-(4-Fluorophenyl)-1,5,6,7-tetrahydro[1,3]-oxazolo[3,4-a]pyridin-3-one



313

To a solution of 60% wt. sodium hydride (10 mg, 0.26 mmol) in tetrahydrofuran (5 mL) was added *tert*-butyl-6-[(4-fluorophenyl)(hydroxy)methyl]-3,4-dihydropyridine-1(2H)-carboxylate (**309**) (40 mg, 0.13 mmol). The mixture was heated to 65 °C for 0.75 h then allyl bromide (34 μL, 0.39 mmol) was added and the mixture stirred for a further 2.25 h. The reaction mixture was cooled to room temperature then quenched with ice. The mixture was concentrated under reduced pressure and the residue extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography (petroleum ether/ethyl acetate 19:1 to 3:1) afforded 1-(4-fluorophenyl)-1,5,6,7-tetrahydro[1,3]-oxazolo[3,4-a]pyridin-3-one (20 mg, 66%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2942 (CH), 1761 (CO), 1697 (C=C), 1512, 1366, 1229; δ_H (400 MHz, $CDCl_3$) 1.72–1.86 (2H, m, 6-H_2), 2.03–2.09 (2H, m, 7-H_2), 3.54 (2H, t, *J* 5.9 Hz, 5-H_2), 4.53 (1H, td, *J* 4.1, 2.1 Hz, 8-H_2), 5.81–5.82 (1H, m, 1-H), 6.99–7.05 (2H, m, ArH), 7.25–7.30 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) 20.2 (CH_2), 20.7 (CH_2), 40.0 (CH_2), 78.7 (CH), 96.6 (CH), 115.8 (CH), 116.0 (CH), 128.9 (CH), 129.0 (CH), 133.1 (C), 136.9 (C), 155.4 (C), 163.2 (d, *J* 248.4 Hz, C); *m/z* (EI) 233.0856 (M^+. $C_{13}H_{12}FNO_2$ requires 233.0852), 188 (67%), 148 (32), 123 (84), 95 (48).

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